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VESICULAR DRUG DELIVERY SYSTEMS WITH SKIN PERMEATION ENHANCERS: A REVIEW OF FORMULATION AND EVALUATION FOR TOPICAL AND TRANSDERMAL APPLICATIONS

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ABSTRACT

Skin permeation remains a major challenge in the effective delivery of drugs through topical and transdermal routes due to the barrier function of the stratum corneum. Vesicular drug delivery systems, such as liposomes, niosomes, transfersomes, and ethosomes, have emerged as promising carriers to enhance drug penetration and improve therapeutic efficacy. This review focuses on the role of skin permeation enhancers incorporated within vesicular systems to overcome the limitations of conventional topical formulations. Permeation enhancers act by disrupting the lipid structure of the stratum corneum, altering protein conformation, or increasing drug partitioning into the skin, thereby facilitating improved drug diffusion. Various classes of permeation enhancers, including chemical agents (such as alcohols, fatty acids, surfactants, and terpenes) and novel biological enhancers, are discussed in relation to their mechanisms and compatibility with vesicular carriers. The synergistic effect of combining vesicular systems with permeation enhancers significantly improves drug bioavailability, targeting efficiency, and controlled release profiles. Additionally, the review highlights recent advancements in deformable vesicles and nanovesicular systems designed for enhanced transdermal delivery. Despite their advantages, issues such as skin irritation, toxicity, and stability remain challenges that need careful consideration. Overall, vesicular drug delivery systems integrated with effective permeation enhancers represent a promising approach for non-invasive drug administration. Future research should focus on optimizing formulations to achieve maximum efficacy with minimal adverse effects, paving the way for improved topical and transdermal therapeutic strategies.

KEYWORDS: Vesicular drug delivery system, Permeation enhancers, Transdermal drug delivery.

INTRODUCTION

The skin, which is the largest organ of the human body, possesses a multi-layered structure made up of the epidermis, dermis, and hypodermis layers. The skin has an estimated surface area of 1.5 to 2.0 m² in the adult body and performs essential roles such as regulating homeostasis, limiting the loss of water from the body (transepidermal water loss, TEWL), and offering protection against physical, chemical, and microbial assaults.In terms of drug delivery, the skin acts as an efficient barrier that greatly reduces the penetration of drugs. Stratum corneum constitutes the main barrier to

transdermal drug delivery. This layer, which consists of corneocytes contained in a lipid-rich extracellular matrix, can be compared to bricks and mortar structures. Corneocytes, also referred to as the bricks, are filled with keratin, while the intercellular lipids (mortar), comprising ceramides, cholesterol, and free fatty acids, form lamellae structures.

Three layers represent the main components of our skin.
Epidermis: The most external part, namely stratum corneum (SC) which is about 15 μm in thickness, represents the primary barrier to penetration. It comprises keratinized cells (corneocytes) structured in the manner of "brick-and-mortar", where corneocytes are bricks, while lipids represent the mortar. Such close packing makes our skin highly impermeable, especially for hydrophilic drugs exceeding 200-350 Da of molecular weight.

Dermis: More massive, hydrophilic structure including collagen, elastin, blood vessels, nerves, and glands. Dermis represents no significant hindrance for almost all substances; however, it is important in maintaining diffusion through the removal of the substance absorbed and provides alternative routes (through hair follicles and glands) to enter the skin.

Hypodermis: The innermost layer represented by fats and connective tissue providing protection and insulation.[4] Three different routes are available for drug penetration, including: transappendicular pathway, paracellular lipid route, and transcellular route.

Transcellular Route: Moiety passes through lipids and keratinocytes via the transcellular route, which travels directly to the dermis.

Paracellular Route: The most typical way that drug molecules enter cells is through the paracellular route. The drug stays in lipid moeity and remains near keratin in this pathway (easier for lipid soluble drug rather than proteins).

Transappendgeal route: It creates a continuous channel for drug penetration, although it is readily impeded by the presence of sweat ducts and hair follicles.[20]

Permeation enhancers are those compounds that, upon addition to any drug formulation, could temporarily lower the barrier property of the stratum corneum, leading to the improved absorption of the drugs across the skin. Such enhancers increase the permeation of the drugs without producing any damage to the integrity of the skin tissue. This technique has received much interest in recent years, owing to the rising need for effective non-invasive drug delivery systems.[4]

An ideal penetration enhancer must have following characteristics.

Pharmaceutically inactive, Nonirritant, non-toxic and non-allergic in nature, good solubility with drugs and excipients, colorless, odorless and tasteless, low cost along with good solvent power.[19]

As the primary barrier for drug entry, the stratum corneum is the outermost layer of skin that also serves as a protective shield. The non-toxic, inert substances called penetration enhancers improve drug absorption and skin permeability without the need for therapeutic use.

They work through different methods.
Chemical techniques: employing substances like pyrrolidones, surfactants and cyclodextrins or terpene' to change the structure of the skin and make it easier for drugs to be taken or through the system.

Physical techniques: Refine the physical characteristics of the skin by means of radiofrequency, pressure waves, electroporation, and magnetophoresis.

A significant number of molecules are able to enter the skin via intercellular channels. The micro-route and numerous enhancing techniques are intended to achieve.

To dilute or obstruct its refined chemical structure.5. Mechanistic analysis of the human skin with simplified design, Analysis of skin permeation.[24]

The function of penetration enhancers is to disrupt lipid structures in the skin, improve membrane fluidity, and facilitate drug distribution and uptake. Ideal enhancers should be non-toxic, antiperspiring and stable when combined with other substances.

Systems such as vesicular carriers are considered enhancers, and they can be chemical, physical, or natural stimuli. Modern techniques for delivering blood through the skin include both non-invasive methods (such as nanocarriers, advanced biofeedback devices like sensors and cameras), or minimally involved forms such as minimal ablation using electrodes. Understanding these mechanisms can aid in the creation of more efficient topical and transdermal formulations, particularly in cosmetic industries.[1]

Topical and transdermal formulations of penetration enhancers are designed to temporarily reduce the barrier function of the stratum corneum (SC), allowing active ingredients to pass through the skin more easily without damaging cells. Drug delivery has been enhanced by technological advancements in pharmaceuticals, leading to improved absorption and bioavailability.

Due to the high demand for cosmetics and cosmeceuticals, many products have little clinical evidence of effectiveness, necessitating improved delivery systems.

Transdermal Drug Delivery System addresses the problem through a means to deliver the drug to the bloodstream after administering it on the skin surface at a controlled rate. The benefits of using Transdermal Drug Delivery System include: Increased efficacy and safety of treatment, Prevention of first-pass effect, Enhanced patient compliance and ease, Prevention of "peak and valley" phenomenon in oral and parenteral dosage forms, avoiding drug degradation in the stomach, maintaining stable plasma levels, and being non-invasive with minimal use, Stopping drug delivery is possible anytime by removing the patch. It also improves bioavailability, prolongs duration of action, improves adherence to care, reduces costs, and is especially effective for children, unconscious or vomiting patients.

They facilitate localized treatment with reduced systemic exposure and a decreased level of toxicity. The treatment can help with hair loss, neuropathic pain, acne, migraines, and other related conditions.

But one major drawback of Transdermal Drug Delivery System is that the skin is a very good protective barrier to drug permeation: the Stratum Corneum being the main component. This consists of a well-organized lipophilic membrane (~15 µm thickness.[9]

TYPES OF PERMEATION ENHANCERS

1. Chemical Permeation Enhancers (CPEs)

CPEs function as Stratum Corneum modifiers in Transdermal Drug Delivery System's, improving drug penetration without damaging the skin. Various types of chemical permeation enhancers used in TDDSs are

1.1 Water

About 15–20% of the water in the human stratum corneum (SC) is found in two different forms: bound water and free (residual) water. Free water is found inside the membrane and serves as a solvent, especially for polar molecules, whereas bound water makes up around 25–30% of the total water and is connected to structural elements. Amino acids and corneocytes containing functional groups like hydroxyl and carboxyl groups, which aid in water retention and skin suppleness, are also present in the stratum corneum.

By enhancing interactions between lipid head groups and increasing the fluidity of lipid domains, particularly those stiffened by cholesterol, hydration is known to improve the penetration of lipophilic drugs.[8]

1.2 Alcohols

Alcohols are widely used as co-solvents with water and are one of the most employed chemical permeation enhancers (CPEs) in transdermal medication delivery. In general, they are categorized as short-chain solvents. When injected at suitable quantities for prolonged periods of time, ethanol in particular has the capacity to remove lipids from the stratum corneum (SC).[8]

Ex: Isopropyl alcohol, Ethanol, Propylene glycol, Polyglycerol polyricinoleate.[1]

1.3. Sulfoxides

One of the most popular penetration enhancers among sulfoxides is dimethyl sulfoxide (DMSO). Colorless, odorless, and hygroscopic, it acts as a potent aprotic solvent. By changing the structure of intercellular keratin from an α-helical form to a β-sheet arrangement, DMSO improves drug penetration. New structural analogues, such as decyl methyl sulfoxide (DCMS), have also been developed. CMS has a reversible and concentration-dependent action on human skin.[8]

1.4 Azones

Azone was developed as a transdermal penetration enhancer and patented in 1976. Chemically, it is described as a cyclic amide and an alkyl chain, with no characteristic aprotic sulfoxide group, which contributes to its mild irritancy. Azone is extremely hydrophobic, but it remains soluble in most organic solvents.[8]

Its permeation-enhancing effect is concentration dependent, and it is often employed in the 1-3% range. Azone interacts with the stratum corneum (SC) lipids, forming a unique domain within the lipid structure known as the "soup spoon" conformation. Electron diffraction experiments confirmed the occurrence of Azone as a distinct phase within stratum corneum (SC)lipids.[8]

1.5 Surfactants

Anionic surfactants possess a negatively charged hydrophilic head group, with examples include soaps, sodium lauryl sulfate (SLS), dioctyl sodium sulfosuccinate, and phosphate esters. These surfactants bind to proteins in the epidermis, increasing the number of anionic sites in the membrane and improving skin moisture. Differential scanning calorimetry (DSC) investigations have found that SLS increases the water content of skin tissues.

Cationic surfactants, on the other hand, have a positively charged hydrophilic head group and bulky lipophilic chains. They are often quaternary ammonium compounds. Common examples include cetyltrimethylammonium bromide (CTAB) and benzalkonium chloride (BKC), which are used in transdermal formulations to improve the penetration of drugs including diazepam, haloperidol, and methyl nicotinate. These surfactants improve penetration primarily via inflating the stratum corneum and reacting with intercellular keratins.

Non-ionic surfactants possess polar hydrophilic head groups that do not dissociate. They improve drug penetration by interacting with the stratum corneum (SC) lipids and enhancing membrane fluidity. They cause less irritation than ionic surfactants and generally are considered safer.[8]

1.6 Terpenes

Terpenes are a class of natural chemicals considered to be safer than synthetic chemical permeation enhancers. Many terpenes, including 1,8-cineole, menthol, and menthone, are categorized as Generally Recognized as Safe (GRAS). They can improve the penetration of both hydrophilic and lipophilic drugs, even at low concentrations, by interacting with stratum corneum (SC) lipids, particularly intercellular lipids and hydrogen bonding inside the lipid bilayer.[8]

Common permeation enhancers include 1,8-cineole, limonene, D-limonene, carveol, carvone, pulegone, nerolidol, L-menthol, and menthone. Among these, 1,8-cineole, a significant component of eucalyptus oil, has been researched for its ability to improve the penetration of drugs like 5-fluorouracil and estradiol through the skin.[1]

1.7 Pyrrolidine

Pyrrolidone is an organic compound with a five-membered lactam ring that acts as a permeation enhancer for both hydrophilic and lipophilic drugs in the skin. The most studied derivatives are N-methyl-2-pyrrolidone (NMP) and 2-pyrrolidone (2P). Differential scanning calorimetry (DSC) experiments have revealed that these chemicals improve drug penetration by interacting with stratum corneum (SC) lipids and enhancing their fluidity. Hydrophilic pyrrolidones interact with the polar regions of the SC, whereas more hydrophobic pyrrolidones interact with the non-polar regions.[8]

1.8 Fatty Acids

Fatty acids are commonly employed as chemical penetration enhancers in topical and transdermal medication delivery systems. They have a considerable impact on increasing medication permeability over the stratum corneum (SC), the principal barrier to transdermal absorption.

Long-chain fatty acids:Oleic acid, lauric acid,myristic acid, and capric acid.

Unsaturated fatty acids: Linoleic, alphalinolenic, and arachidonic acids.[1]

Oleic acid, also known as octadec-9-enoic acid, contains a double bond at the C-9 position in the cis (Z) configuration. Due to its beneficial properties, it is commonly employed as a permeation enhancer in topical and transdermal drug delivery systems. Its mode of action includes increased lipid fluidity and improved skin diffusivity.

Long-chain fatty acids: Oleic acid, lauric acid, myristic acid, and capric acid.

Unsaturated fatty acids: Linoleic, alphalinolenic, and arachidonic acids.[8]

At greater concentrations, oleic acid can exist as its own phase within lipid bilayers, resulting in the creation of different lipid domains. These domains cause structural disruptions or "defects" in the lipid bilayer, allowing drugs to permeate more easily, especially hydrophilic compounds. This impact is mostly due to the presence of a double bond in the structure.

1.9 Phospholipids

Phospholipids (PLs) are amphiphilic lipids made up of a hydrophilic head and two hydrophobic tails connected by an alcohol group. They are commonly employed in the development of vesicular systems such as liposomes and ethosomes for topical and transdermal drug delivery, with the goal of increasing bioavailability, lowering toxicity, and improving drug flow over the skin. Phospholipids can integrate with stratum corneum (SC) lipids by forming vesicles within the skin. Phospholipids are considered to interact readily with stratum corneum lipids and form localized lipid domains within the membrane.

1.10 Urea

Urea is an organic molecule containing two amine (-NH_2) groups connected to a carbonyl group (C=O). It is colorless, odorless, and very soluble in water. Urea is widely utilized in topical and transdermal preparations due to its hydrotropic characteristics, which increase skin moisture. It is commonly used to treat illnesses including psoriasis, xerosis, ichthyosis, and other hyperkeratotic disorders.

Urea's ability to raise water content in the stratum corneum, as well as its keratolytic activity, are the primary reasons for its permeation-enhancing effect. Water-in-oil emulsions containing urea have been shown to significantly improve skin moisture.

1.11 Cyclodextrins

Cyclodextrins (CDs) are a type of permeation enhancer that has various advantages over conventional enhancers. Certain CD derivatives can form inclusion complexes with drug molecules, which quickly reach equilibrium with the free drug in the formulation, enhancing drug availability.

Cyclodextrins improve penetration by facilitating drug molecules' passage over the water barrier from the bulk solution to the lipophilic surface of biological membranes, where the drug is liberated from the complex and partitioned into the membrane.[23]

Common permeation enhancers include α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin

HP-β-CD.[1]

2. Lipid synthesis inhibitors(LSIs)

Stratum corneum (SC) lipids, which are primarily composed of cholesterol, ceramides, fatty acids, and glycerol, play an important part in the skin's barrier function. A decrease in the synthesis of any of these key lipid components may compromise this barrier. Based on this concept, it has been suggested that blocking skin lipid metabolism can improve transdermal drug delivery.

Lipid synthesis inhibitors (LSIs) such as 5-(tetradecyloxy)-2-furancarboxylic acid (TOFA), fluvastatin (FLU), and cholesterol sulfate (CS) have been studied to improve transdermal drug delivery of lidocaine and caffeine. These substances increase drug absorption by affecting the skin's barrier homeostasis and thermodynamic characteristics.

3. Cell-Penetrating Peptides (CPPs)

Cell-penetrating peptides (CPPs) are short, positively charged peptides composed of 5-30 amino acids that can pass biological membranes. Because of their high transduction efficiency and low cytotoxicity, CPPs have received a lot of interest as viable transdermal drug delivery methods. Drugs can relate to CPPs via covalent or non-covalent interactions to aid in their transport over the skin.

4. Ionic Liquids (ILs)

Ionic liquids (ILs) are a class of compounds characterized by low vapor pressure, low melting point, high solubility, and thermal stability, as well as customizable physicochemical features. They consist of two components: a cation and an anion. This combination lowers crystallinity, allowing ILs to remain liquid even at low temperatures.

ILs have been extensively studied as chemical penetration enhancers in transdermal drug delivery. They improve drug transport via both paracellular and transcellular channels, effectively overcoming the stratum corneum's barrier function. Their mode of action includes disturbance of cellular integrity, increased lipid fluidity, the development of diffusion routes, and the extraction of lipids from the Stratum Corneum.

5. Microneedles

Microneedles are a novel approach for optimizing medicine administration by increasing percutaneous absorption. This technique uses micron-sized needles (1-100 µm in length) placed on a transdermal patch. They are frequently made from silicon, metals, ceramics, silica glass, polysaccharides, and biodegradable polymers.

Drugs can be added to microneedle devices in the form of liquids, microparticles, or gels in a reservoir. This technique solves the disadvantages of traditional transdermal delivery, namely low skin penetration, while also providing benefits such as macromolecule distribution, convenience of administration, and minimal pain, as the needles do not reach the deeper dermal layers containing nerve endings.

6. Ceramides

A series of ceramide analogues with eight different polar head groups and six different chain lengths were produced and tested as permeation enhancers in vitro on pig skin. The findings offer useful insights that can aid in the rational design of more effective permeation enhancers for transdermal medication delivery systems.

7. Nano sized vesicular delivery system

Nano-sized vesicular delivery systems act as carrier-based permeation enhancers in transdermal drug delivery. Their nanoscale size and deformable nature enable them to penetrate deeper skin layers or deliver drugs efficiently across the barrier.

Nanocrystals, Nanomaterial, SLNs, NLCs, Nanoparticle, Nanospheres, Liposomes, Ethosomes,

Transfersomes, Niosomes, Phytosomes, Photosomes are common nano sized vesicular delivery systems.

METHODS OF PREPARATION

Cold Method

The cold technique is an effortless and uncomplicated approach for creating ethosomal and transethosomal gels. Using ethanol or a hydroalcoholic solution, the medication and phospholipids are dissolved. The lipid bilayer is liquefied by ethanol, which enhances the skin's capacity to absorb chemicals. Phospholipids, medication, an edge activator or surfactant like Tween 80 (for transethosomes), and a penetration enhancer like propylene glycol must all be dissolved in ethanol in a closed vessel in order to prepare gel forms. A magnetic stirrer is then used to agitate the mixture at room temperature (around 25°C) until all of the ingredients are fully dissolved. Distilled water is heated independently to roughly 30°C at the same time. After that, the ethanolic lipid phase is gradually mixed with the aqueous phase while being constantly stirred for 30 to 60 minutes at 700 to 1000 RPM. The procedure aids in the production of nanometric vesicles. To reduce the vesicle size and provide a more uniform particle distribution, the resulting dispersion is either sonicated or put through a high-pressure homogenizer. Finally, the gel is stabilized at 4°C and neutralized with the appropriate neutralizing agent to attain the necessary consistency.[2]

Hot Method

For ethosomes, phospholipids are suspended in aqueous ethanol that has been heated to about 60°C. Transethosomes are made similarly, but with the addition of edge activators like sodium cholate or surfactants like Tween 80 to improve permeability and deformability. In both cases, ethanol that has been heated to the same temperature as the lipid phase is used to dissolve the medication after the lipid phase has been dissolved in distilled water that has been preheated to a temperature of 40–70°C. For efficient vesicle production, the ethanol phase is gradually added to the lipid dispersion while being continuously stirred at 700–1000 RPM for 30–60 minutes at the same temperature. To reduce vesicle size, the resultant dispersion is subsequently subjected to additional sonication or high-pressure homogenization.

Ethanol Injection Method

Niosomes, ethosomes, and transethosomes can be prepared using the straightforward and efficient ethanol injection procedure. This method involves dissolving the phospholipids in the lipid phase with a little amount of an organic solvent, like ethanol. After that, the aqueous

phase—that is, water or an aqueous buffer—is gradually filled with this solution while being continuously stirred. Surfactants such as Span 60 or Tween 80 are utilized to improve the penetration and deformability of transethosomes. Gel-forming chemicals, such as Carbopol 934 or HPMC (hydroxypropyl methylcellulose), are added to generate a gel. For transethosomes, phospholipid and surfactant (such as Tween 80) and medication; for ethosomes, phospholipids and medication. These materials are combined with ethanol and heated to between 30 and 40 degrees Celsius. Stir the mixture continuously until it dissolves completely. Heat the distilled water to between 30 and 40 degrees Celsius. Stir the mixture continuously until it dissolves completely. Heat the distilled water to between 30 and 40 degrees Celsius. Now, slowly and dropwise introduce the ethanolic phase into the aqueous phase while continuously stirring with a homogenizer or a magnetic stirrer. The ethanolic phase gives rise to ethosomes and transethosomes. They formed vesicles by self-assembling. These days, extrusion or probe-sonication are utilized to both achieve consistent particle sizes and minimize the size of the vesicles.

Mechanical Dispersion / Thin Film Hydration Method

Lipid vesicles are generated using the thin film hydration approach, which involves creating a thin lipid layer and then hydrating it to create vesicles. In order to create vesicular delivery systems, phospholipids are often dissolved in an organic solvent such as ethanol, methanol, or chloroform in a round-bottom flask. A rotary evaporator is then used to entirely evaporate the solvent under vacuum, leaving a thin layer of lipid on the inside of the flask. A small layer of lipid is left on the inner surface of the flask after the solvent is completely evaporated at low pressure using a rotary evaporator. Large multilamellar vesicles (MLVs) are produced by hydrating this dried film with distilled water or isotonic phosphate-buffered saline (PBS); this process can be improved by employing an ultrasonic bath. To create tiny unilamellar vesicles (SUVs), these MLVs are then sonicated (2).

Sonication method

This process involves heating the lipid components at 60 °C in a water bath until a homogenous mixture is achieved. The medication is heated to the same temperature and dissolved in the aqueous phase at the same time. To guarantee adequate mixing, both phases are then mixed together while being continuously stirred. To aid in the development of niosomes, the resultant dispersion is then exposed to probe sonication for about five minutes.[3]

Solvent Diffusion Method

100 mg of quercetin were dissolved in 1.75 ml of molten surfactant (GMO) using the solvent diffusion method. A primary emulsion was then created by progressively adding 12.5 ml of 0.1% poloxamer 188 solution and sonicating the mixture for three minutes at 18 W. The final nanoemulsion was subsequently created by adding a 2.4% solution of Eudragit S100 to this emulsion. A fine powder of nanoparticles was produced by freeze-drying the mixture for 48 hours with mannitol acting as a cryoprotectant. Before being used again, the white lyophilized product was gathered and kept at 4°C.[3]

Patch Incorporation Method

To create a drug-in-adhesive transdermal patch for site-specific anastrozole delivery, the produced gel is integrated into an isopropyl myristate (IPM) membrane. Rat skin was used to test several formulations with varying adhesive matrices, permeation enhancers, and medication doses for in vitro skin penetration. The formulation with the highest penetration efficiency included DURO-TAK®, 8% IPM, and 8% anastrozole.[25]

LITERATURE REVIEW

S.NO	TITLE & AUTHOR	YEAR	CONCLUSION	LITERATURE GAP	REFERENCE
1.	Permeation Enhancers for Enhanced Topical Delivery of Pharmaceutical and Cosmeceutical Products. Maha N. Abu Hajleh[1], Hamdi Nsairat[2] , Lidia K. Al-Halaseh[3] , Ali Al-Samydai[2], Alia K. Ibrahim[4] , Emad A. Al-Dujaili[5]	2025	The transdermal enhancement technology has developed to the point where it can bypass the skin barrier that restricts topical formulations. Physical and chemical techniques can be used to enhance the penetration of active substances into the skin. Penetration enhancers should be safe, non-irritating, non-toxic, pharmacologically inactive, and cosmetically acceptable.	Further studies are required to explore the various enhancers, their mechanisms, and safety to create effective formulations for the delivery of active cosmetic agents.	[1]
2.	A Brief Review on: Vesicular Drug Delivery System - For Its Anti-Inflammatory Activity as Ethosomes and Transethosomes Gel Formulations Nabamita Sen[1]*, Fowad Khurshid[2], M. Ganga Raju[3], Vaidehi Sammanwar[4], Sruthi	2025	The release profile explains how a medication is progressively released from ethosomal and transethosomal vesicles; because of their lipid bilayer structure, these vesicles usually exhibit persistent release. In vitro diffusion techniques, such as Franz diffusion cells or dialysis membranes, are		[2]

	Vottela[5], Sree Ganganagunta[6]		frequently used to study this. A membrane (MWCO 12,000–14,000 Da) is soaked overnight, cleaned, and then loaded with the formulation in the dialysis membrane procedure. After that, it is sealed and kept at 37°C in a phosphate buffer (pH 6.8–7.4) to replicate physiological conditions. To keep the system consistent, it is stirred.		
3.	Niosome As A Promising Tool for Increasing the Effectiveness of Anti-Diabetic Drug for Vesicular Drug Delivery System. Nabamita Sen*[1] Fowad Khurshid[2], M. Ganga Raju[3], J. Tejaswi, B. Tejaswini, M. Sruthi[6]	2025	Researchers have paid close attention to nanoscale and microsized vesicular drug delivery devices in recent decades. During oral delivery, these systems shield medications from severe gastrointestinal conditions and increase the stability of pharmaceuticals that are susceptible to environmental factors. Additionally, they improve the absorption of medications that are poorly absorbed. Originally created for industrial and cosmetic uses, niosomes—a vesicular drug delivery system composed of non-ionic surfactants—are currently being extensively researched for use in medicinal applications. These restrictions can be addressed and focused medication administration made possible by vesicular systems. Such systems may be used in the future to minimize side effects and lower oral dosage requirements for medications like antidiabetics, with potential uses even in cancer treatment.		[3]
4.	Skin Penetration and Permeation Properties of Transcutol® in Complex Formulations Jasmine Musakhanian[1], David W. Osborne[2], Jean‑David Rodier[3]	2024	Drug characteristics, skin affinity, and formulation concentration all affect passive diffusion across the stratum corneum (SC). A key component is the drug delivery system (vehicle), which needs to be customized to the medicine and the therapeutic objectives.To increase drug absorption through the skin, penetration enhancers have been utilized extensively. Despite improving permeability, some chemical enhancers—such as terpenes, sulfoxides, and amides—can harm the skin barrier. As a result, current methods concentrate on safer tactics by combining several gentle, less invasive enhancers, which are backed by better knowledge of skin biology and sophisticated analytical instruments.		[4]
5.	A Comprehensive Review on Potential Chemical and Herbal Permeation Enhancers Used in Transdermal Drug Delivery Systems Rajat Singh Raghav[1], Sushma	2024	Natural compounds have become a new source of permeation enhancers since they can temporarily lower the skin barrier resistance and increase drug transport through the stratum corneum layer, facilitating drug delivery. The research related to the structure-activity		[5]

	Verma[1], Monika[1]		relationship of natural compounds indicates the significance of the chemical structure of these agents in their ability to promote drug permeation across the skin barrier.		
6.	Implementing Nanovesicles for Boosting the Skin Permeation of Non-steroidal Anti-inflammatory Drugs Manar Adel Abdelbari[1], Ahmed Hassen Elshafeey[2], Aly Ahmed Abdelbary[2,3], Shaimaa Mosallam[1]	2023	Improved medication delivery systems are required to overcome the drawbacks of traditional approaches since inflammatory disorders need to be treated quickly. Advanced vesicular carriers improve the way NSAIDs are delivered to the skin, direct the medication to the site of action, minimize side effects, and increase therapeutic efficacy. These systems have unique parts that improve drug absorption and skin penetration. Advanced vesicular carriers may take the place of traditional drug delivery methods when additional formulations become available.		[6]
7.	Natural Ingredients of Transdermal Drug Delivery Systems as Permeation Enhancers of Active Substances through the Stratum Corneum Natalia Schafer, Radosław Balwierz,* Paweł Biernat, Wioletta Ochędzan-Siodłak, and Jacek Lipok	2023	By rupturing lipid layers and improving drug transport, natural compounds including urea, terpenes, and hyaluronic acid (HA) aid in improving medication penetration through the stratum corneum (SC). Because of their polar and non-polar nature, terpenes can improve the penetration of both lipophilic and hydrophilic medicines. Additionally, HA offers regulated medication release and mucoadhesive qualities. Because it interacts with both lipids and proteins of the Stratum Corneum to improve drug transport channels, using a combination of permeation enhancers is more successful than using a single enhancer. Additionally, this method enhances the efficacy of transdermal medication delivery systems and reduces skin irritation brought on by high doses of a single enhancer.		[7]
8.	Mucus‐penetrating and permeation enhancer albumin‐based nanoparticles for oral delivery of macromolecules: Application to bevacizumab Cristina Pangua[1]· Socorro Espuelas[1]· María Cristina Martínez‐Ohárriz[2] José Luis Vizmanos[3]	2023	The work demonstrates that bevacizumab can be successfully encapsulated in PEG-coated albumin nanoparticles, particularly when DS is used as a counterion, improving oral bioavailability. To improve stability and mucus penetration, these desolvation-prepared nanoparticles were coated with PEG. Intestinal epithelial integrity was shown to be disrupted by both DS and DOCU (free or encapsulated), although C. elegans survival was unaffected. Compared to oral peptide medications like semaglutide (~1%) and octreotide (~0.7%), bevacizumab's oral bioavailability was up to 3.7%.Through		[8]

			mechanisms such tight junction disruption, enhanced membrane mobility, and suppression of enzymatic degradation, sodium deoxycholate plays a crucial role in improving absorption.		
9.	Improved Topical Drug Delivery: Role of Permeation Enhancers and Advanced Approaches Victor Hmingthansanga[1], Nidhi Singh[1], Superna Banerjee[1], Sivakumar Manickam[2], Ravichandiran Velayutham[3], Subramanian Natesan[1],	2022	The skin is an ideal location for drug delivery due to its large surface area and accessibility. The transdermal route bypasses the first-pass effect in the intestines and liver and provides a constant level of the drug in the bloodstream. It is also easy to use, inexpensive, and patient-friendly. The drug can diffuse through the skin in three ways: transcellular , paracellular, and transappendageal. The stratum corneum is the major barrier to diffusion. The combination of chemical penetration enhancers (CPEs) can lead to synergistic effects, and new enhancers with improved penetration and reduced toxicity have been synthesized.However, in vivo research is more complicated because of the skin's sensitivity.	The mechanism still needs to be studied and validated.	[9]
10.	Current Status of Amino Acid-Based Permeation Enhancers in Transdermal Drug Delivery Rui Pereira [1], Sandra G. Silva [1], Marina Pinheiro[2] , Salette Reis[2] and M. Luísa do Vale [1]	2021	This review focuses on amino acid-based skin permeation enhancers in transdermal drug delivery (TDD). These enhancers have great potential because of their versatility, efficacy, and safety compared to conventional chemical permeation enhancers. They have the potential to enhance skin permeability and drug solubility in various ways. The combination of amino acid-based enhancers with other chemical or physical techniques may result in synergistic effects, which may help increase the scope of TDD for more drugs, especially hydrophilic and high molecular weight drugs.	The mechanisms of action of these enhancers are not yet clear, and more research is required.	[10]
11.	Potential of Nanoparticles such as Permeation Enhancers and Targeted Delivery Options for Skin: Advantages and Disadvantages Parisa Ghasemiyeh & Soliman Mohammadi-Samani	2020	Lipid-based nanocarriers like (SLNs) and (NLCs), and vesicular carriers like liposomes, niosomes, transfersomes, and ethosomes are the most widely employed. NLCs have advantages over SLNs and other vesicular carriers in terms of their higher drug loading capacity and targeted delivery to skin organelles. Transfersomes and ethosomes have been found to be more efficient due to their enhanced ability to penetrate the skin. Hence, the choice of a suitable nanocarrier is based on the nature of the drug, the target of drug delivery (transdermal or targeted), and its compatibility with the skin.	There are no comprehensive comparative analyses of their efficiency, safety, and stability. Moreover, there is little information on the exact mechanisms of skin permeation and targeted delivery to skin organelles for various nanocarriers. Further research is also needed to optimize the properties of nanocarriers and to confirm their efficacy	[11]

				through in vivo experiments.	
12.	Ionic Liquids as Potential and Synergistic Permeation Enhancers for Transdermal Drug Delivery Zainul Sidat, Thashree Marimuthu, Pradeep Kumar, Lisa C. du Toit, Pierre P. D. Kondiah, Yahya E. Choonara and Viness Pillay	2019	Ionic Liquids (ILs) have been found to be promising candidates as permeation enhancers or drug delivery systems because of their versatility and non-toxic nature. ILs can be used in combination with other formulation methods to improve transdermal drug permeation.	Their efficacy as standalone agents needs further validation.	[12]
13.	Application of Permeation Enhancers in Oral Delivery of Macromolecules: An Update	2019	One of the main areas of research is the creation of safe and efficient penetration enhancers (PEs) for the oral delivery of macromolecules. Targeting tight junction (TJ) opening and utilizing drugs that have been shown to be safe in people are two tactics.The behavior of PEs in the intestinal environment, the impact of GI circumstances (such as fluid composition, tonicity, and exposure duration), the physicochemical characteristics of PEs, the consequences of mixing enhancers, and insights from clinical investigations have all been the subject of recent research.These results highlight the difficulties in putting research into practice, particularly the requirement to maximize the simultaneous presence of the medication and PE at the intestinal wall in high concentrations for enough time to enhance absorption and therapeutic success.		[13]
14.	Preparation and optimization of lidocaine transferosomal gel containing permeation enhancers: a promising approach for enhancement of skin permeation Mahmoud M Omar, Omiya Ali Hasan & Amani M El Sisi	2019	Transfersomes are efficient carriers for the improvement of skin drug permeation. The addition of transferosomal lidocaine to a gel will enhance drug permeation and the stability of the vesicles. The addition of skin permeation enhancers to the gel will further potentiate the delivery of the drug without damaging the skin.		[14]
15.	Effect of Chemical Permeation Enhancers on Skin Permeability: *In silico* screening using Molecular Dynamics simulations	2019	Chemical permeation enhancers (CPEs) can be screened using in-silico skin models with the use of computer simulations, especially coarse-grained molecular dynamics (CG MD). The structure, size, and hydrophobicity (log P) of CPEs all affect how well they partition into the skin lipid layer.Once within the lipid layer, interactions with lipids and other enhancer molecules determine how they move and behave, resulting in behaviors like as dispersion, aggregation, or clustering. These interactions have the potential to increase permeability and disturb lipid structure.In order to increase		[15]

			permeability, an ideal permeation enhancer should both successfully penetrate the skin's lipid layer and cause transient structural alterations.		
16.	Penetration Enhancers in Ocular Drug Delivery	2019	Ocular medication administration is difficult because of obstacles like nasolacrimal drainage, blinking, tear reflex, and limited corneal permeability. Three primary processes are used by penetration enhancers to promote drug delivery: loosening tight junctions, changing epithelial cell membranes, and rupturing the tear film and mucous layer. Membrane permeability can be increased by a variety of enhancers, including as cyclodextrins, bile salts, chelating compounds, and peptides.Ocular distribution is still challenging despite advancements, necessitating improved formulations that maximize efficacy while reducing adverse effects. Although the toxicity of various enhancers has been investigated, most studies concentrate on short-term exposure, leaving little information regarding long-term safety.		[16]
17.	New Insights on the Mechanism of Fatty Acids as Buccal Permeation Enhancers Cristina Padula, Silvia Pescina, Sara Nicoli and Patrizia Santi	2018	The structure–activity relationship of fatty acids as penetration enhancers for mucosal administration of a hydrophilic chemical (FD-4) is investigated in this study. Fatty acid lipophilicity and permeation enhancement were shown to have a parabolic relationship, with optimal activity at C10 (log P = 4), suggesting optimal lipophilicity for interaction with mucosal lipids. Skin results showed a similar pattern, with maximal increase at C12 (log P = 5), indicating that skin is more lipophilic. Enhancement was not significantly affected by the presence of double bonds. Furthermore, interactions with tissue lipids are influenced by variables such as fatty acid chain length and solvent type, underscoring the significance of co-solvents. In general, the work advances our knowledge of how fatty acids promote buccal medication penetration.		[17]
18.	Development of essential oils as skin permeation enhancers: penetration enhancement effect and mechanism of action. Qiudong Jiang, Yeming Wu, Hui Zhang, Pei Liu, Junhong Yao, Peijun Yao, Jun Chen & Jinao Duan	2017	Compared to conventional agents like azone, essential oils (EOs) are less toxic and more effective penetration enhancers. Chuanxiong oil had the greatest improvement in ibuprofen skin absorption among them.EOs that promote the drug's partitioning into the stratum corneum (SC) include turpentine, chuanxiong, cyperus,		[18]

			cinnamon, and clove oils. Instead of removing lipids, their primary action involves upsetting the SC's orderly lipid structure. Lipid disruption and enhanced efficiency were found to be strongly correlated by ATR-FTIR studies. Furthermore, it was discovered that EOs with moderate volatility provide the best penetration improvement.		
19.	Natural permeation enhancer for transdermal drug delivery system and permeation evaluation: a review Asha Das*, Abdul Baquee Ahmed	2017	Because of its many benefits, transdermal medication administration is developing quickly; nonetheless, skin is a significant barrier to drug penetration. Permeation enhancers are used to increase drug absorption and preserve bioavailability in order to get around this. `The review highlights several novel permeation enhancers (NPEs) that can successfully improve drug penetration through the skin and focuses on various delivery strategies and permeation evaluation techniques.		[19]
20.	Permeation enhancer strategies in transdermal drug delivery Harneet Marwah, Tarun Garg, Amit K. Goyal & Goutam Rath	2014	The technology of skin permeation enhancement is rapidly developing and has the potential to increase the number of drugs that can be delivered transdermally. The transdermal route of drug administration has several advantages over the oral route, which has encouraged research efforts to develop methods to overcome the skin barrier using penetration enhancers. In the future, penetration enhancers will play an important role in the development of effective transdermal drug products.	Many effective penetration enhancers have been found from which, most of them are toxic and further needs to be optimized.	[20]
21.	Penetration enhancers in proniosomes as a new strategy for enhanced transdermal drug delivery Gamal M. El Maghraby *, Amal A. Ahmed, Mohamed A. Osman	2014	Proniosomes are promising transdermal drug delivery systems whose efficacy depends on their composition. Careful selection of the components of the proniosomes may result in improved use of these systems. Penetration enhancer containing proniosomes were found to be better than the simple formulation.The study thus presented a new composition for transdermal proniosomes and unlocked doors for future studies on the optimisation of the composition and the mechanisms.	The mechanism(s) of enhanced transdermal delivery of proniosomes needs further studies although the data recorded and the impact of composition implied the potential for combined mechanisms.	[21]
22.	Liposomes coated with thiolated chitosan enhance oral peptide delivery to rats K. Gradauer , J. Barthelmes , C. Vonach , G. Almer , H. Mangge , B. Teubl , E. Roblegg , S. Dünnhaupt , E. Fröhlich , A.	2014	Drug penetration is improved by coating liposomes with thiolated chitosan, particularly S-protected thiomers, which increases the liposomes' capacity to pass through intestinal mucus and reach the epithelium. Thiomer-coated liposomes improved the transit of salmon calcitonin into rat		[22]

	Bernkop-Schnürch , R. Prassl		intestinal mucosa, according to ex vivo investigations. Improved medication absorption was demonstrated by a considerable (~35%) decrease in blood calcium levels following oral delivery in in vivo tests that further validated efficacy.		
23.	The effects of chemical and physical penetration enhancers on the percutaneous permeation of lidocaine through equine skin Jessica Stahl* and Manfred Kietzmann	2014	According to the study, lidocaine's transdermal penetration varies greatly depending on the vehicle. Furthermore, lidocaine penetration through equine skin is significantly increased by microneedle pretreatment, suggesting significant potential for enhancing transdermal medication delivery.		[23]
24.	Permeation Enhancer for TDDS from Natural and Synthetic Sources: A Review Dhruba Sankar Goswami[1], Nidhi Uppal[1] , Sandeep Goya[1]l, Naveen Mehta[2], Anil Kumar Gupta[3]	2013	The skin acts as a protective barrier that limits drug absorption, making permeation enhancers essential for improving the delivery of poorly permeable drugs. These enhancers do not possess therapeutic activity but facilitate drug transport across the skin. Various approaches, including synthetic and natural enhancers such as Azone, sulfoxides, fatty acids, terpenes, and herbal compounds, are used based on their mechanisms and properties.This strategy is particularly important in transdermal drug delivery systems, as it expands the range of drugs that can be effectively delivered through the skin.		[24]
25.	A Review on Transdermal Patches Prasanth T A[*1], Remya S B[2], Prasobh G R[3], Subash Chandran M P[4]	2022	Transdermal patches provide many advantages over traditional dosing forms because they avoid first-pass metabolism and maintain constant plasma medication levels. Drug penetration and treatment efficacy are further enhanced by the use of appropriate polymers, adhesives, and permeation enhancers. Notwithstanding obvious drawbacks such skin irritation and limited medication compatibility, ongoing improvements in vesicular systems and formulation techniques have increased their potential uses. All things considered, transdermal patches have become a popular and efficient drug delivery method in contemporary pharmaceutical research and treatment.		[25]

EVALUATION TESTS

ZETA POTENTIAL

Zeta potential, measured through laser Doppler electrophoresis or dynamic light scattering, reflects the surface charge of particles in a composition. Zeta potential is influenced by the total charge on lipid structures and helps assess liposomal dispersion stability by giving a measure of the extent of electrostatic repulsion that happens among particles. Negative zeta potential, often derived from ethanol, enhances vesicle stability by preventing aggregation and promotes greater transdermal drug absorption. Principle values around ±25 mV signify significant repulsive forces and stable dispersions, while values nearing zero suggest an inclination towards vesicle aggregation and lack of stability. The zeta potential measurement of ethosomes and transethosomes is crucial for assessing their stability and electric charge on the surface. Start by thinning the

mixture with double-distilled water or a buffer like PBS to a concentration that minimizes multiple scattering, ideally a dilution of 1:10 to 1:100. Prevent air bubbles; brief sonication may be beneficial but must not heat or break the vesicular structure.

After preparing the sample, place it into a suitable cuvette or capillary cell for the zeta potential instrument, which is a Malvern Zetasizer or ELS device. Adjust the device and configure settings such as temperature (typically 25°C or 37°C), viscosity, refractive coefficient, and electric permittivity. Aqueous systems are modeled using the Smoluchowski approach to calculate the Zeta potential derived from electrophoretic mobility.

The measurement exposes the sample to an electric field, detecting particle movement to determine zeta potential. Threefold measurements are recommended for accuracy. Zeta potential measurements indicate stability: >±30 mV signifies good stability, and ±20–30 mV reflects moderate stability, and <±20 mV indicates low stability and a chance of vesicle clustering. Ethanol in ethosomes can reduce surface charge and edge. Activators within transethosomes can affect zeta potential values. They are used to assess short-term stability and track changes over the duration of a stability assessment.[2]

Ex-Vivo Permeation Studies

A vertical Franz diffusion cell was used to assess diffusion across rat skin over a 12-hour period. With the dermal side toward the receptor fluid, excised skin samples were positioned between the donor and receptor compartments. Phosphate-buffered saline (PBS-T, pH 7.4) with 10% Tween 80 was the receptor media. The skin's effective diffusion area was 0.64 cm^2.

To enable pre-equilibration, PBS-T was first added to the donor (1 mL) and receptor (5 mL) compartments. Following equilibration, the solutions were taken out and a circular DIE patch was gently applied to the skin's surface, applying just enough pressure to guarantee good contact. After that, the receptor compartment was replaced with new PBS-T, constantly agitated at 600 rpm, and kept at 37 ± 0.5 °C with a circulating water bath.[3]

Entrapment Efficiency

The ultra-centrifugation method was employed to calculate entrapment efficiency. For one hour, a niosomal formulation with a defined concentration was centrifuged at 4 °C. The amount of unentrapped (free) medication was determined by analyzing the supernatant that was collected after an appropriate dilution. The following formula was then used to determine the entrapment efficiency.[3]

$$\text{Efficiency of Entrapment} = \frac{\text{Amount of entrapped drug}}{\text{Total amount of drug}} \times 100$$

In Vivo Dermal Absorption Study

For the in vivo dermal absorption study, the dorsal side of rabbit skin (about 4 cm × 3 cm) was shaved 24 hours prior to the experiment to prepare the site for application. This area was then treated with a specified quantity of the test formulation. At predefined intervals of two, six, twelve, and twenty-four hours, one milliliter of blood was drawn from the central ear artery. Plasma was separated from the obtained blood by centrifugation and kept at -20°C until further examination.[19]

Viscosity determination

The developed formulations showed shear-thinning properties and non-Newtonian flow behavior. As shown in Fig. 2, this indicates that viscosity dropped as the shear rate increased. Viscosity measurements were made at a constant speed of 50 rpm because of this non-Newtonian nature. Table 2 lists the observed viscosity values. Plain proniosomes had the highest viscosity of all the formulations, but the viscosity decreased when penetration enhancers were added. It's interesting to note that adding propylene glycol to formulations containing oleic acid decreased the viscosity-lowering effect of oleic acid, but the overall viscosity was still lower than in the basic formulation.[21]

Transmission Electron Microscope [TEM]

Transmission electron microscopy was used to study the morphology of niosomes. A 2% uranyl acetate solution was used to adversely stain the samples. Control formulations were further diluted to prevent particle agglomeration and allow for the clear observation of individual vesicles. Before analysis, the prepared samples were put on copper grids coated with carbon and let to air dry at room temperature.[3]

Cell viability assay

Even though most permeation enhancers successfully increase medication penetration through the skin, many are linked to toxicity or discomfort, which restricts their practical application. Using the MTT test on HaCaT skin cells, the cytotoxic effects of azone and six essential oils (EOs) were assessed. The results showed that every EO test caused cytotoxicity that was dose dependent. Turpentine, Angelica, chuanxiong, Cyperus, cinnamon, clove oils, and azone all had IC50 values of 118.48, 53.26, 58.14, 81.80, 42.62, 109.03, and 21.13 µg/mL, respectively.

Azone was the most toxic of these, with cinnamon oil, angelica oil, chuanxiong oil, cyperus oil, clove oil, and turpentine oil following. In general, synthetic boosters were more likely to cause skin irritation than natural essential oils. Additionally, no direct correlation was observed between cytotoxicity and permeation-enhancing ability.[18]

DIFFERENTIAL SCANNING CALORIMETRY (DSC) ANALYSIS

The physical condition of the medication and excipients inside ethosomal vesicles was assessed using Differential Scanning Calorimetry (DSC) technique. A Mettler DSC 60 equipment was used to evaluate samples that included pure karanjin, a physical combination, and freeze-dried ethosomal formulation (K-ETH) over a temperature range of 30–250 °C at a heating rate of 10 °C/min in a nitrogen atmosphere. To evaluate thermal properties and potential interactions between formulation components, the transition temperature (Tm) was measured.[2]

In-vitro Skin Permeation Study

The cumulative amount of drug penetrated (QT) was plotted against time during the in-vitro permeation test. Fick's law of diffusion was used to evaluate drug penetration since it accurately characterizes steady-state skin transport. The drug concentration in the receptor compartment is still much lower than that in the donor compartment under sink circumstances.

The drug permeation rate per unit area, or steady-state flux (Jss), is calculated as follows.

$Jss = P \times Cd \times D/e$

Parameters including steady-state flux (Jss), permeability coefficient (Kp), and lag time (Tlag) were calculated from the linear part of the QT versus time plot. Jss (μg/cm²/h) was calculated using the slope of this linear region, and the permeability coefficient was derived using:

$Kp = Jss/cd$[2]

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was used to assess the niosomal emulgel formulation's shape. A few drops of the formulation were put onto a stub covered with double-sided adhesive tape after it had been diluted with water in a 1:10 ratio. To improve image clarity, a tiny layer of gold was applied to the sample after it had dried. Small, spherical vesicles were found evenly throughout the polymeric network, according to SEM photographs. The medication was efficiently solubilized in the formulation, as evidenced by the lack of visible insulin crystals.[3]

CONCLUSION

Skin permeation enhancers play a vital role in improving the effectiveness of vesicular drug delivery systems for topical and transdermal applications. By overcoming the barrier properties of the stratum corneum, these enhancers facilitate better drug penetration, bioavailability, and therapeutic outcomes. Vesicular carriers such as liposomes, niosomes, transfersomes, and ethosomes, when combined with suitable permeation enhancers, provide a synergistic approach for controlled and targeted drug delivery. However, challenges such as potential skin irritation, toxicity, and formulation stability must be carefully addressed. Overall, the integration of permeation enhancers with advanced vesicular systems offers a promising and non-invasive strategy, with future research needed to optimize safety, efficacy, and clinical applicability. In this review article various evaluation parameters were also discussed based upon its widespread research work and formulations for vesicular drug delivery were developed to minimize the first pass metabolism caused due to oral drug delivery.

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