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TRANSETHOSOMES FOR SYSTEMIC LUPUS ERYTHEMATOSUS: A PROMISING APPROACH IN TARGETED DRUG DELIVERY

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ABSTRACT

Systemic lupus erythematosus (SLE) is a multifaceted autoimmune disorder characterized by widespread inflammation and tissue damage. The management of SLE is challenging due to its heterogeneous nature and the limitations of current therapeutic options. Traditional drug delivery systems often face issues such as poor bioavailability and undesirable side effects, highlighting the need for innovative approaches. Transethosomes, lipid-based carriers, offer improved drug permeability through the skin, making them promising for the transdermal delivery of therapeutic agents. The incorporation of ethanol and surfactants into transethosomes enhances their stability and drug-loading capacity, thereby increasing therapeutic efficacy. This review aims to explore the formulation of transethosomes and their potential advantages in the treatment of SLE, emphasizing the need for further research in this field. The article underscores the importance of targeted drug delivery systems in improving patient compliance and therapeutic outcomes, particularly in chronic conditions like systemic lupus erythematosus that require long-term management.

KEYWORDS: Transdermal Drug Delivery System, Liposomes, Niosomes, Transferosomes,

Ethosome, Transethosomes, Systemic lupus erythematosus.

INTRODUCTION

Drug delivery technologies have evolved significantly due to stagnation in the discovery of novel therapeutic entities. Modern drug delivery systems aim to improve bioavailability, minimize side effects, and enhance patient adherence. Among these, transdermal drug delivery systems (TDDS) bypass first-pass metabolism and offer controlled release, especially useful in chronic conditions like SLE. Drug delivery technologies enable older pharmaceuticals to remain competitive in the growing market by improving their performance. These systems enhance drug efficacy through controlled release, taking into account factors such as the carrier system, route of administration, and the target site of therapeutic action. Ultimately, effective drug delivery systems can improve patient adherence, therapeutic outcomes, and bioavailability (Almandil, 2016).

Currently, there is growing interest among researchers in delivering active pharmaceutical ingredients via the transdermal route. However, achieving efficient drug administration through the skin remains a challenge. The transdermal drug delivery system was first developed in the 1950s in the United States. In this system, the drug permeates from the skin's surface into the bloodstream by passing through the three main layers of the skin: the epidermis, dermis, and hypodermis (Freitas, 2005).

Transdermal Drug Delivery Systems (TDDS)

Transdermal drug delivery technology offers several advantages over conventional administration methods. Drugs delivered via the transdermal route bypass the gastrointestinal tract, thereby avoiding degradation in the stomach (Godin & Touitou, 2004). This system enables the direct entry of drugs into the bloodstream through the skin, thus also bypassing pre-systemic (first-pass) metabolism. The transdermal approach is particularly suitable for drugs with a short half-life and a narrow therapeutic index (Honeywell-Nguyen & Bouwstra, 2005). Additionally, it allows for better regulation of plasma drug levels and enables the rapid discontinuation of therapy in the event of toxicity. However, this technique also presents several challenges, including its inability to deliver drugs that require large blood volumes (V. Pandey et al., 2014). Some patients may experience skin irritation due to the use of patches and pharmaceutical excipients, making it a less cost-effective option for certain individuals.

When developing a transdermal drug delivery system, several critical factors must be

considered, such as drug properties, skin characteristics, formulation components, adhesive selection, and overall system design. Drug penetration through the skin is influenced by multiple factors, including the structural and functional properties of the skin, the physicochemical characteristics of the drug molecule, and the mechanisms used to deliver the drug to the skin surface (Schreier & Bouwstra, 1994).

Vesicular Drug Carriers

Various vesicular drug delivery systems have been developed to enhance transdermal permeation and overcome the limitations of conventional formulations. These include Liposomes, Ethosomes, Transferosomes, Nanoethosomes, and Transethosomes. Each system possesses unique structural features, benefits, and limitations, and plays a crucial role in improving therapeutic outcomes, particularly for transdermal applications. These systems are illustrated in Figure 1.

Liposomes are among the earliest vesicular carriers developed for drug delivery. They are composed of phospholipid bilayers that can encapsulate both hydrophilic and lipophilic drugs. Despite their biocompatibility and simplicity, liposomes suffer from poor skin penetration and moderate stability. Their rigidity and lack of deformability limit their ability to traverse the skin's stratum corneum.

Ethosomes, developed by Touitou in 1996, are vesicles containing a high concentration of ethanol, usually between 20–45%. Ethanol significantly enhances membrane fluidity and disrupts the tightly packed lipids of the stratum corneum, thereby facilitating deeper skin penetration. Ethosomes are particularly effective for the delivery of lipophilic drugs and are well-suited for transdermal applications.

Transferosomes, on the other hand, are highly elastic and ultra-deformable vesicles that incorporate edge activators such as Span 80, Tween 80, and sodium cholate. These agents impart flexibility, allowing the vesicles to squeeze through narrow intercellular gaps in the skin. While transferosomes offer improved skin permeation compared to liposomes, their ability to deeply penetrate the stratum corneum remains limited.

Nanoethosomes are a refined version of ethosomes with particle sizes in the nanometer range. These vesicles maintain the composition of traditional ethosomes but benefit from a smaller size and a high surface charge induced by ethanol. This configuration reduces particle

aggregation, enhances stability, and allows for improved dermal and transdermal drug delivery performance.

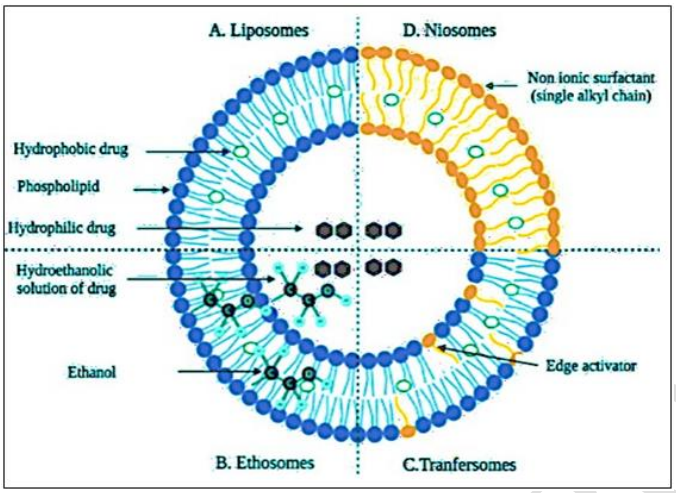

Figure 1: Transdermal Drug Delivery Systems (A) Liposomes, (B) Niosomes, (c) Transferosomes and (D) Ethosome (M. Pandey et al., 2021).

Transethosomes

Transethosomes are an advanced hybrid vesicular system that integrate the advantageous features of both Ethosomes and Transferosomes. By combining the ethanol- mediated skin permeability of Ethosomes with the deformability and elasticity imparted by transferosomes, Transethosomes significantly enhance transdermal drug delivery performance. These systems are particularly promising for chronic diseases such as systemic lupus erythematosus (SLE), where targeted and sustained therapy is essential.

Composition of Transethosomes

Structurally, Transethosomes are composed of phospholipids, ethanol, water, edge activators (such as Span 80, Tween 80, or sodium cholate), and the active pharmaceutical ingredient (API). This unique composition enables the encapsulation of both hydrophilic and lipophilic drugs, making them highly versatile for a broad range of therapeutic applications. Ethanol plays a dual role by enhancing the fluidity of the vesicle membrane and disrupting the lipid structure of the stratum corneum, thereby increasing skin permeability. Edge activators, which are typically non-ionic surfactants, contribute to vesicle elasticity and deformability, allowing the vesicles to traverse narrow intercellular spaces within the skin barrier. Phospholipids form the bilayer structure that stabilizes and encapsulates the drug, while maintaining biocompatibility. The distinct composition of Transethosomes not only enhances

skin penetration but also improves entrapment efficiency, drug-loading capacity, and systemic absorption. Their biodegradability, formulation simplicity, and lack of need for additional pharmaceutical aids further support their application in long-term therapeutic strategies. A comparative overview of Vesicular Drug Carriers is provided in Table 1, summarizing their structural characteristics and drug delivery capabilities.

Table 1: Comparisons between Vesicular Drug Carriers. (Cevc & Blume, 2001) & (Mishra et al., 2019).

Variables	Liposome	Ethosomes	Transferosomes	Transethosomes
Composition	Phospholipid, polyglycol and surfactant	Phospholipids, ethanol and water	Phospholipids, Edge stimulator and water	Phospholipids, Edge stimulator, Ethanol and water
Encapsulation Efficiency	Good	Higher than liposome	Higher than ethosomes	Higher than liposome, ethosomes and Transferosomes
Transdermal Flux rate	Depends on formulation	Greater than liposome	Equal or higher than ethosomes	Flux rate is Higher as comparative.
Permeation Mechanism	Can increase or reduce penetration depends on drug solubility	Adipose disruption	Vesicular deformation	Alteration in vesicular structure

The key components of Transethosomes include

Phospholipids: These constitute the fundamental structural matrix of the vesicles, forming a bilayer lipid membrane that encapsulates the active pharmaceutical ingredient (API). Phospholipids provide biocompatibility and stability to the formulation (Regnier et al., 1999).

Ethanol: Ethanol enhances the fluidity of the vesicular membrane and disrupts the lipid structure of the stratum corneum, thereby increasing skin permeability. It facilitates the deep penetration of the vesicles and improves the diffusion of the encapsulated drug into systemic circulation.

Edge Activators (Surfactants): Non-ionic surfactants such as Span 80, Tween 80, or sodium cholate are included to increase vesicle flexibility and stability. These agents act as edge activators, reducing membrane rigidity and enhancing deformability, which is critical for traversing the narrow pores of the skin barrier (Regnier et al., 1999).

Active Pharmaceutical Ingredient (API): This is the drug or therapeutic agent intended for delivery. Transethosomes can encapsulate a wide range of APIs, accommodating both

hydrophilic and lipophilic molecules.

Mechanism of Action of Transethosomes (Skin Penetration)

Transethosomes deliver drugs through a combination of mechanisms that enhance skin permeability and enable deep tissue targeting. Their unique composition comprising ethanol, phospholipids, and edge activators facilitates the effective transdermal transport of therapeutic agents.

The principal mechanisms involved in Transethosomal drug delivery include

*Vesicle Fusion and Skin Penetration***:** The ultra-deformable and elastic nature of Transethosomes allows them to fuse with the lipid bilayers of the stratum corneum. This facilitates the direct penetration of the encapsulated drug into the deeper layers of the skin, bypassing the superficial barriers (Li et al., 2017).

*Enhancement of Skin Permeability***:** The high ethanol and surfactant content in Transethosomes disrupts the tightly packed lipid structure of the stratum corneum. This increases membrane fluidity, weakens the skin barrier, and enables greater permeation of the drug into systemic circulation (Kumar, 2018; Sharma et al., 2022).

*Targeted and Sustained Drug Release***:** The lipid matrix of Transethosomes provides the potential for sustained and controlled drug release. This mechanism allows for prolonged therapeutic action at specific sites, such as inflamed joints or dermal layers, maintaining drug levels over an extended period (Kumar, 2018; Sharma et al., 2022).

Advantages of Transethosomes

Transethosomes offer several significant advantages over conventional and other vesicular drug delivery systems, making them a promising approach for transdermal and systemic therapy

Enhanced Skin Permeability and Bioavailability: Transethosomes significantly increase drug penetration through the skin, thereby enhancing the bioavailability of drugs with poor absorption profiles (Zhou et al., 2010).

Targeted Drug Delivery: These vesicles can be engineered to target specific tissues or sites of action, potentially reducing systemic side effects and improving localized therapeutic efficacy (Zhou et al., 2010).

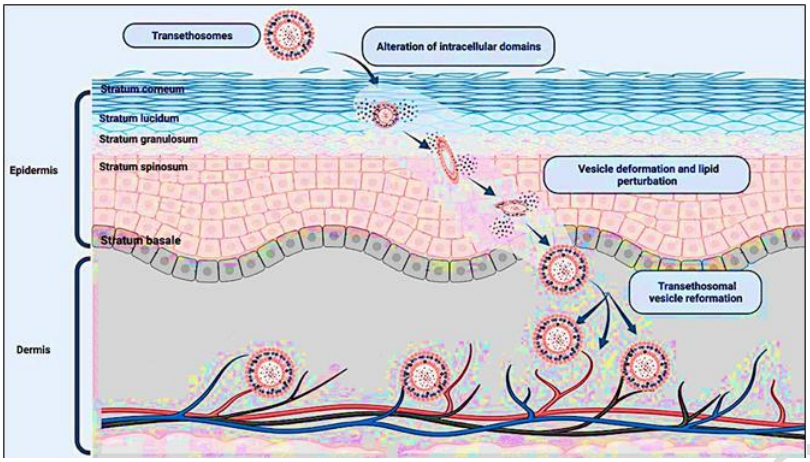

Figure 2: Mechanism of Action of Transethosomes. (Kumar, 2018 & Sharma et al., 2022) *Avoidance of First-Pass Metabolism*: Transethosomes bypass the gastrointestinal tract and hepatic first-pass metabolism, thereby minimizing the loss of drug activity and improving therapeutic outcomes (Zhou et al., 2010).

Improved Stability and Deeper Penetration: Compared to other vesicular systems Transethosomes exhibit greater stability and enhanced ability to penetrate through multiple layers of the skin (Verma & Pathak, 2010).

Controlled and Sustained Drug Release: Transethosomes can encapsulate drugs in a manner that allows for controlled and prolonged drug release, maintaining therapeutic levels over extended periods (Verma & Pathak, 2010).

Improved Patient Compliance: The non-invasive nature of transdermal delivery, combined with reduced dosing frequency, improves patient adherence to treatment regimens (Zhou et al., 2010).

Disadvantages of Transethosomes

Despite their numerous benefits, Transethosomes also present some limitations and challenges that must be considered

Skin Irritation and Allergic Reactions: The presence of ethanol and surfactants may cause local irritation, dermatitis, or allergic responses in sensitive individuals (Verma & Pathak, 2010).

Component Instability During Solvent Transition: Certain drugs or excipients may degrade or lose efficacy during the transition from alcoholic to aqueous environments during formulation or application (Zhou et al., 2010).

Vesicle Fusion and Instability: Inadequate vesicle production or improper formulation conditions may lead to vesicle fusion, aggregation, or instability, compromising drug delivery efficiency (Mishra et al., 2019).

Comparison of Transethosomes with other Vesicular carriers

Compared to traditional systems, Transethosomes offer distinct advantages in transdermal drug delivery applications. Table 2 provides a comparative summary of the advantages and disadvantages of Transethosomes alongside other vesicular carriers. This comparison highlights the unique attributes that make Transethosomes a promising system, especially for chronic and systemic conditions such as SLE.

Table 2: ***Comparison of Advantages and Disadvantages of Transethosomes with Other Vesicular Carriers (Sources: Mishra et al., 2019; Patel et al., 2013).***

Vesicular Carriers	Advantages	Disadvantages
Liposomes	Phospholipid vesicle, biocompatible	Less Skin Penetration less stable
Iontophoresis	Increase penetration of intermediate molecule (size changed)	Only for charged drugs, transfer efficiency is less than 10 %.
Niosomes	Non-ionic surfactants vesicles	Easy handling, less penetrate deeper into skin
Transferosomes	More stable, high penetration due to high elasticity, biocompatible and biodegradable, suitable for both low and high molecular weight drugs. also, for both hydrophilic and lipophilic drugs.	Unable to penetrate stratum corneum
Transethosomes	Increased drug permeation through skin for transdermal drug delivery. Pharmaceutical additives are non- toxic in nature. • More stable • Can administered in semi-solid form. • avoid first pass metabolism. • Biocompatible and biodegradable.	Drug and product lossduring transition between alcohol and aqueous media. • Skin irritation or allergic reaction on contact dermatitis. • Ineffective vesicle production can lead to the coagulation of Transethosomes.

Systemic Lupus Erythematosus (SLE)

Overview and Epidemiology

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that affects multiple organs and systems, including the skin, joints, kidneys, brain, and other vital tissues. It primarily affects women of reproductive age and has an estimated prevalence ranging from 20 to 150 cases per 100,000 individuals (Du et al., 2022). The disease is more common in women, with a female-to-male ratio of approximately 9:1, and typically manifests during the reproductive years, with a peak incidence between the ages of 15 and 45 (Yildirim-Toruner & Diamond, 2011). The disease is marked by alternating periods of exacerbation and remission, with clinical manifestations ranging from mild discomfort to life-threatening organ complications.

Pathogenesis and Immunology

The pathogenesis of SLE is multifactorial, involving genetic, epigenetic, hormonal, and environmental components. Genetic predisposition plays a significant role, as demonstrated by the higher incidence among individuals with a family history of SLE or related autoimmune diseases. Genome-wide association studies have identified numerous risk alleles related to immune regulation and inflammation. Environmental triggers—such as ultraviolet radiation, viral infections, certain medications, and chemical exposures—are also implicated in the initiation or exacerbation of SLE. These triggers may cause epigenetic alterations, activate innate immune pathways, and disrupt immune tolerance, contributing to chronic inflammation and multi-organ damage (Goodman, 2011; Yildirim-Toruner & Diamond, 2011).

Clinical Manifestations

SLE presents with a broad array of clinical symptoms affecting multiple systems. Dermatological manifestations include malar rash, discoid lupus, and photosensitivity. Musculoskeletal symptoms often involve arthralgia and arthritis. Renal involvement, particularly lupus nephritis, can progress to chronic kidney disease. Hematologic abnormalities may include anemia, leukopenia, and thrombocytopenia. Neurological symptoms such as seizures, psychosis, and peripheral neuropathy can occur, while cardiovascular manifestations may include pericarditis and an increased risk of atherosclerosis (Goodman, 2011). The wide range of symptoms contributes to diagnostic complexity and challenges in long-term management.

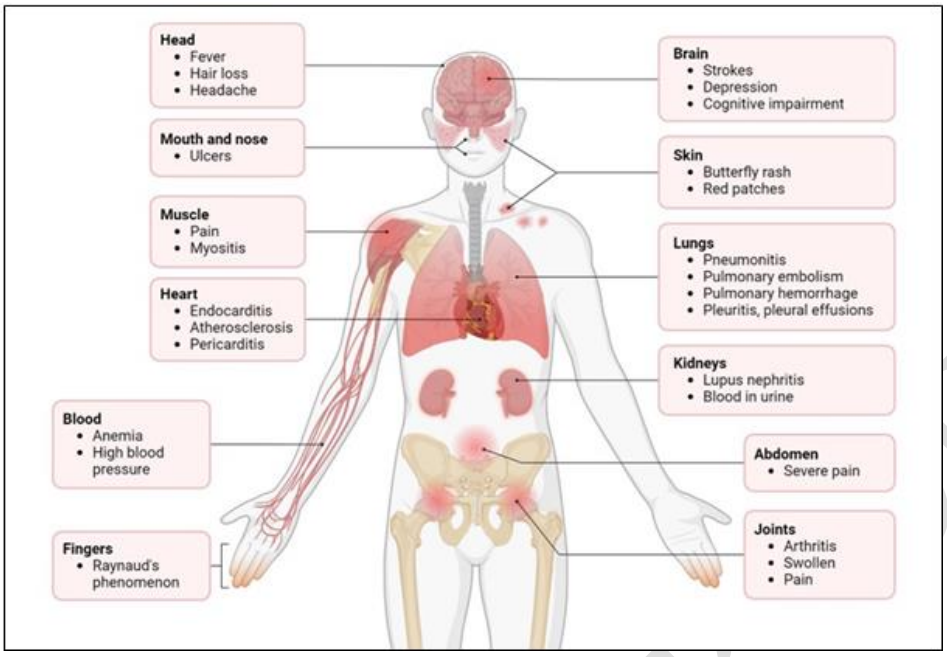

Figure 3: Symptoms of SLE.

Diagnosis and Biomarkers

The diagnosis of SLE is primarily clinical but is supported by laboratory investigations, including antinuclear antibodies (ANA), anti-dsDNA, and anti-Smith antibodies. Ongoing research aims to identify reliable biomarkers that aid in early diagnosis, disease monitoring, and treatment response prediction. Despite advancements, universally accepted biomarkers for precision therapy in SLE remain limited.

Current Therapeutic strategies

The management of SLE requires a multidisciplinary approach involving specialists such as rheumatologists, nephrologists, and dermatologists, depending on organ involvement (Du et al., 2022). The therapeutic strategy is guided by disease severity and the specific organ systems affected. Antimalarial agents like hydroxychloroquine serve as a foundation due to their immunomodulatory and anti-inflammatory effects. Corticosteroids are commonly used to manage acute flares. Immunosuppressive agents such as methotrexate, azathioprine, and mycophenolate mofetil are employed for long-term disease control and organ protection (Yildirim-Toruner & Diamond, 2011; Ameer et al., 2022).

Recent advances have introduced targeted biologic therapies, including belimumab an anti-B cell activating factor (BAFF) monoclonal antibody and anifrolumab, a type I interferon receptor antagonist. These biologics offer new hope for patients with refractory disease and

have shown efficacy in clinical trials by selectively modulating immune responses (Ameer et al., 2022). Their use represents a shift toward personalized medicine in the treatment of autoimmune diseases.

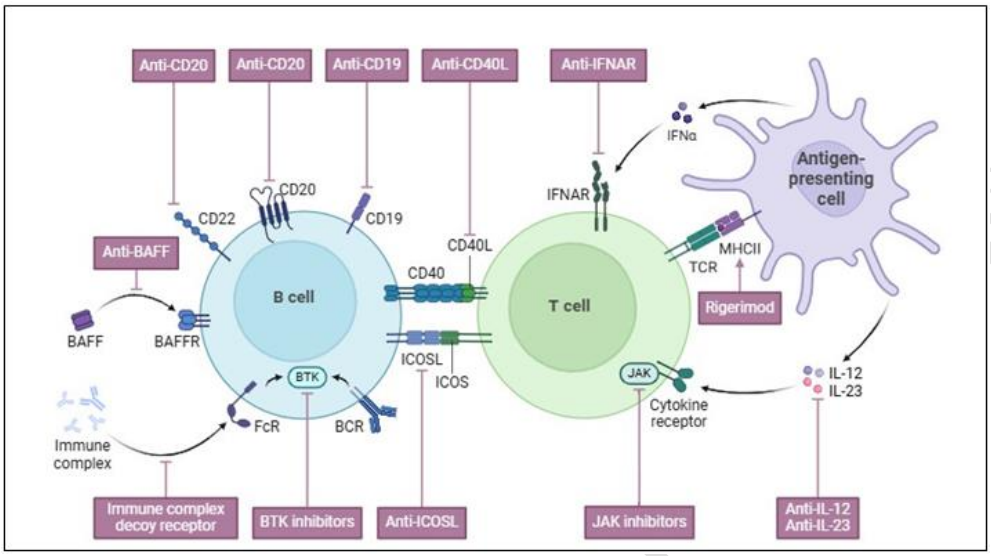

Figure 4: Therapeutic Agents for SLE (www.biorender.com).

Need for Targeted Drug Delivery

The need for targeted and localized drug delivery systems has become increasingly apparent to minimize systemic toxicity while maintaining or enhancing therapeutic efficacy. In this context, transdermal drug delivery using novel vesicular carriers like Transethosomes presents a promising alternative. Their ability to penetrate the stratum corneum, coupled with sustained drug release and improved bioavailability, makes them suitable for chronic diseases like SLE that require long-term treatment. This review aims to provide an in-depth examination of Transethosomes as a novel drug delivery system for SLE, highlighting their formulation, mechanism of action, and therapeutic potential.

Transethosomes for Systemic Lupus Erythematosus (SLE)

The design of an efficient drug delivery system for the treatment of systemic lupus erythematosus (SLE) is of paramount importance, given that existing therapies often show limited efficacy and are associated with substantial side effects (Touma and Gladman, 2017). Transethosomes, a novel vesicular system that combines the advantages of Ethosomes and Transferosomes, have emerged as a promising tool for the transdermal delivery of drugs in SLE. These carriers are specifically engineered to encapsulate therapeutic agents such as immunosuppressants or biologics and to enhance their transport through the skin to reach

targeted tissues and organs. The transdermal mode of administration provided by Transethosomes offers the added benefits of improved patient compliance and reduced gastrointestinal side effects often associated with oral formulations (Sguizzato et al., 2021).

Application of Transethosomes in SLE Treatment

Transethosomes have a wide range of potential applications in SLE therapy. Targeted delivery of anti-inflammatory agents such as NSAIDs and corticosteroids through Transethosomes can result in drug localization at the site of inflammation, thereby minimizing systemic exposure and reducing adverse effects. Incorporating immunomodulatory agents like azathioprine or cyclosporine into Transethosomal formulations could enhance therapeutic outcomes while improving the safety profile. Furthermore, Transethosomes enable combination therapy by co-delivering multiple drugs in a single formulation, which could optimize treatment regimens for SLE patients and improve overall efficacy.

Literature Related to Transethosomes and SLE

Despite their potential, the direct application of Transethosomes in SLE has not been extensively explored. Table 3 summarizes recent literature on Transethosomes in drug delivery. While many studies have demonstrated the efficacy of Transethosomes in delivering various therapeutic agents Transdermally, most have not directly addressed SLE. This gap highlights the need for further research to assess the utility of Transethosomes specifically in the context of autoimmune diseases like SLE.

Table 3: Literature related to Transethosomes and SLE

Therapeutic potential of Transethosmes	**Key finding**	Reference
Methotrexate against rheumatoid Arthritis	The goal is to create and optimize Methotrexate-loaded Transethosomal Film-Forming Gel for transdermal rheumatoid arthritis treatment. This paper discusses Transethosomes in medicine delivery but not SLE. Beyond this publication, Transethosomes and SLE literature needs more research.	(N et al., 2024)
Transethosomes: Cutting edge approach for drug permeation enhancement in TDDS	Transethosomes (TEs) are a novel vesicular mechanism for transdermal drug absorption, but the paper does not mention literature on them and systemic lupus erythematosus. It discusses the composition, benefits, and usage of TEs to Deliver bioactive compounds including	(Nayak et al., 2023)

	Antifungals and anti-inflammatories without discussing SLE or related studies.	
xploring the potential of Transethosomes in therapeutic delivery	The paper does not discuss Transethosome and SLE literature. It examines Transethosome characteristics, manufacturing, and medication delivery pathways.	(Chowdary et al., 2023)
Natural Plant based compounds	Traditional formulations encounter difficulties related to the skin's barrier, particularly the stratum corneum. Transethosomes (TEs) provide a mechanism for disrupting lipid bilayers, thereby improving drug permeation.	(Malang et al., 2024)
Transethosomes for drug delivery through the skin	It focuses on the formulation and advantages of Transethosomes for drug delivery through the skin, without addressing SLE or related studies.	(Bajaj et al., 2021)
Fistein for Dermal Delivery	Skin treated with transethosomal gel demonstrated a significantly higher maximum concentration and area under the curve from 0 to 8 hours in both the epidermis and dermis, compared to the conventional gel.	(Moolakkadath et al., 2018)
Olmesartan Medoxomil antihypertensive drugs used for transdermal delivery	The dermatokinetic study demonstrated that Transethosomes showed significantly greater maximum concentration and area under the curve from 0 to 10 hours compared to the drug suspension.	(Albash et al., 2019)
Azelaic acid for cutaneous delivery	Transethosomal preparations demonstrate significant potential as carriers for enhancing the anti-dermatophyte efficacy of azelaic acid by promoting its deep penetration through the skin layers.	(Nasr et al., 2023)
Ginger extract for topical delivery	The Transethosomal hydrogel was found to be appropriate for topical skin application, exhibiting improved skin permeability and enhanced anti-inflammatory effects in a rat-paw edema model.	(Hassan et al., 2023)
Metformin for topical delivery	The Transethosmal preparation significantly enhances the transdermal penetration of metformin, resulting in a markedly variable reduction in fasting blood glucose levels relative to oral metformin outcomes.	(Nousheen et al., 2023b)
Econazole nitrate-loaded Transethosomal gel	Comparison of econazole nitrate-loaded Transethosomal gel with commercial econazole nitrate topical cream to assess the antifungal activity of the drug. Transethosomal gel	(Verma & Utreja, 2018)
	demonstrated significant cutaneous maintenance and antifungal properties. The Transethosomal gel exhibits a consistent drug release pattern, effectively treating cutaneous candidiasis.	

Palmitoyl pentapeptide as peptide delivy system	Peptides are unable to penetrate the stratum corneum due to their larger size. Consequently, transdermal peptide delivery presents significant challenges. The transdermal administration of encapsulated palmitoyl pentapeptide was observed in a Transethosomal formulation. The study concluded that the incorporation of palmitoyl pentapeptide into a Transethosomal formulation enhanced elasticity, thereby increasing skin penetration.	(Kim et al., 2019)
Ketorolac Tromethamine for Transdermal Delivery	NSAIDs are often administered orally, although they are linked to numerous gastrointestinal side effects. To resolve this difficulty, researchers endeavored to provide the drug via transdermal delivery employing highly deformable vesicles. An experiment was conducted utilizing ketorolac tromethamine as the active ingredient to manufacture a Transethosomal gel related to Ethosomes. This investigation produced favorable results as the gel permeated the skin more effectively than the Ethosomes owing to its elastic properties.	(Shaji, J., & Garude, S. 2014).
Piroxicam loaded Transethosmal gel for Rheumatoid arthritis	This paper details the synthesis, optimization, characterisation, and ex vivo analysis of a piroxicam-loaded Transethosomal gel utilizing central composite design. Based on the pre-screening investigation, the lipid percentage was maintained between 2–4% w/v, while the ethanol concentration ranged from 0–40% v/v. The formulation was optimized by assessing drug retention in the skin, drug penetration, entrapment efficiency, and vesicle size. The optimized formulation was integrated into hydrogel and compared with other similar vesicular gels for the specified responses.	(Garg et al., 2016)
Hexatriacontane-Loaded Transethosmal Gel for Antimicrobial Treatment	The HTC-loaded Transethosome was identified as an efficient inhibitor of pathogenic bacterial proliferation (S. aureus and E. coli) at a dose of 10 mg/mL. Both pathogenic strains were found to	(Aodah et al., 2023)
	be sensitive to free HTC. Findings indicate that HTC-TES gel can be utilized to improve therapeutic results via antimicrobial activity.	
Etodolac Loaded Transethosomes for Transdermal Delivery	Etodolac is utilized in the management of rheumatoid arthritis, osteoarthritis, and several inflammatory disorders. Oral dosing is claimed to induce ulcerative colitis, gastrointestinal irritation, edema, and peptic ulceration. Consequently, an alternate delivery strategy has been developed in the form of Transethosomes. This paper details the synthesis, optimization,	(Gondkar et al., 2017)

	characterization, and ex vivo analysis of etodolac-loaded Transethosomal gel utilizing central composite design.	
Fluvastatin loaded Transethosomes	The objective of this research is to create new, skin-compatible, and stable drug delivery technologies that enhance the efficacy of psoriasis treatment. This will be accomplished by directing the active compound, fluvastatin, which is thought to possess possible antipsoriatic properties, particularly to the afflicted skin region.	(Yurtsever et al., 2023)
Ultradeformable vesicles (UDV)	This study sought to compare the attributes of several UDVs and their impact on the transdermal distribution of caffeine and vitamin E. The release profile is contingent upon the chemical characteristics of the actives and their ionization energy in UDV formulations. A prolonged release will be more readily achieved for compounds with higher incorporation, such as vitamin E. Despite low ionic strength, effective skin retention and penetration of caffeine-loaded UDV were attained compared to solution controls.	(Ascenso et al., 2015)
Transethosomal gel containing green tea	The objective of this work was to enhance the penetration of epigallocatechin gallate (EGCG) from the extract utilizing a Transethosomal gel.	Ramadon, D. & Anwar, E. (2017).
Propranolol hydrochloride Transethosomes for Trandermal Delivery	The aim of this study was to manufacture Transethosomes containing propranolol hydrochloride utilizing Lipoid S100 as the phospholipid and oleic acid as the permeation enhancer, and to assess their efficacy in sustained release, in-vitro skin permeation, and in-vivo plasma concentration.	(L. Kumar & Utreja, 2019)
Colchicine for Transdermal delivery	The findings indicated that Transethosomal gels are effective carriers for the transdermal delivery of colchicine, offering an alternate method for drug administration.	(Abdulbaqi et al., 2018)

Patents Related to Transethosomes

The first patent concerning Nanoethosomes was awarded in 1986 to Professor Elka Touitou of the Hebrew University School of Pharmacy in Jerusalem. Since then, numerous patents have been granted for innovations related to Ethosomal and Transethosomal drug delivery systems. These patents cover a variety of bioactive agents and therapeutic applications. Table 4 presents selected patents that involve Ethosomal or Transethosomal formulations for transdermal drug delivery.

Table 4: Selected Patents Related to Ethosomes and Transethosomes.

Title of the patent	Brief description	Inventors	Patent Number
Ethosome preparation of male hormone medicaments and its preparation method	This patent explains how to produce Ethosomes with male hormones for treating male disorders such as sterility, erectile dysfunction, and climacteric syndrome.	Guan Yan Min, MengShu, Li Jianxin, Dan	CN102406605 A
Method of preparing bioactive substance-encapsulated Ethosome, composition, and cosmetic composition	Preparing a bioactive substance- encapsulated Ethosome involves dissolving lipids in ethanol, mixing and agitating the lipid- dissolved solution and the bioactive substance aqueous solution, and adding purified lipids.	Yu Mi KimGi Hyun Jang	US11452679B2
Progesterone Ethosome, and preparation method and application	This invention involves encapsulating progesterone (0.1- 1%) in Ethosomes to treat secondar amenorrhea, dysfunctional bleeding, and premenstrual syndrome.	Zhang Shu, Deng Hong, Li Huaqing, Zhang Xiaoling	CN102397255 B
Transdermal composition for treating pain	This innovation introduces Ethosomal material for transdermal pain management, targeting muscle, nociceptive, and neuropathic pain.	Moheb Maalawy	WO2015123750 A1
Preparation method of lidocaine Ethosome	This invention describes a technique for producing lidocaine Ethosomes with lecithin and ethanol as the main ingredients. The Ethosomes demonstrated up to 80.93% entrapment and good skin compatibility.	Liang Ju, Wu Wenlan, Li, Miao Juan, Wei Xuefeng, Chen Shan, Wang Xiaotaro	CN103006562 B
Phenasteride gel preparation	This invention describes preparing Phenasteroid using 0.5-4% phospholipid and dispersing it in 0.25-1.5%) carbomer gel for topical use.	Liang Wen-right, Rao Yuefeng	CN1555804 A
Bullatacin Ethosome gel and preparation method	This invention discloses a technique for preparing Ethosomal gel utilizing Brad he octyl, phospholipid, low-molecular-weight alcohol, cholesterol, stabilizer, and antioxidant. The Ethosome size is 30–400 nm.	Tan Jianping, Jiang Lixin, often calm, Zhou Zhiwen	CN102552147 B

Acyclovir Ethosome and preparation method	This invention discloses acyclovir loaded Ethosomes with improved stability by addition of polyethylene glycol or chitosan for percutaneous administration	Wuxue Wen, Xiong Yan	CN102133183 B

Conclusion and Future Perspectives

Transethosomes offer an advanced and versatile approach for the transdermal delivery of therapeutic agents, combining the benefits of enhanced permeability, high drug encapsulation efficiency, and deformability. Their application in systemic lupus erythematosus represents a novel and promising direction in targeted drug delivery. Although current literature demonstrates their efficacy across a variety of drugs and therapeutic areas, specific studies on their use in SLE remain limited. Future research should focus on the formulation of Transethosomal systems tailored to SLE therapeutics, including corticosteroids, immunomodulators, and biologics. Clinical evaluations are necessary to confirm their safety, efficacy, and patient acceptability in comparison to existing treatment modalities. Furthermore, innovations in formulation techniques and large-scale production must be addressed to translate Transethosomes from the research phase into clinical and commercial application. In conclusion, Transethosomes stand out as a promising drug delivery system with the potential to transform the therapeutic landscape for chronic and autoimmune disorders like systemic lupus erythematosus.

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