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The Transethosomal Revolution: Where Flexibility Meets Functionality in Drug Delivery

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ABSTRACT:

Transethosomes are a novel type of ultra-deformable lipid-based nano-vesicular carriers that show promise as a platform for improved cutaneous and transdermal drug administration. This thorough analysis highlights transethosome's better penetration capabilities over traditional liposomes and ethosomes while examining their therapeutic uses in a variety of medical specialties. Phospholipids, ethanol, and edge activators make up transethosomes, which work together to promote vesicular deformability, rupture lipid bilayers, and fluidize membranes to increase skin permeability. Transethosomal applications in dermatological disorders (acne, psoriasis, eczema, fungal infections, skin cancer), pain management (NSAIDs, local anaesthetics), anti-inflammatory therapy, cosmeceuticals, vaccine delivery, hormone replacement therapy, cardiovascular diseases, diabetes management, neurological disorders, and gene therapy are all thoroughly examined in this review propranolol hydrochloride for cardiovascular treatment has better bioavailability than oral formulations, tacrolimus for psoriasis (85.32% drug release, 76.34 % penetration), and caryophyllene oxide for analgesia (80.5% maximum potential effect). Transethosomes represent a versatile delivery system for both local and systemic drug delivery due to their improved therapeutic efficacy, decreased side effects, reduced systemic absorption, and capacity to avoid hepatic first-pass metabolism. Clinical translation is still limited despite encouraging preclinical results, which calls for stringent clinical trials, standardized manufacturing procedures, and all creation of regulatory frameworks. Future directions include biologics and nucleic acid delivery, hybrid delivery systems, stimuli-responsive formulations, optimization driven by artificial intelligence, and applications in global health. While highlighting important research gaps and chances for innovation in next-generation transdermal drug delivery systems, showcasing the transformative promise of transethosomes in creating non-invasive, patient-centric therapeutic methods.

Keywords: Transethosomes, Transdermal drug delivery; Ultra-deformable vesicles; Edge activators; Skin penetration; Nano-vesicular carriers; Therapeutic applications.

INTRODUCTION:

Drug administration via transdermal means provides many benefits over traditional methods, such as prolonged release, preventing first-pass metabolism, fewer systemic reactions, and increased compliance among patients [1]. Although the stratum corneum (SC), the exterior 10-20 micrometer layer of skin, forms a difficult barrier to penetrate [2]. This structure is limited to smaller molecular weights less than 500 daltons, uncharged and mildly lipophilic (log P 1-3) molecules [3]. Conventional methods of improvement include chemical boosters, physical techniques (such as iontophoresis and microneedles, and others), skin allergic reactions, unpredictability, equipment specifications, and low effectiveness for biomolecules. These are common problems with formulation techniques [1, 3].

Classical liposomes, which mainly served as reservoirs on the surface with restricted penetration, were the first vesicular carriers developed in an effort to get through skin barriers [4]. Cevc developed transferosomes, which are ultra-deformable vesicles capable of squeezing through narrow spaces via an osmotic gradient by adding edge-activating agents, which are surfactants like Span 80 and Tween 80 [5]. While Touitou created ethosomes that had high ethanol concentrations (20-45% w/w), which improved the fluidity of the membrane and broken up SC lipids to achieve better penetration than firm liposomes [4, 5]. Although ethosomes delivered ethanol-induced improvement and transferosomes showed remarkable deformability, each system had unique drawbacks, which sparked curiosity in combinations of both systems [5].

In 2012, Song *et al*. published the first study on transethosomes, which combine phospholipids, ethanol concentration around 20-40% w/w, edge activators, water and were used to deliver voriconazole [6]**.** This rational design synergistically incorporated ethanol-mediated lipid fluidization with edge activator-driven deformability, producing ultra-flexible vesicles with dual mechanisms where

ethanol distorts SC lipid organization while surfactants lower membrane interfacial tension, enabling vesicles to deform and penetrate through intercellular spaces [7, 8]. Compared to ethosomes, transferosomes, and traditional compositions, early research showed increases in drug flow, more profound penetration through the skin, and more effective entrapment efficiency, which were two to five times greater [8, 9]. Transethosomes are highly effective carriers for transdermal distribution since their deformability index (>20-30) greatly exceeds that of regular liposomes (<10) [9].

In order to improve vesicular functioning over a variety of therapeutic fields, investigators have significantly refined and diversified transethosomes since their creation by improving phospholipid types, ethanol concentrations, edge activator choices, and production techniques. [10]. Effective incorporation of water-soluble, lipophilic and also amphiphilic medications as well as new uses in the delivery of peptides, proteins, and genetic elements have shown how diverse transethosomal techniques are [11]. Apart from basic drug delivery systems, Transethosomes have developed into complex networks that include targeting ligands, stimuli-responsive elements, and hybrid compositions including transethosomal gels, patches, and films that offer the advantages of vesicular distribution with useful dosage forms [10, 11-12]. Transethosome's clinical application potential is becoming more widely acknowledged in a number of clinical fields, including pain treatment, anti-inflammatory therapy, cosmeceutical applications, skin conditions (psoriasis, acne, fungal infections) and vaccine administration [11,12]. Comparison research showed that transethosomes function better than traditional preparations and single-mechanism vesicular systems in terms of skin penetration parameters, bioavailability improvement, and effectiveness for treatment [10]. Transethosomes are positioned as a paradigm change in resolving the long-standing difficulties of transdermal medication delivery because of the dual-action mechanism, which offers synergistic effects that cannot be obtained by ethanol or edge activators alone [12].

1.1 Objectives:

Table 1. Objectives of Transethosomal drug delivery

Objectives	Objective Description
Fundamental Understanding and Mechanism Elucidation	Elucidate physicochemical principles, structural characteristics, formation mechanisms, and synergistic effects of ethanol-mediated lipid fluidization and edge activator-induced membrane flexibility [11, 12].
Formulation Science and Optimization Strategies	Evaluate component selection (phospholipids, ethanol 7-40% v/v, edge activators), preparation methods, and statistical designs (Box-Behnken, factorial) achieving 100-500 nm vesicles with 80-90% entrapment efficiency [4, 5].
Characterization and Quality Assessment	Examine particle size analysis (DLS), deformability assessment, entrapment efficiency, stability evaluation, and advanced imaging (TEM, AFM, CLSM) for quality control and regulatory compliance [13, 14].
Therapeutic Applications and Clinical Translation	Analyze applications in dermatology (psoriasis, acne, fungal infections, skin cancer), pain management (NSAIDs, analgesics), cosmeceuticals (anti-aging, skin whitening), and systemic delivery (cardiovascular, hormones, neurological agents) [8, 15].
Translation Challenges and Regulatory Pathways	Identify barriers: stability issues, batch variability, scale-up difficulties, regulatory requirements, manufacturing complexities, and cost-effectiveness [16, 17].

2. SKIN ANATOMY AND BARRIERS TO DRUG PERMEATION

2.1 Skin Structure: Epidermis, Dermis, and Hypodermis

Skin is the largest organ in the human body, functions as a sophisticated exterior barrier that regulates body temperature and water loss while guarding against diseases, UV rays, toxins, and mechanical damage [18]. This integumentary system is composed of three distinct layers: the epidermis, dermis, and hypodermis. Each layer has distinct anatomical characteristic and functions [19].

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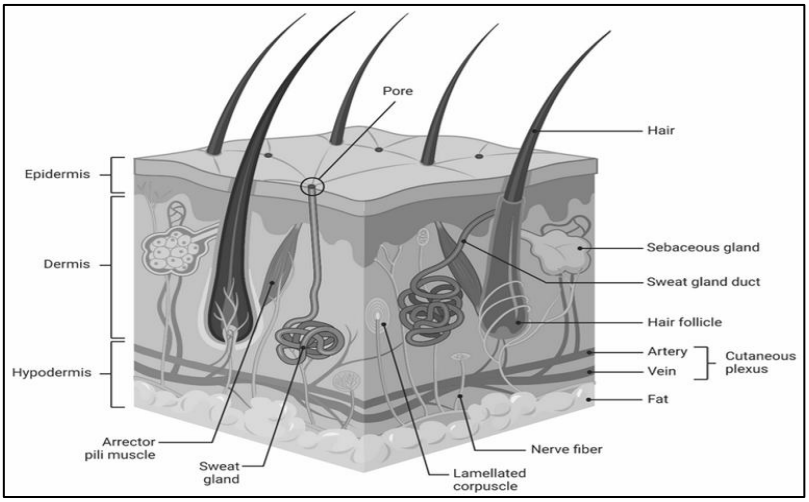

Figure 1. Layers of the Skin involved in Transdermal Drug Delivery

2.2 The Main Defence: The SC

As the primary barrier to drug penetration in transdermal drug delivery systems, the SC, the topmost layer of the epidermis, is composed of multiple layers of fully cornified, anucleate keratinocytes called corneocytes embedded in a lipid-rich extracellular matrix, creating a unique "brick and mortar" architecture with intercellular lipids serving as the mortar and corneocytes as the bricks. The SC has a complex, many-layered structure that is typically 10-20µm thick and composed of approximately 15-20 layers of corneocytes [20]. The primary pathway of transepidermal drug penetration and a crucial component of barrier function is the SC's intercellular lipid matrix. Unlike traditional biological membranes composed of phospholipids, the SC lipid matrix is mostly composed of three lipid classes in nearly equimolar ratios: ceramides (50%), cholesterol (25%), and free fatty acids (25%) [21, 22].

2.3 Pathways of Drug Penetration

The transepidermal pathway and the transappendageal pathway are the two primary routes the medication components can enter the skin with no damage. The transepidermal route, which can be further separated into intracellular and intercellular paths, requires passing through the SC directly [23].

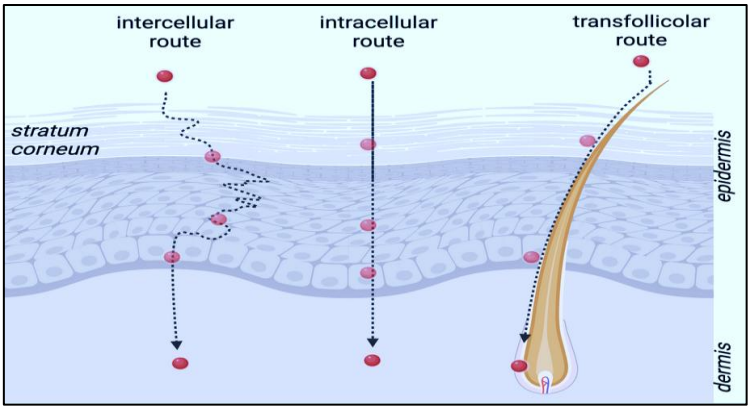

Figure 2. Major Routes of Drug Transport Across the Skin

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2.4 Physicochemical Factors Affecting Drug Permeation

Table 2. Physicochemical Properties Influencing Transdermal Drug Permeation [24-26]

Factor	Optimal Range	Effect on Permeation	Mechanism
Molecular Weight	< 500 Da	Smaller molecules exhibit higher permeability	Larger molecules cannot pass through the stratum corneum due to the tightly packed nature of lipids and the narrow aqueous pore size. As molecule weight rises, the diffusion coefficient falls rapidly.
Lipophilicity (log P)	1-3	Optimal permeation at intermediate lipophilicity	Molecules must be sufficiently lipophilic to partition into stratum corneum lipids, yet not so lipophilic that they become trapped. Very hydrophilic molecules (log P < 1) cannot partition into lipid matrix; very hydrophobic molecules (log P > 5) show excessive retention and poor release.
Partition Coefficient (log P/log D)	log P: 1-3 log D at physiological pH preferred for ionizable drugs	Determines partitioning between lipophilic and aqueous environments	Represents relative affinity for lipophilic versus aqueous phases. Log D accounts for all molecular forms (ionized and unionized) at specified pH, providing more accurate permeability prediction for ionizable compounds.
Ionization State	Unionized form preferred	Ionized molecules show markedly reduced permeability compared to unionized counterparts	Charged, highly polar ionized molecules cannot effectively penetrate lipophilic stratum corneum. Fraction of unionized drug determined by pKa and local pH via Henderson-Hasselbalch equation.
pKa	Should favour unionized form at skin pH (4.5-6.5) and formulation pH	Influences fraction of unionized drug available for permeation	For weak acids: unionized form predominates at pH < pKa For weak bases: unionized form predominates at pH > pKa, pH gradients across skin (surface pH 4.5-6.5; viable epidermis pH ~7.4) influence permeation.
Hydrogen Bond Donors (HBD)	<5 (more restrictive than oral: < 5 combined HBD+HBA)	Excessive HBDs reduce permeation	Strong interactions with water molecules must be broken to partition into lipophilic stratum corneum, creating energetic barrier. May also reduce solubility in lipophilic vehicles.
Hydrogen Bond Acceptors (HBA)	<10 (Lipinski); < 5 combined for transdermal	Excessive HBAs reduce permeation	Same mechanism as HBDs: hydrogen bonding with water creates barrier to lipid partitioning. Transdermal delivery requires more restrictive criteria than oral bioavailability.
Melting Point	< 200°C	Lower melting point correlates with better permeability	Lower melting points indicate reduced crystal lattice energy, leading to enhanced solubility and dissolution.
Aqueous Solubility	Sufficient to maintain concentration gradient (Dose number < 1)	Essential for creating driving force for diffusion	According to Fick's first law, flux is proportional to both permeability coefficient and drug concentration in vehicle. Insufficient solubility limits concentration gradient and reduces flux. Creates fundamental challenge as increased aqueous solubility often reduces lipophilicity.
Lipophilic Permeability Efficiency (LPE)	Optimized balance	Captures opposing effects of lipophilicity on permeability and solubility	Single metric combining membrane permeability and aqueous solubility effects. Particularly relevant for "beyond rule of five" molecules.
Vehicle Composition	Optimized for drug properties and delivery requirements	Profoundly influences permeation rate and extent	Affects drug thermodynamic activity, solubility, and partitioning behaviour. Can alter drug release rates, modify stratum corneum properties, and influence effective partition coefficient between vehicle and skin.

3. TRANSETHOSOMES: CONCEPT AND UNIQUE CHARACTERISTICS

3.1 Definition of Transethosomes

Transethosomes belongs to a cutting-edge family of lipid-based ultra-deformable nanocarriers designed to improve transdermal medication delivery by overcoming the SC's strong barrier [10]. Transethosomes were hypothetically created to combine the beneficial effects of both traditional ethosomes and flexible liposomes (transferosomes) through a single, more effective delivery mechanism. They were first presented by Song *et al.* in 2012 [5, 27]. These novel compounds have exceptional abilities to facilitate drug penetration through intact skin barriers, enabling delivery to the more extended dermal and epidermal layers while maintaining therapeutic efficacy [28].

Transethosomes are defined architecturally as sphere-shaped, extremely deformable vesicles having a circular bilayer of lipids organization and an uneven shape [29]. In order to create distinct aqueous and lipophilic regions that can capture water-soluble and lipid-soluble substances, phospholipids molecules are designed to align one another with the heads that are hydrophilic facing outside toward the aqueous environment and their tails that are hydrophobic kept within the double-layered cell membrane [30]. Transethosomes can exhibit extremely high drug-loading capability and outstanding entrapment efficiency throughout a broad molecular weight range, which ranges from tiny components (130.077 Da) to big macromolecules such as peptides as well as proteins, that are large as 325 kDa, owing to its amphiphilic structure [31, 32].

3.2 The Dual Mechanism: Ethanol + Edge Activators

Transethosome's unique dual mechanism, which involves the synergistic interplay of ethanol and edge stimulating agents to drastically enhances skin permeability and drug penetration accounts for their exceptional efficacy in transdermal delivery of drugs [33]. Compared to traditional vesicular systems that depend on a single penetration enhancing mechanism, this combination offers a substantial improvement.

3.2.1 Ethanol-Mediated Mechanisms

Ethanol increases penetration via a number of interrelated ways. By connecting between the molecules of lipid and enhancing the permeability in both vesicular membranes and skin lipids, ethanol impairs the SC's densely organized, extremely structured bilayer of lipid structure at its molecular level. This fluidization impact creates temporary pores in water and increases membrane permeability by promoting the transition from rigid crystalline states to more fluid liquid- crystalline phases and reducing the phase transition temperature of SC lipids [34]. Furthermore, by altering the tissue's solubility properties, ethanol makes it easier for medications to separate into the SC. Ethanol's interconnected impact on phospholipid bilayers improve fluidity of the membrane and vesicle elasticity, making it easier for the vesicle to distort and pass through constricted intercellular routes [35]. By altering the normal configuration of lipid molecule structures in the SC, enhancing total lipid fluidity, and widening paracellular spaces, ethanol also improves permeation into the skin capabilities [33]. Ethanol exhibits the best permeation improvement at quantities commonly used in transethosomal compositions (20-40%) without producing appreciable irritation to the skin or toxicity [10]. Ethanol provides the vesicles flexibility and makes it easier for the medicine to pass through the SC because it interacts with the lipids in the vesicles as well as the skin [36].

3.2.2 Edge Activator-Mediated Deformability

By giving the vesicular membrane ultra-deformability, edge activators enhance and intensify the effects of ethanol. Because these surfactants weaken the hard bilayer composition and lower the interfacial tension at the lipid-water interface, the vesicles become extremely flexible and can go through pores smaller than their diameter [37]. By weakening the lipid bilayers and increasing vesicular deformability, edge activators facilitate effective penetration through the SC barrier. Transethosomal characteristics are affected differently by different edge activators. These typically contain surfactants like Tween 80, Span 80, or sodium cholate, which increase the vesicle's elasticity and deformability, allowing for greater penetration through the skin's SC [38].

3.3 Mechanisms of Enhanced Skin Penetration

3.3.1 Role of Ethanol in Lipid Fluidization

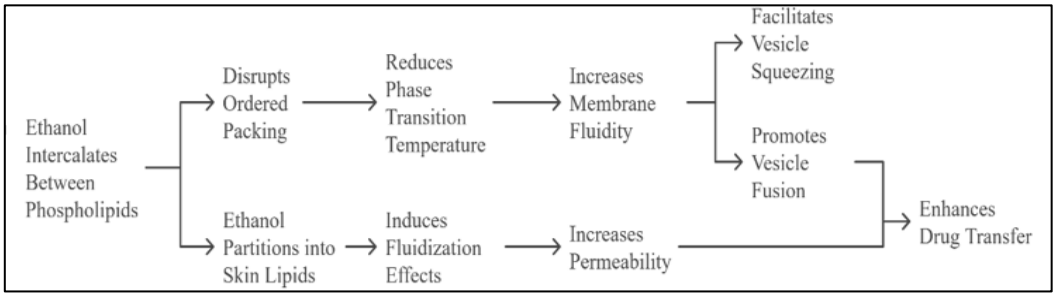

Figure 3. Ethanol's role in enhanced skin penetration

3.3.2 Edge Activator-Mediated Membrane Destabilization

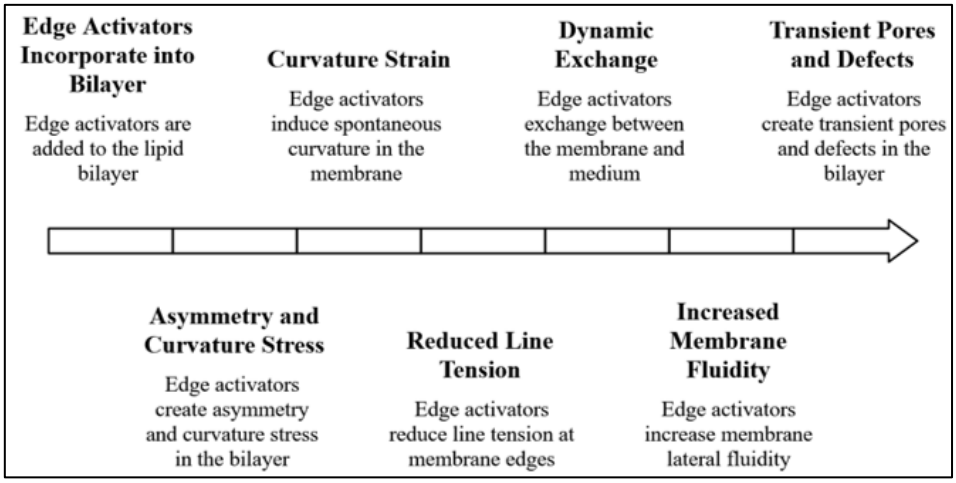

Figure 4. Edge Activator-Mediated Membrane Destabilization

3.3.3 Vesicle Deformation Through Narrow Pores

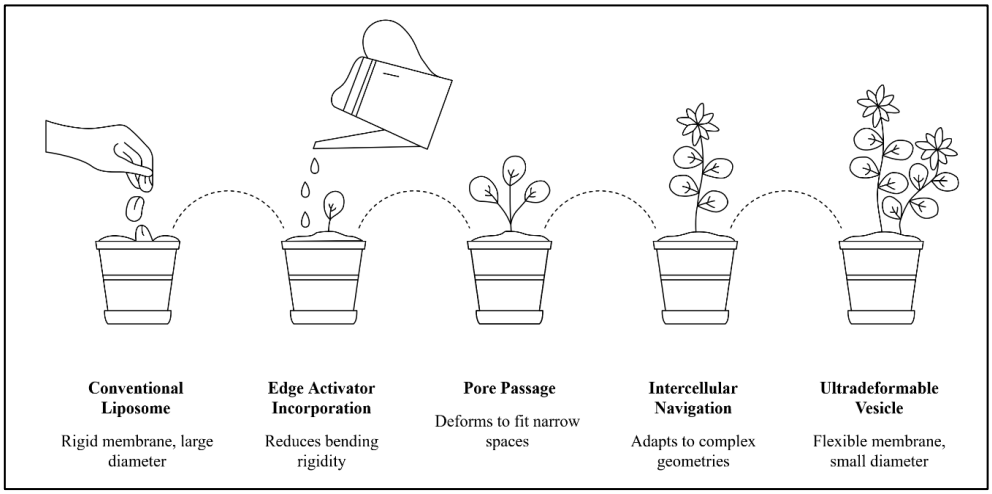

Figure 5. Vesicle Deformation Through Narrow Pores

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3.4 Advantages of Transethosomes Over Conventional Vesicular Systems

Table 3. Comparative of Transethosomes Over Conventional Vesicular Systems [5, 10, 27, 30, 32, 36, 52]

Parameter	Liposomes	Ethosomes	Transferosomes	Transethosomes
Primary components	Phospholipids, cholesterol, water	Phospholipids, ethanol, water	Phospholipids, edge activators, water	Phospholipids, ethanol, edge activators, water
Membrane flexibility	Rigid, limited deformability	Moderate, ethanol-induced fluidity	High; edge activator-driven	Ultra-high; dual ethanol+ edge activator synergy
Deformability index	<10	10-25	15-25	>20-30
Entrapment efficiency	50-80%	60-85%	55-80%	70-95%
SC penetration depth	Superficial; upper SC only	Deeper than liposomes; reaches viable epidermis	Full SC; reaches dermis	Full Sc + dermis; potential systemic access
Vesicle size (optimized)	100-400 nm	150-500nm	100-300nm	100-500nm; typically 100-300nm for optimal permeation
Zeta Potential	-10 to -30mV	-25 to -50mV	-20 to -40 mV	-20 to -60mV; ethanol contributes to negative surface charge
Drug release profile	Immediate to sustained	Sustained 12-24 hr	Sustained 12-24 hr	Biphasic; burst (20-40% in 1-2hr) then sustained 12-24hr
Ethanol concentration	None	20-45% w/w	none	20-40% v/v

4. FORMULATION AND DESIGN OF TRANSETHOSOMES

4.1 Components of Transethosomal Systems

Transethosome's core composition consists of five major components that cooperate to give them their distinctive qualities: Water, phospholipids, ethanol, and edge activators, stabilizers [10, 39].

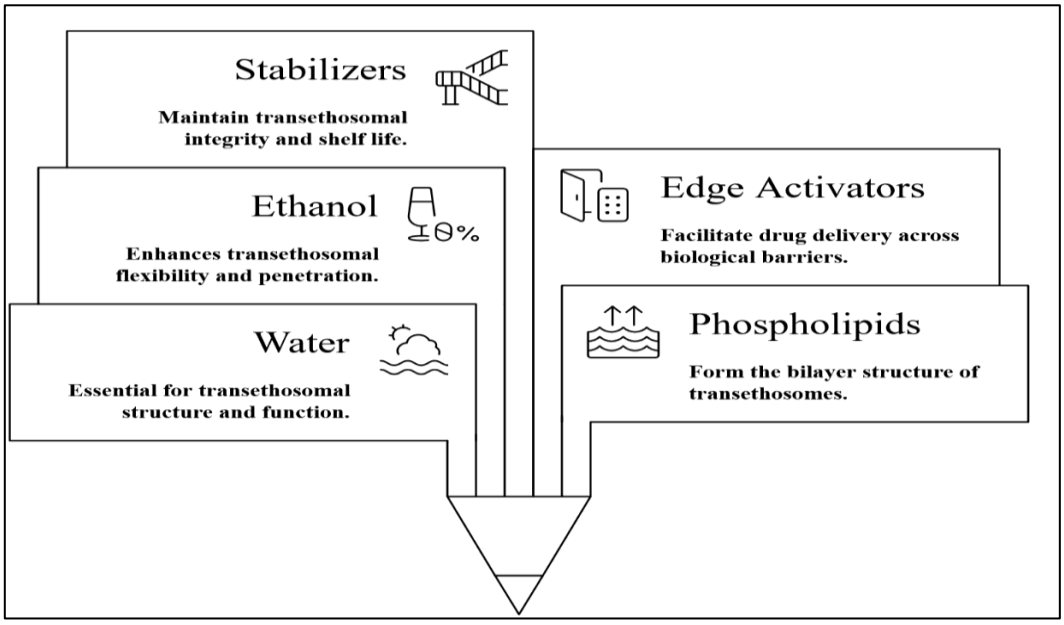

Figure 6. Schematic illustration of the key structural components of a transethosomal vesicle

4.1.1 Phospholipids

Phospholipids serve as the primary structural building blocks, typically comprising 2-5% (w/v) of the formulation [10, 40]. Various sources of phospholipids can be utilized, including phosphatidylcholine from soybean lecithin, 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and egg phosphatidylcholine [30]. The type of phospholipids and their concentration exert profound effects on critical vesicular properties including size, zeta potential, and entrapment efficiency. Due to their biocompatible and biodegradable nature and abundance in eukaryotic cells, phospholipids provide an ideal foundation for drug encapsulation while ensuring safety for both topical and systemic administration [10].

4.1.2 Ethanol

Ethanol constitutes the second critical component, typically present at concentrations ranging from 20-40% (v/v) or 7-30% depending on the formulation requirements [10, 41]. Ethanol serves multiple crucial functions within the transethosomal system. First, it disturbs the SC's highly ordered lipid bilayers by acting as a strong penetration enhancer, increasing lipid fluidity and creating transient permeation pathways [42]. Second, ethanol imparts enhanced flexibility and deformability to the vesicular membrane through its interdigitating effect on the phospholipid bilayer, enabling vesicles to squeeze through narrow intercellular channels [39]. Third, ethanol increases the loading efficiency of hydrophobic medications within the vesicles by acting as an efficient solubilizing agent [43]. Additionally, presence of ethanol contributes to the characteristically negative zeta potential of transethosomes, which enhances colloidal stability and prevents vesicle aggregation [44].

4.1.3 Edge activators

The feature that sets transethosomes apart from typical ethosomes is edge activators [39, 45]. These surfactants are applied to the membrane to improve its flexibility and deformability. In addition to oleic acid as a penetration enhancer, non-ionic surfactants such as Tween-20, Tween-80, Span-60, Span-80 and sodium deoxycholate are frequently utilized edge activators [14, 30]. Depending on the particular surfactant chosen, Edge activator concentrations typically range from 0.3 and 2% (w/v) [46]. By decreasing interfacial tension and boosting fluidity within the membrane, these drugs disrupt the lipid bilayers of the vesicles, improving their capacity for distortion and pass via the SC's convoluted routes [47]. Moreover, edge activators can create new penetration routes by interfering with the stacking of lipids and proteins inside the SC [48].

4.1.4 Water Phase

The water phase creates ideal circumstances for vesicle production and acts as a hydrating vehicle for phospholipid layers [44]. According to the needs for solubility of drugs and consistency, purified water, phosphate buffered saline (PBS) or alternative water-based media could be used [5]. Drug ionization behaviour, soluble state, and immobilization inside vesicles are all significantly influenced by the pH value of the hydrating media [45].

4.1.5 Stabilizers

Stabilizers to give the transethosomal matrix a stable structure, stabilizers like cholesterol can be added, especially at higher ethanolic concentrations [49]. For polar substances, the water phase concludes the preparation by acting as an agent for vesicle generation and drug dispersion. The pH levels of the fluid medium have a major impact on the solubility of pharmaceuticals and the extent of drug entrapment within the vesicles [10, 50].

4.2 METHODS OF PREPARATION

4.2.1 Cold Method

One of the most popular methods for transethosomal preparation is the cold method, which is especially useful for heat-sensitive thermolabile medications [27, 45]. This process involves dissolving phospholipids and edge activators in ethanol in a closed vial at ambient temperature or in a refrigerator (2-8 °C) [9]. After adding the medication to the organic phase, the mixture is shaken until it dissolves completely. The lipid-ethanol mixture is then continuously stirred at room temperature while the aqueous phase is added dropwise, causing spontaneous vesicle formation [5]. The cold approach is perfect for heat-sensitive compounds because it has the benefits of simplicity, scalability, and drug integrity preservation [48].

4.2.2 Hot Method

Phospholipids are dissolved in ethanol using the hot technique at high temperature (30-40 °C) while stirring constantly [51]. After incorporating the medication into the lipid-ethanol phase, the heated aqueous phase (at the same temperature) is gradually added while being vigorously stirred [52]. To guarantee full vesicle formation, the mixture is kept at a steady temperature throughout. The transethosomal dispersion is obtained after cooling to room temperature [53]. This approach can enhance lipid solubilization and vesicle formation for specific formulations, but it might not be appropriate for thermolabile medications [54].

4.2.3 Thin Film Hydration

A traditional technique modified for transethosomal preparation is thin film hydration [55, 56]. In a round-bottom flask, phospholipids, medication and edge activator are dissolved in an organic solvent mixture (usually chloroform: methanol or ethanol) [45]. To create a thin lipid layer on the flask walls, the organic solvent is evaporated using a rotary evaporator at 40-50°C under low pressure [54, 57]. After that, the film is hydrated with an aqueous-ethanolic phase while rotating, which results in the creation of vesicles on its own. Size reduction methods like sonication or extrusion are applied to the resultant dispersion [58, 59]. For sinapic acid-loaded transethosomes, recent research by Bin Larden et.al. effectively used thin film hydration, producing optimal formulations with vesicle size of 111.67nm, zeta potential of -7,253 mV, and entrapment effectiveness of 74.36% [45]. The identical findings were obtained when methotrexate-loaded transethosomes were manufactured utilizing this technique with Box-Behnken design of optimization [60].

4.2.4 Sonication Techniques

In order to increase size distribution homogeneity and decrease vesicle size, sonication is frequently used as a post-formation processing step [38]. It is possible to use both bath and probe sonication [61]. In order to avoid overheating, probe sonication is the direct application of ultrasonic energy using a titanium probe submerged in the transethosomal dispersion. This process is usually carried out for 5-15 minutes at 20-50% amplitude in pulsed mode [62]. A kinder option is bath sonication, which involves submerging the vesicular dispersion in an ultrasonic bath for 15 to 30 minutes [37]. Large vesicles and multilamellar structures are broken up by sonication, resulting in smaller, more homogeneous nanovesicles with improved stability and penetration capacity [63].

4.2.5 Microfluidic Approaches

Emerging technologies for regulated, repeated transethosomal manufacturing include microfluidic methods [64]. These techniques produce monodisperse vesicles with limited size distributions by carefully controlling the mixing of lipid and aqueous phases using microchannels [65]. Compared to traditional methods, microfluidic systems have the advantages of continuous production, scalability, precise control over formulation parameters, and decreased batch-to-batch variability [66, 67].

4.3 Quality by Design in Transethosomal Formulation

A methodical approach to pharmaceutical development known as “Quality by Design”. Places a strong emphasis on comprehending formulation and process variables in order to guarantee consistent product quality [68, 69]. Critical Quality Attributes (CQAs), Critical process Parameters (CPPs), and Quality Target Product Profile (QTPP) must be identified in order to apply QbD principles to transethosomal formulations [70]. Recent research has effectively applied QbD techniques for transethosomal optimization. In order to optimize tacrolimus-loaded transethosomes, Deshmukh *et al.* used a 3^2factorial design. They found that ethanol and lipid concentrations were important parameters that affected drug release, vesicle size, and entrapment efficiency. The enhanced formulation (F1 batch) was shown to have a zeta potential of -36Mv, an entrapment efficacy of 85%, and a vesicle size of 168nm [71]. Similarly, other groups optimized transethosomal formulations systematically using a Box-Behnken design [33 ,60, 72]. This method makes it easier to identify the ideal formulation space and allows examination of the interaction effects of formulation factors [73].

4.4 Scale-Up Considerations

Transethosomal manufacturing scale-up from laboratory to industrial scale poses special difficulties that necessitate careful evaluation of equipment selection, process parameters, and quality control procedures [74].

The following are essential elements for a successful scale-up:

Process Consistency: To guarantee repeatable vesicle formation during scale-up, maintain equal mixing energy, temperature control, and addition rates [75, 76].

Equipment Selection: Selecting suitable large-scale equipment that can distribute energy uniformly, such as industrial sonicators, homogenizers, and high-shear mixers [77].

Quality Control: Using reliable analytical techniques to monitor important quality features in real time throughout production is known as quality control [78].

Stability Considerations: Using suitable packaging, storage conditions, and the inclusion of stabilizers to ensure sufficient stability throughout shelf life [79].

5. CHARACTERIZATION OF TRANSETHOSOMES

5.1 MORPHOLOGICAL ANALYSIS

5.1.1 Transmission Electron Microscopy (TEM)

The most reliable techniques for observing transethosomal morphology at nanoscale resolution is TEM [29, 64]. After applying a small amount of diluted transethosomal dispersion to carbon-coated copper grids, the sample is made by using either phosphor-tungstic acid or uranyl acetate for negative staining [80]. Vesicle size, form, lamellarity, and structural integrity are all visible with unique lipid bilayers that are spherical or irregularly shaped [33, 81].

5.1.2 Scanning Electron Microscopy (SEM)

Transethosome's three-dimensional surface shape is revealed by SEM [82]. Before imaging, samples are usually lyophilized and sputter-coated with platinum or gold 66. Particle form, surface properties, and possible aggregation are revealed by SEM [84].

5.1.3 Atomic Force Microscopy (AFM)

Transethosomal topography can be visualized and quantified using AFM in ambient or near-physiological settings without requiring significant sample preparation [85, 86]. On a recently cut mice surface, a tiny amount of transethosomal dispersion is applied, and tapping mode imaging is performed [87]. Vesicle size, height profile, surface roughness, and mechanical characteristics are all revealed by AFM [88]. Caryophyllene oxide transethosomes have been successfully characterized by AFM in recent research, shown spherical nanovesicles measuring of 450.7 ± 55.03 nm on average [89].

5.2 Particle Size and Distribution

Most popular method for figuring out transethosomal particle size and size distribution is dynamic light scattering [90, 91]. A particle size analyzer is used to measure samples at 25°C after they have been suitably diluted (usually 1:100) with distilled water or PBS [92].

Measured key parameters consist of:

- Mean particle size: For optimum formulations, the mean particle size (Z-average) usually falls between 100 and 500nm [33, 93].
- Polydispersity Index (PDI): Narrow, uniform size distribution is indicated by values less than 0.3 [94].

Particles with diameters between 100-300 nm are typically seen in ideal transethosomal formulations, which enable penetration via skin intercellular channels while preserving sufficient drug loading capacity [10, 95].

5.3 Zeta Potential

Zeta potential measurements can be used to assess the surface charge and colloidal stability of transethosomes [96]. Laser Doppler electrophoresis, which measures particle mobility by subjecting diluted samples to an electric field, is used for the analysis [48]. Generally, transethosomes have negative zeta potential values from -20 and -60mV [45].

A negative zeta potential prevents aggregation and enhances colloidal stability by generating electrostatic repulsion between vesicles [40]. Research has shown that formulations with compared to positively charged or neutral vesicles, negatively charged transethosomes exhibit improved epidermal penetration [44].

5.4 Entrapment Efficiency (EE%)

The % of drug that is successfully incorporated within vesicles in relation to the total amount of drug added is measured by EE% [97]. Indirect procedures are frequently used for determination, such as ultracentrifugation (15,000-20,000 rpm for 1-3 hours at 4°C) or ultrafiltration [48, 91], which separate free (unentrapped) medication from vesicles. EE% is computed using the following formula after spectrophotometric or chromatographic analysis of the free drug-containing supernatant:

$$\mathbf{EE\% = [(Total\ drug - Free\ drug) / Total\ drug] \times 100}$$

Depending on the drug's characteristics and the composition of the optimized transethosomal preparations usually attain entrapment efficiencies between 70 and 955 [28, 33, 71].

5.5 Deformability Index (DI) and Elasticity Measurements

Transethosomes are known for their deformability, which allows them to pass through small intercellular spaces [38, 81]. Transethosomes are extruded using filters made of polycarbonate membrane with predetermined particle diameters (usually 50-100 nm) narrower than the actual vesicle diameter employing a mini-extruder at a controlled pressure in order to calculate the deformability index [37].

$$\mathbf{DI = J \times (rv/rp)^2}$$

Where: J = Amount of vesicle suspension extruded in 5 minutes,

rv = vesicle size after extrusion,

rp = pore size of membrane

Enhanced vesicular flexibility and deformability are indicated by higher DI values [1, 99]. Comparative investigations consistently show that transethosomes have far greater deformability indices than ethosomes, transferosomes, and ordinary liposomes [5, 14].

5.6 Studies on Drug Release (DR)

DR release studies conducted *in vitro* can help to understand the DR kinetics and mechanisms from transethosomal dosage forms [94]. Franz diffusion cells or dialysis bags are the most often used technique [100]. Transethosomal dispersions are put in dialysis membranes with a molecular weight threshold of 12,000-14,000 Da, submerged inside receptor media (usually phosphate buffer with a pH of 7.4 or biological fluid simulators), and kept at 32-37°C while being constantly stirred [101]. At prearranged intervals, samples are taken out and their drug content is examined [102]. Release profiles usually show biphasic patterns: a continuous, regulated release over 12-24 hours [35, 103] after an initial burst release (20-40% in first 1-2 hours). Release mechanisms are clarified using mathematical modelling utilizing zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations [70, 71].

5.7 Stability Studies

5.7.1 Physical Stability

Assessing variation in particle size, PDI, zeta potential, and visual appearance during storage is part of the physical stability evaluation procedure [104]. Samples are kept for 30 to 180 days at different temperatures (4°C, 25°C ±2°C/60% RH, 40°C±2°C/75% RH ± 5% RH) [19, 105]. With little variation (<10% deviation) in measured parameters, stable formulations retain constant physical properties [106].

5.7.2 Chemical Stability

Drug deterioration and preservation of chemical integrity during storage are tracked by chemical stability evaluation [35]. Validated chromatographic techniques (HPLC or UPLC) are used to examine samples in order to determine degradation products and quantify medication content [44]. Transethosomes can retain their chemical stability for three to six months in either ambient or refrigerated environments, according to studies [71].

5.7.3 Storage Conditions

Transethosomal preparations are best stored at 2-8°C in airtight, amber-coloured containers to prevent oxidation and light damage [107]. Excellent stability for five to six months under these circumstances has been observed in studies [71, 100].

6. THERAPEUTIC APPLICATIONS OF TRANSETHOSOMES

Table 4. Therapeutic Applications of Transethosomes in Transdermal Drug Delivery System

Therapeutic category	Subcategory	Drug(s)	Key Findings & References
Dermatological Applications	Acne Treatment	Anti-acne agents	Enhanced penetration to sebaceous glands and hair follicle [109, 111]
Dermatological Applications	Psoriasis	Tacrolimus	85.32% drug release, 76.34% drug permeation after 24h; reduced hyperkeratosis and inflammation within 7 days [71]
Dermatological Applications	Psoriasis	Fluvastatin	Enhanced dermal penetration and significant therapeutic benefits [14]
Dermatological Applications	Eczema and Dermatitis	Corticosteroids and immunomodulators	Minimized systemic absorption and adverse effects [110]
Dermatological Applications	Fungal Infections	Econazole, Voriconazole, Nystatin	Enhanced penetration and improved therapeutic outcomes [80, 111]
Dermatological Applications	Skin Cancer (PDT)	Ferrous chlorophyllin	Effective for melanoma treatment via photodynamic therapy with deep tissue localization [112, 120]
Pain Management	NSAIDs Delivery	Ketorolac tromethamine, Flurbiprofen, Meloxicam, Naproxen	Circumvented gastrointestinal side effects [113, 114, 115]
Pain Management	Analgesic	Caryophyllene oxide	Superior skin penetration (40.3±0.881 µg/cm² vs 29.5±10.5 µg/cm²); 80.5% maximum possible effect vs 24.7% conventional [89]
Pain Management	Local Anaesthetics	Local anaesthetic agents	Prolonged anaesthetic effects with reduced systemic exposure [116]
Anti-Inflammatory Therapy	-	Corticosteroids and anti-inflammatory agents	Enhanced therapeutic efficacy with reduced adverse effects; minimized systemic absorption [117, 118]
Anti-Aging and Cosmeceuticals	Anti-aging	Retinyl acetate	Enhanced stability, bioavailability, and skin penetration while minimizing irritancy [119]
Anti-Aging and Cosmeceuticals	Antimicrobial/Anti-aging	Rutin	Excellent antimicrobial efficacy against Gram-positive bacteria with enhanced skin permeation [120]
Vaccine Delivery	-	Vaccine adjuvants	Non-invasive transcutaneous immunization alternative [106]
Hormone Replacement Therapy	-	Hormones	Sustained, controlled release avoiding hepatic first-pass metabolism [121]
Cardiovascular Drugs	-	Propranolol hydrochloride	Maintained effective plasma concentrations superior to oral tablets; enhanced bioavailability [122, 123]
Cardiovascular Drugs	-	Olmesartan medoxomil	Successful transdermal cardiovascular therapy [91]
Diabetes Management	Antidiabetic	Metformin HCl	Sustained release, improved transdermal flux, enhanced antidiabetic response [108]
Neurological Disorders	-	Neurotherapeutic agents	Delivery across skin barrier for improved treatment outcomes [124, 125]
Gene Therapy	siRNA Delivery	Nucleic acids and biomacromolecules	Potential vectors for gene therapy applications [126]

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7. FUTURE PERSPECTIVES AND EMERGING TRENDS OF TRANSETHOSOMES

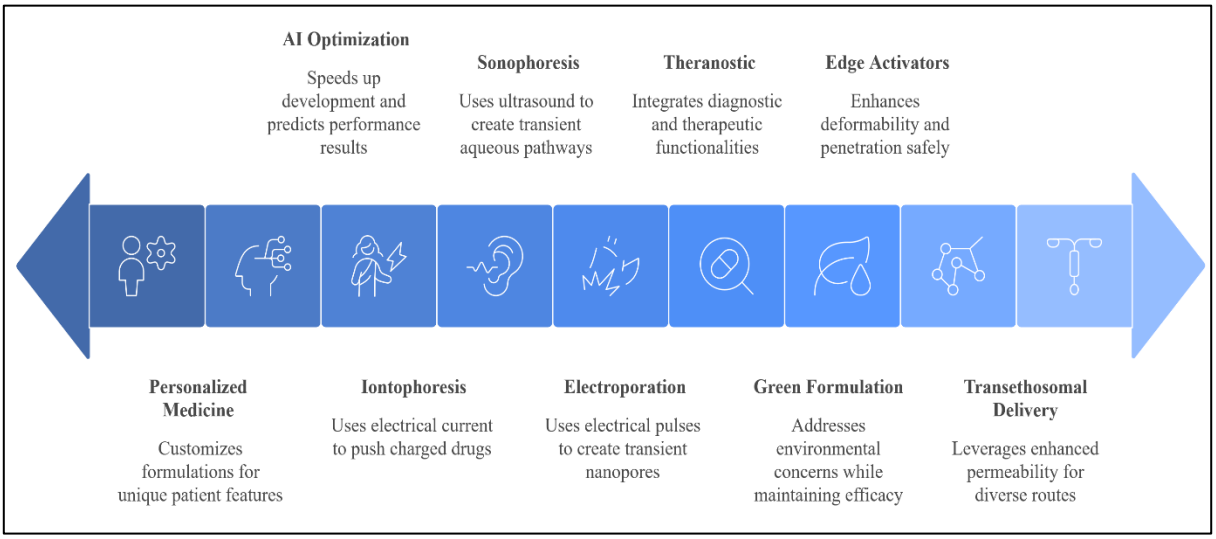

Figure 7. Future perspective and emerging trends

8. CONCLUSION

In comparison to traditional liposomes and ethosomes, transethosomes have greater penetration capacities, marking a significant improvement in transdermal drug delivery methods. The thorough analysis in therapeutic uses highlights the adaptability and therapeutic potential of transethosomal formulations in a variety of therapeutic areas. Through a variety of methods, such as membrane fluidization, lipid bilayer breakdown, and greater deformability, the special makeup of transethosomes which combines phospholipids, ethanol, and edge activators allows for increased skin permeability. Transethosomes efficiency in delivering range of therapeutic substances, from biomacromolecules to tiny chemicals is validated by the clinical evidence given throughout this review.

Successful formulations for dermatological conditions (acne, psoriasis, eczema, fungal infections), pain management (NSAIDs), local anaesthetics), anti-inflammatory therapy, cosmeceutical applications, cardiovascular medications, diabetes management, and new uses in vaccine delivery and gene therapy are among the major therapeutic accomplishments. When compared to traditional formulations, transethosomal formulations of tacrolimus, caryophyllene oxide, retinyl acetate, and propranolol hydrochloride have shown improved bioavailability, increased therapeutic efficacy, and fewer side effects. Trasethosomes are an appealing substrate for both local and systemic medicinal applications because they can accomplish localized dermal and transdermal distribution while reducing systemic absorption. Hepatic first-pass metabolism, gastrointestinal side effects and patient compliance problems with injectable formulations are just a few of the significant drawbacks of traditional drug delivery methods that the technique resolves.

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Author contributions

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REFERENCES:

1. Ita K. Transdermal iontophoretic drug delivery: Advances and challenges. Journal of drug targeting. 2016 May 27;24(5):386-91.
2. Cheng T, Tai Z, Shen M, Li Y, Yu J, Wang J, *et al*. Advance and challenges in the treatment of skin diseases with the transdermal drug delivery system. Pharmaceutics. 2023 Aug 21;15(8):2165.
3. Vitorino C, Sousa J, Pais A. Overcoming the skin permeation barrier: challenges and opportunities. Current Pharmaceutical Design. 2015 Jun 1;21(20):2698-712.
4. Garg V, Singh H, Bimbrawh S, Kumar Singh S, Gulati M, Vaidya Y, *et al*. Ethosomes and transfersomes: Principles, perspectives and practices. Current drug delivery. 2017 Aug 1;14(5):613-33.
5. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praça FG, et al. Development, characterization, and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes, and transethosomes. International journal of nanomedicine. 2015 Sep 18:5837-51.
6. Abdel-Hafez SM, Hathout RM, Sammour OA. Towards better modeling of chitosan nanoparticles production: screening different factors and comparing two experimental designs. International journal of biological macromolecules. 2014 Mar 1;64:334-40.
7. Garg V, Singh H, Bhatia A, Raza K, Singh SK, Singh B, *et al*. Systematic development of transethosomal gel system of piroxicam: formulation optimization, *in vitro* evaluation, and *ex vivo* assessment. AAPS pharmscitech. 2017 Jan;18(1):58-71.
8. Farooq M, Usman F, Zaib S, Shah HS, Jamil QA, Akbar Sheikh F, *et al*. Fabrication and evaluation of voriconazole loaded transethosomal gel for enhanced antifungal and antileishmanial activity. Molecules. 2022 May 23;27(10):3347.
9. Chowdary P, Padmakumar A, Rengan AK. Exploring the potential of transethosomes in therapeutic delivery: A comprehensive review. MedComm–Biomaterials and Applications. 2023 Dec;2(4):e59.
10. Seenivasan R, Halagali P, Nayak D, Tippavajhala VK. Transethosomes: A comprehensive review of ultra-deformable vesicular systems for enhanced transdermal drug delivery. AAPS PharmSciTech. 2025 Jan 17;26(1):41.
11. Malang SD, Shambhavi, Sahu AN. Transethosomal gel for enhancing transdermal delivery of natural therapeutics. Nanomedicine. 2024 Sep 13;19(21-22):1801-19.
12. Munir M, Zaman M, Waqar MA, Hameed H, Riaz T. A comprehensive review on transethosomes as a novel vesicular approach for drug delivery through transdermal route. Journal of Liposome Research. 2024 Jan 2;34(1):203-18.
13. Kashyap B, Khan A, Kapoor DN. Eugenol-loaded transethosomal gel for improved skin delivery and treatment of atopic dermatitis. AAPS PharmSciTech. 2024 Apr 4;25(4):72.
14. Yurtsever AG, Ekmekcioglu A, Muftuoglu M, Güngör S, Erdal MS. Formulation development and evaluation of fluvastatin loaded transethosomes: Characterization, stability, *in vitro* dermal penetration, cytotoxicity and antipsoriatic activity studies. Journal of Drug Delivery Science and Technology. 2024 Jan 1;91:105234.
15. Rady MM, Salama MM, Kuşvuran S, Kuşvuran A, Ahmed AF, Ali EF, *et al*. Exploring the role of novel biostimulators in suppressing oxidative stress and reinforcing the antioxidant defense systems in Cucurbita pepo plants exposed to cadmium and lead toxicity. Agronomy. 2023 Jul 20;13(7):1916.
16. El-Sonbaty MM, Akl MA, Khalid M, Kassem AA. Does the technical methodology influence the quality attributes and the potential of skin permeation of Luliconazole loaded transethosomes?. Journal of Drug Delivery Science and Technology. 2022 Feb 1;68:103096.
17. Abdallah HH. Development and characterization of transethosomes for enhanced skin delivery of 5-fluorouracil. Drug Dev Ind Pharm. 2019;45(4):620-9.
18. Yousef H, Alhajj M, Sharma S. Anatomy, skin (integument), epidermis.
19. Lopez-Ojeda W, Pandey A, Alhajj M, Oakley AM. Anatomy, skin (integument). StatPearls. Treasure Island. 2021.
20. Bouwer F, Brits M, Viljoen JM. Cracking the Skin Barrier: Models and Methods Driving Dermal Drug Delivery. Pharmaceutics. 2025 Dec 9;17(12):1586.
21. Bouwstra JV. Stratum corneum lipids: their role for the skin barrier function in healthy subjects and atopic dermatitis patients. Skin barrier function. 2016 Feb 4;49:8-26.
22. Radhakrishnan N, Kaul SC, Wadhwa R, Yang LW, Sundar D. Establishing a General Atomistic Model for the Stratum Corneum Lipid Matrix Based on Experimental Data for Skin Permeation Studies. International Journal of Molecular Sciences. 2025 Jan 15;26(2):674.

23. Alvarez-Román R, Naik A, Kalia YN, Guy RH, Fessi H. Skin penetration and distribution of polymeric nanoparticles. Journal of controlled release. 2004 Sep 14;99(1):53-62.
24. Avdeef A. Physicochemical profiling (solubility, permeability and charge state). Current topics in medicinal chemistry. 2001 Sep 1;1(4):277-351.
25. Crasta A, Painginkar T, Sreedevi A, Pawar SD, Sathyanarayana MB, Vasantharaju SG, *et al*. Transdermal drug delivery system: A comprehensive review of innovative strategies, applications, and regulatory perspectives. OpenNano. 2025 Jul 1;24:100245.
26. Ishikawa M, Tomoshige S, Sato S. Challenges of Aufheben to promote Druglikeness: Chemical modification strategies to improve aqueous solubility and permeability. Journal of Medicinal Chemistry. 2025 Oct 8;68(20):20859-902.
27. Song CK, Balakrishnan P, Shim CK, Chung SJ, Chong S, Kim DD. A novel vesicular carrier, transethosome, for enhanced skin delivery of voriconazole: characterization and *in vitro*/*in vivo* evaluation. Colloids and surfaces B: biointerfaces. 2012 Apr 1;92:299-304.
28. Wongsirojkul N, Takagi M, Wongngam Y, Sattayakhom A, Prachongsai I, Chunglok W, *et al*. Enhancing transdermal delivery of retinyl acetate via transethosomes with emphasis on the impact of edge activators on penetration, safety, and efficacy. Scientific Reports. 2025 Oct 8;15(1):35172.
29. Khalil R, Abd-Elbary A, Kassem MA, Ridy MS, Samra MM, Awad GE, *et al*. Formulation and characterization of nystatin-loaded nanostructured lipid carriers for topical delivery against cutaneous candidiasis. British Journal of Pharmaceutical Research. 2014 Dec 24;4(4):490-512.
30. Moolakkadath T, Aqil M, Ahad A, Imam SS, Iqbal B, Sultana Y, *et al*. Development of transethosomes formulation for dermal fisetin delivery: Box–Behnken design, optimization, *in vitro* skin penetration, vesicles–skin interaction and dermatokinetic studies. Artificial cells, nanomedicine, and biotechnology. 2018 Nov 5;46(sup2):755-65.
31. Abdulbaqi IM, Darwis Y, Assi RA, Khan NA. Transethosomal gels as carriers for the transdermal delivery of colchicine: statistical optimization, characterization, and *ex vivo* evaluation. Drug design, development and therapy. 2018 Apr 9:795-813.
32. Abdulbaqi IM, Darwis Y, Khan NA, Assi RA, Khan AA. Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, *in vivo* studies, and clinical trials. International journal of nanomedicine. 2016 May 25:2279-304.
33. Bin Jardan YA, Ahad A, Raish M, Al-Jenoobi FI. Preparation and characterization of transethosome formulation for the enhanced delivery of sinapic acid. Pharmaceutics. 2023 Sep 27;15(10):2391.
34. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: A review. Biomaterials research. 2021 Jul 28;25(1):24.
35. Rezigue M, Mashaqbeh H, Aljabali AA, Mansour RS, Hamzeh I. Development and Evaluation of Azithromycin-Loaded Transethosomes for Enhanced Dermal Delivery and Antibacterial Efficacy. Pharmaceutics. 2025 Mar 21;17(4):400.
36. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. Journal of controlled release. 2000 Apr 3;65(3):403-18.
37. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. Biochimica et Biophysica Acta (BBA)-Biomembranes. 1992 Feb 17;1104(1):226-32.
38. Cevc G. Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration, and transdermal drug delivery. Critical reviews™ in therapeutic drug carrier systems. 1996;13(3-4).
39. Raj A, Dua K, Nair RS, Chandran CS, Alex AT. Transethosome: An ultra-deformable ethanolic vesicle for enhanced transdermal drug delivery. Chemistry and physics of lipids. 2023 Sep 1;255:105315.
40. Gadad AP, Patil AS, Singh Y, Dandagi PM, Bolmal UB, Basu A. Development and evaluation of flurbiprofen loaded transethosomes to improve transdermal delivery. Indian J Pharm Educ Res. 2020 Oct 1;54(4):954-62.
41. Caddeo C, Nácher A, Díez-Sales O, Merino-Sanjuán M, Fadda AM, Manconi M. Chitosan–xanthan gum microparticle-based oral tablet for colon-targeted and sustained delivery of quercetin. Journal of microencapsulation. 2014 Nov 1;31(7):694-9.
42. Dudhipala N, Veerabrahma K. Improved anti-hyperlipidemic activity of Rosuvastatin Calcium via lipid nanoparticles: Pharmacokinetic and pharmacodynamic evaluation. European Journal of Pharmaceutics and Biopharmaceutics. 2017 Jan 1;110:47-57.
43. Albash R, Abdelbary AA, Refai H, El-Nabarawi MA. Use of transethosomes for enhancing the transdermal delivery of olmesartan medoxomil: *in vitro*, *ex vivo*, and *in vivo* evaluation. International journal of nanomedicine. 2019 Mar 15:1953-68.
44. Lombardo D, Kiselev MA. Methods of liposomes preparation: formation and control factors of versatile nanocarriers for biomedical and nanomedicine application. Pharmaceutics. 2022 Feb 28;14(3):543.
45. Allam AA, Fathalla D, Safwat MA, Soliman GM. Transferosomes versus transethosomes for the dermal delivery for minoxidil: Preparation and in vitro/ex vivo appraisal. Journal of Drug Delivery Science and Technology. 2022 Oct 1;76:103790.
46. Lane ME. Skin penetration enhancers. International journal of pharmaceutics. 2013 Apr 15;447(1-2):12-21.
47. Zhao J, Mao S. Tuning the membrane fluidity of liposomes for desirable in vivo fate with enhanced drug delivery. InAdvances in biomembranes and lipid self-assembly 2021 Jan 1 (Vol. 34, pp. 67-106). Academic Press.
48. Williams AC, Barry BW. Penetration enhancers. Advanced drug delivery reviews. 2012 Dec 1;64:128-37.
49. El Maghraby GM, Williams AC, Barry BW. Skin delivery of oestradiol from lipid vesicles: importance of liposome structure. International journal of pharmaceutics. 2000 Jun 20;204(1-2):159-69.

50. Sun X, Pan C, Ying Z, Yu D, Duan X, Huang F, Ling J, Ouyang XK. Stabilization of zein nanoparticles with k-carrageenan and tween 80 for encapsulation of curcumin. International journal of biological macromolecules. 2020 Mar 1;146:549-59.
51. Paiva-Santos AC, Herdade AM, Guerra C, Peixoto D, Pereira-Silva M, Zeinali M, Mascarenhas-Melo F, Paranhos A, Veiga F. Plant-mediated green synthesis of metal-based nanoparticles for dermopharmaceutical and cosmetic applications. International Journal of Pharmaceutics. 2021 Mar 15;597:120311.
52. Opatha SA, Titapiwatanakun V, Chutoprapat R. Transfersomes: A promising nanoencapsulation technique for transdermal drug delivery. Pharmaceutics. 2020 Sep 9;12(9):855.
53. Manosroi A, Jantrawut P, Manosroi J. Anti-inflammatory activity of gel containing novel elastic niosomes entrapped with diclofenac diethylammonium. International journal of pharmaceutics. 2008 Aug 6;360(1-2):156-63.
54. Elsayed MM, Abdallah OY, Naggar VF, Khalafallah NM. Deformable liposomes and ethosomes as carriers for skin delivery of ketotifen. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2007 Feb 1;62(2):133-7.
55. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. Journal of molecular biology. 1965 Aug 1;13(1):238-IN27.
56. Sharma G, Goyal H, Thakur K, Raza K, Katare OP. Novel elastic membrane vesicles (EMVs) and ethosomes-mediated effective topical delivery of aceclofenac: a new therapeutic approach for pain and inflammation. Drug delivery. 2016 Oct 12;23(8):3135-45.
57. D'Souza GG, Zhang H, editors. Liposomes: methods and protocols. Springer Nature; 2023 Feb 13.
58. Kulkarni VS, Shaw C. Essential chemistry for formulators of semisolid and liquid dosages. Academic Press; 2015 Oct 15.
59. Dayan N, Touitou E. Carriers for skin delivery of trihexyphenidyl HCl: ethosomes vs. liposomes. Biomaterials. 2000 Sep 1;21(18):1879-85.
60. Zeb A, Qureshi OS, Kim HS, Cha JH, Kim HS, Kim JK. Improved skin permeation of methotrexate via nanosized ultradeformable liposomes. International journal of nanomedicine. 2016 Aug 8:3813-24.
61. Verma DD, Verma S, Blume G, Fahr A. Particle size of liposomes influences dermal delivery of substances into skin. International journal of pharmaceutics. 2003 Jun 4;258(1-2):141-51.
62. Dragicevic-Curic N, Scheglmann D, Albrecht V, Fahr A. Temoporfin-loaded invasomes: development, characterization and in vitro skin penetration studies. Journal of Controlled Release. 2008 Apr 7;127(1):59-69.
63. Benson HA. Transfersomes for transdermal drug delivery. Expert opinion on drug delivery. 2006 Nov 1;3(6):727-37.
64. Chen Y, Lu Y, Chen J, Lai J, Sun J, Hu F, Wu W. Enhanced bioavailability of the poorly water-soluble drug fenofibrate by using liposomes containing a bile salt. International journal of pharmaceutics. 2009 Jul 6;376(1-2):153-60.
65. Jahn A, Vreeland WN, Gaitan M, Locascio LE. Controlled vesicle self-assembly in microfluidic channels with hydrodynamic focusing. Journal of the American chemical society. 2004 Mar 10;126(9):2674-5.
66. Stroock AD, Dertinger SK, Ajdari A, Mezic I, Stone HA, Whitesides GM. Chaotic mixer for microchannels. Science. 2002 Jan 25;295(5555):647-51.
67. Carugo D, Bottaro E, Owen J, Stride E, Nastruzzi C. Liposome production by microfluidics: potential and limiting factors. Scientific reports. 2016 May 19;6(1):25876.
68. Yu LX. Pharmaceutical quality by design: product and process development, understanding, and control. Pharmaceutical research. 2008 Apr;25(4):781-91.
69. Guideline IH. Pharmaceutical development. Q8 (2R). As revised in August. 2009 Aug 23;23.
70. Pallagi E, Ismail R, Paál TL, Csóka I. Initial Risk Assessment as part of the Quality by Design in peptide drug containing formulation development. European Journal of Pharmaceutical Sciences. 2018 Sep 15;122:160-9.
71. Jadhav V, Sutar KP, S. Sammasagi S, Usulkar S, Patil V. Enhanced Tacrolimus efficacy in psoriasis with innovative transethosomes: a promising preclinical study on Wistar rats. Drug Development and Industrial Pharmacy. 2025 May 4;51(5):454-66.
72. Mahmood S, Taher M, Mandal UK. Experimental design and optimization of raloxifene hydrochloride loaded nanotransfersomes for transdermal application. International journal of nanomedicine. 2014 Sep 12:4331-46.
73. Ferreira SC, Bruns RE, Ferreira HS, Matos GD, David JM, Brandão GC, da Silva EP, Portugal LA, Dos Reis PS, Souza AS, Dos Santos WN. Box-Behnken design: An alternative for the optimization of analytical methods. Analytica chimica acta. 2007 Aug 10;597(2):179-86.
74. Rathore AS, Winkle H. Quality by design for biopharmaceuticals. Nature biotechnology. 2009 Jan;27(1):26-34.
75. Mbah CC, Builders PF, Attama AA. Nanovesicular carriers as alternative drug delivery systems: ethosomes in focus. Expert opinion on drug delivery. 2014 Jan 1;11(1):45-59.
76. Bhalaria MK, Naik S, Misra AN. Ethosomes: a novel delivery system for antifungal drugs in the treatment of topical fungal diseases. Indian journal of experimental biology. 2009 May 1;47(5):368-75.
77. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. Nature reviews Drug discovery. 2004 Feb 1;3(2):115-24.
78. Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery systems: current and future prospects. Drug delivery. 2006 Jan 1;13(3):175-87.
79. Ammala A. Biodegradable polymers as encapsulation materials for cosmetics and personal care markets. International journal of cosmetic science. 2013 Apr;35(2):113-24.

80. Muzzalupo R, Pérez L, Pinazo A, Tavano L. Pharmaceutical versatility of cationic niosomes derived from amino acid-based surfactants: Skin penetration behavior and controlled drug release. International journal of pharmaceutics. 2017 Aug 30;529(1-2):245-52.
81. Moolakkadath T, Aqil M, Ahad A, Imam SS, Iqbal B, Sultana Y, Mujeeb M, Iqbal Z. Development of transethosomes formulation for dermal fisetin delivery: Box–Behnken design, optimization, in vitro skin penetration, vesicles–skin interaction and dermatokinetic studies. Artificial cells, nanomedicine, and biotechnology. 2018 Nov 5;46(sup2):755-65.
82. Sala M, Diab R, Elaissari A, Fessi H. Lipid nanocarriers as skin drug delivery systems: Properties, mechanisms of skin interactions and medical applications. International journal of pharmaceutics. 2018 Jan 15;535(1-2):1-7.
83. Jain S, Jain P, Umamaheshwari RB, Jain NK. Transfersomes—a novel vesicular carrier for enhanced transdermal delivery: development, characterization, and performance evaluation. Drug development and industrial pharmacy. 2003 Jan 1;29(9):1013-26.
84. Manca ML, Castangia I, Zaru M, Nácher A, Valenti D, Fernàndez-Busquets X, Fadda AM, Manconi M. Development of curcumin loaded sodium hyaluronate immobilized vesicles (hyalurosomes) and their potential on skin inflammation and wound restoring. Biomaterials. 2015 Dec 1;71:100-9.
85. Zhang Y, Zhang H, Zhang K, Li Z, Guo T, Wu T, Hou X, Feng N. Co-hybridized composite nanovesicles for enhanced transdermal eugenol and cinnamaldehyde delivery and their potential efficacy in ulcerative colitis. Nanomedicine: Nanotechnology, Biology and Medicine. 2020 Aug 1;28:102212.
86. Ruan H, Shen L, Hou X, Li J, Guo T, Zhu C, Feng N, Zhang Y. Phytosterol-mediated glycerosomes combined with peppermint oil enhance transdermal delivery of lappaconitine by modulating the lipid composition of the stratum corneum. Drug Delivery and Translational Research. 2023 Dec;13(12):3014-29.
87. Fang JY, Hung CF, Hwang TL, Wong WW. Transdermal delivery of tea catechins by electrically assisted methods. Skin pharmacology and physiology. 2005 Dec 7;19(1):28-37.
88. Natsheh H, Touitou E. Phospholipid vesicles for dermal/transdermal and nasal administration of active molecules: The effect of surfactants and alcohols on the fluidity of their lipid bilayers and penetration enhancement properties. Molecules. 2020 Jun 27;25(13):2959.
89. Natsheh H, Qneibi M, Kittana N, Jaradat N, Assali M, Shaqour B, Abualhasan M, Mayyala A, Dawoud Y, Melhem T, Abd Alhadi S. Transethosomal system for enhanced transdermal delivery and therapeutic effect of caryophyllene oxide. International Journal of Pharmaceutics. 2025 Feb 10;670:125111.
90. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: A review. Biomaterials research. 2021 Jul 28;25(1):24.
91. Albash R, El-Nabarawi MA, Refai H, Abdelbary AA. Tailoring of PEGylated bilosomes for promoting the transdermal delivery of olmesartan medoxomil: in-vitro characterization, ex-vivo permeation and in-vivo assessment. International journal of nanomedicine. 2019 Aug 15:6555-74.
92. Chibowski E, Szcześ A. Zeta potential and surface charge of DPPC and DOPC liposomes in the presence of PLC enzyme. Adsorption. 2016 May;22(4):755-65.
93. Mohd H, Dopierała K, Zidar A, Virani A, Michniak-Kohn B. Effect of Edge Activator Combinations in Transethosomal Formulations for Skin Delivery of Thymoquinone via Langmuir Technique. Scientia Pharmaceutica. 2024 May 27;92(2):29.
94. Honeywell-Nguyen PL, de Graaff AM, Groenink HW, Bouwstra JA. The in vivo and in vitro interactions of elastic and rigid vesicles with human skin. Biochimica et Biophysica Acta (BBA)-General Subjects. 2002 Nov 14;1573(2):130-40.
95. Ahmed OA, Badr-Eldin SM. Development of an optimized avanafil-loaded invasomal transdermal film: Ex vivo skin permeation and in vivo evaluation. International journal of pharmaceutics. 2019 Oct 30;570:118657.
96. Barupal AK, Gupta V, Ramteke S. Preparation and characterization of ethosomes for topical delivery of aceclofenac. Indian journal of pharmaceutical sciences. 2010 Sep;72(5):582.
97. Godin B, Touitou E. Ethosomes: new prospects in transdermal delivery. Critical reviews™ in therapeutic drug carrier systems. 2003;20(1).
98. Cevc G, Blume G. New, highly efficient formulation of diclofenac for the topical, transdermal administration in ultradeformable drug carriers, Transfersomes. Biochimica et biophysica acta (BBA)-biomembranes. 2001 Oct 1;1514(2):191-205.
99. Jain S, Tiwary AK, Sapra B, Jain NK. Formulation and evaluation of ethosomes for transdermal delivery of lamivudine. Aaps Pharmscitech. 2007 Oct;8(4):111.
100. Rai VK, Mishra N, Yadav KS, Yadav NP. Nanoemulsion as pharmaceutical carrier for dermal and transdermal drug delivery: Formulation development, stability issues, basic considerations and applications. Journal of controlled release. 2018 Jan 28;270:203-25.
101. Trotta M, Peira E, Carlotti ME, Gallarate M. Deformable liposomes for dermal administration of methotrexate. International journal of pharmaceutics. 2004 Feb 11;270(1-2):119-25.
102. Patel R, Singh SK, Singh S, Sheth NR, Gendle R. Development and characterization of curcumin loaded transfersome for transdermal delivery. Journal of pharmaceutical sciences and research. 2009 Dec 1;1(4):71.
103. Dubey V, Mishra D, Dutta T, Nahar M, Saraf DK, Jain NK. Dermal and transdermal delivery of an anti-psoriatic agent via ethanolic liposomes. Journal of controlled release. 2007 Nov 6;123(2):148-54.

104. Paolino D, Lucania G, Mardente D, Alhaique F, Fresta M. Ethosomes for skin delivery of ammonium glycyrrhizinate: in vitro percutaneous permeation through human skin and in vivo anti-inflammatory activity on human volunteers. Journal of controlled release. 2005 Aug 18;106(1-2):99-110.
105. Salem HF, Ahmed SM, Omar MM. Liposomal flucytosine capped with gold nanoparticle formulations for improved ocular delivery. Drug design, development and therapy. 2016 Jan 13:277-95.
106. Mishra D, Dubey V, Asthana A, Saraf DK, Jain NK. Elastic liposomes mediated transcutaneous immunization against Hepatitis B. Vaccine. 2006 May 29;24(22):4847-55.
107. Chessa M, Caddeo C, Valenti D, Manconi M, Sinico C, Fadda AM. Effect of penetration enhancer containing vesicles on the percutaneous delivery of quercetin through new born pig skin. Pharmaceutics. 2011 Aug 12;3(3):497-509.
108. Nousheen K, Din FU, Jamshaid H, Afza R, Khan SU, Malik M, Ali Z, Batool S, Zeb A, Yousaf AM, Almari AH. Metformin HCl-loaded transethosomal gel; development, characterization, and antidiabetic potential evaluation in the diabetes-induced rat model. Drug delivery. 2023 Dec 31;30(1):2251720.
109. Uchegbu IF, Schätzlein AG, Cheng WP, Lalatsa A, editors. Fundamentals of pharmaceutical nanoscience. New York: Springer; 2013 Jan 1.
110. Cevc G, Blume G. Hydrocortisone and dexamethasone in very deformable drug carriers have increased biological potency, prolonged effect, and reduced therapeutic dosage. Biochimica et Biophysica Acta (BBA)-Biomembranes. 2004 May 27;1663(1-2):61-73.
111. Mohapatra M, Pradhan D, Mohapatra S, Kar RK, Jena GK. Development and Characterization of Voriconazole-loaded Nanostructured Lipid Carriers for Enhanced Topical Antifungal Therapy. BioNanoScience. 2025 Jun;15(2):222.
112. Mahmoud NN, Alkilany AM, Dietrich D, Karst U, Al-Bakri AG, Khalil EA. Preferential accumulation of gold nanorods into human skin hair follicles: Effect of nanoparticle surface chemistry. Journal of colloid and interface science. 2017 Oct 1;503:95-102.
113. Barry BW. Mode of action of penetration enhancers in human skin. Journal of controlled release. 1987 Dec 1;6(1):85-97.
114. Song YH, Gwak HS, Chun IK. The effects of terpenes on the permeation of lidocaine and ofloxacin from moisture-activated patches. Drug Delivery. 2009 Feb 1;16(2):75-81.
115. Duangjit S, Obata Y, Sano H, Onuki Y, Opanasopit P, Ngawhirunpat T, Miyoshi T, Kato S, Takayama K. Comparative study of novel ultradeformable liposomes: menthosomes, transfersomes and liposomes for enhancing skin permeation of meloxicam. Biological and pharmaceutical bulletin. 2014 Feb 1;37(2):239-47.
116. Gupta PN, Mishra V, Rawat A, Dubey P, Mahor S, Jain S, Chatterji DP, Vyas SP. Non-invasive vaccine delivery in transfersomes, niosomes and liposomes: a comparative study. International journal of pharmaceutics. 2005 Apr 11;293(1-2):73-82.
117. Akhtar N, Pathak K. Cavamax W7 composite ethosomal gel of clotrimazole for improved topical delivery: development and comparison with ethosomal gel. AAPS pharmscitech. 2012 Mar;13(1):344-55.
118. Sakran W, Abdel-Rashid RS, Saleh F, Abdel-Monem R. Ethosomal gel for rectal transmucosal delivery of domperidone: design of experiment, in vitro, and in vivo evaluation. Drug Delivery. 2022 Dec 31;29(1):1477-91.
119. Patra P. Cutting-edge advances in transethosomes and nanoethosomes for transdermal drug delivery. Discover Chemistry. 2025 Dec;2(1):1-25.
120. Al-Mahallawi AM, Abdelbary AA, Aburahma MH. Investigating the potential of employing bilosomes as a novel vesicular carrier for transdermal delivery of tenoxicam. International journal of pharmaceutics. 2015 May 15;485(1-2):329-40.
121. Prausnitz MR, Langer R. Transdermal drug delivery. Nature biotechnology. 2008 Nov;26(11):1261-8.
122. Ahad A, Aqil M, Kohli K, Sultana Y, Mujeeb M, Ali A. Role of novel terpenes in transcutaneous permeation of valsartan: effectiveness and mechanism of action. Drug development and industrial pharmacy. 2011 May 1;37(5):583-96.
123. Ahmed TA, Khalid M, Aljaeid BM, Fahmy UA, Abd-Allah FI. Transdermal glimepiride delivery system based on optimized ethosomal nano-vesicles: Preparation, characterization, in vitro, ex vivo and clinical evaluation. International journal of pharmaceutics. 2016 Mar 16;500(1-2):245-54.
124. Naqvi S, Panghal A, Flora SJ. Nanotechnology: a promising approach for delivery of neuroprotective drugs. Frontiers in neuroscience. 2020 Jun 9;14:494.
125. Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: An overview. Journal of advanced pharmaceutical technology & research. 2010 Jul 1;1(3):274-82.
126. Ain QU, Khan H, Mubarak MS, Pervaiz A. Plant alkaloids as antiplatelet agent: drugs of the future in the light of recent developments. Frontiers in pharmacology. 2016 Sep 22;7:292.

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