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Review Article

Transdermal Drug Delivery Systems: A New Frontier in Skin Permeation Enhancers

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ABSTRACT

Currently, approximately 74% of drugs are administered orally, but they often fall short of achieving the desired effectiveness. Transdermal drug release systems were introduced as an effective and controlled drug or macromolecule delivery through skin without causing pain. This review looks at recent advancements in skin permeation enhancers, including chemical, physical, and bioinspired methods that effectively overcome the skin's barrier properties to improve drug absorption. Because they increase efficacy, patient compliance, and personalized treatment options, smart hydrogels, microneedles, and AI-driven formulation optimization are given special consideration. With the combination of innovative permeation enhancers and state-of-the-art delivery technologies, transdermal therapeutics is entering a new phase that expands the therapeutic scope of medications, biologics, and macromolecules. Future prospects highlight the importance of biocompatibility, safety, and regulatory frameworks that will guide the transformation of these technologies into effective clinical applications.

INTRODUCTION

Skin is the biggest organ in our body and it's our body's first line of protection, the skin is a desirable location for medication delivery. The stratum corneum, however, is a strong and resilient barrier that prevents most medications from permeating the skin by passive diffusion. While this protective function of the stratum corneum maintains homeostasis and shields against harmful substances, it also poses a major challenge to transdermal drug delivery.[1] TDDS, commonly called "patches," are customized dosage forms devised to deliver a drug in an efficient manner across the skin of the patient. TDDS ensure controlled release of the drugs across the skin, maintaining constant blood levels to enhance efficacy and minimize side effects, in contrast to

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oral or injectable routes. The morphological, biophysical, and physicochemical characteristics of the skin affect drug absorption and patch design, which in turn affects how well transdermal systems work.[3] Scopolamine patches, sold under the brand name Transderm-Scop, were the first transdermal drug delivery system authorized by the FDA in the United States. This patch, which was also approved in 1979, was developed to prevent nausea and vomiting related to travel, specifically sea sickness. This marks a significant advancement in drug delivery technology, providing a convenient, noninvasive alternative for motion sickness management.[9]

Advantages of Drug Delivery:-[3, 4]

- Bypasses Hepatic and Presystemic Metabolism (avoids first-pass effect).
- Enhances Bioavailability of the drug.
- Reduces the risk and inconvenience associated with intravenous (IV) administration.
- Allows self-administration.
- Prevents fluctuations in drug concentration levels.
- Termination therapy of drugs is easy.
- Enables targeted drug delivery to a specific site.
- Reduces Gastrointestinal (GI) side effects.
- Compared to the Buccal or Nasal Cavity, it has a relatively large area of application.

BRIEF HISTORY OF TRANSDERMAL PRODUCTS:[13]

The use of skin for the delivery of compounds dates back thousands of years. Ancient African communities used plants and minerals for cosmetics and to treat skin conditions. While the Ebers Papyrus (1500 BC) recorded a variety of treatments, including the application of tiger nuts for wound care, the Egyptians utilized natural ingredients like henna, ochre, and kohl for skincare around 4000 BC. Centuries later, Galen developed the first cold cream—an emulsion of oil, beeswax, and water—for use on wounds, burns, and joint pain. Ancient Chinese medicine advanced with herbal plasters made from natural gums for localized therapy. By the 15th century, Unguentum Hydrargyri, a mercury-based ointment, was used to treat syphilis. In 1880, Paul Carl Beiersdorf created gutta-percha plaster gauze for skin disorders, while belladonna plaster became popular for treating tuberculosis and tumors. Systemic drug delivery through the skin hasn't been widely accepted, though. In 20th century, accidental skin poisoning cases, such as phenol spills, highlighted the potential for transdermal absorption. This led to the development of the first transdermal product in the 1950s, Nitrol (2% nitroglycerin ointment), for angina pectoris. However, its greasy texture, inconsistent dosing, and need for multiple daily applications limit its use. These drawbacks have encouraged the development of controlled, measured-dose transdermal systems to improve convenience and therapeutic consistency.

PHYSIOLOGY OF SKIN: [5]

The skin is the largest organ in the human body. In the average adult, it covers about 2 m^2 (22 ft^2) of surface area. This surface area varies depending on a person's age, sex, body size, and stature. The skin is highly vascularized (rich in blood vessels). Around 1/3 of the body's circulating blood volume

can be present in the skin at any time. There are 3 main layers of the skin:

- The most superficial layer is called the epidermis.
- The middle layer - dermis.
- The innermost layer is the hypodermis.

Epidermis:-

Sublayers of the outermost layer of the skin is epidermis. The four sublayers that compose the epidermis are called stratum corneum, cutis granulosum (or simply stratum granulosum), cutis spinosum (also called prickly layer or spinous/ prickle cell layer), and basement membrane. Its constituent cells are melanocytes (pigmentation), Langerhans cells (immune function), Merkel cells (sensory perception), and keratinocytes (about 95% of the cells in it). The palms and soles have a thin epidermis that reaches 0.8 mm. Rich in keratin (approximately 70%) and lipids (20%), the stratum corneum serves as a waterproof barrier that keeps moisture in and shields the skin from the elements. It is also blood vessel-free. Its keratinocytes give it protection and toughness.[6]

Dermis:-

The dermis is significantly thicker and located directly beneath the epidermis, ranging from 3-5 mm**.** It functions as a supportive layer that supplies nutrients to the epidermis and contains several essential skin structures and sensory elements. Major Components of the Dermis:-

- **Blood vessels** – deliver oxygen and nutrients while removing metabolic waste.
- **Hair follicles** – serve as roots for hair growth and contribute to thermoregulation.
- **Sweat glands** – help check body temperature by releasing sweat.
- **Sebaceous glands** – secrete oils that keep the skin lubricated and protected.
- **Nerve endings** – sense tactile air puffs, pain, temperature and pressure.
- **Collagen and Elastin fibers** – provide resilience, flexibility, and structural integrity to the skin.

A dense capillary network in the dermis, which is located around 0.2 mm beneath the skin's surface, rapidly eliminates substances while preserving a concentration gradient that promotes diffusion. Rich in water, the dermis slows the passage of lipophilic compounds because it is aqueous, but it provides little resistance to hydrophilic molecules.[7]

Subcutaneous tissue (hypodermis):-

The innermost layer of the skin, referred to as the hypodermis, is a layer that consists largely of connective tissue and fat. Although many treatments act locally within the stratum corneum and other skin layers, topical medications must travel through the layers of the skin to enter the bloodstream.[8]

ROUTES OF SKIN PERMEATION:

Drugs absorption through the skin can occur via multiple pathways, and the route largely depends on the physicochemical characteristics of the compound. Hydrophilic and lipophilic drugs utilize different mechanisms for permeation. Despite the stratum corneum being a strong barrier to penetration it is still possible for drugs to traverse through and into the systemic circulation (fig.1).[1] Following are the routes-

- **Transfollicular route**, considered the shortest pathway, which offering a relatively large surface area for diffusion through structures such as underneath the surface) sweat glands, oil (sebaceous) glands, hair follicles and their duct passages. These ducts form direct channels through the stratum corneum; however, the transport efficiency may vary depending on the type and amount of glandular secretions. Despite this, the appendageal route accounts for only approximately 0.1% of the total skin surface; therefore its contribution is relatively minor.[10]

- **Transcellular route**, where drugs pass directly through the corneocytes. Corneocytes contain highly hydrated keratin, creating a hydrophilic environment suitable for the passage of water-soluble drugs. To cross the cell membrane, drugs must undergo multiple steps of partitioning and diffusion through the cell cytoplasm, making this the most common route of penetration for hydrophilic molecules.[10]

- **Intercellular route** is also involved, by which the drug is released from a lipid matrix connected to and surrounding the corneocytes between cells_DICT:[i.e.,] where the drug permeates between the cells within this lipid environment. Because of its tortuous and alternating lipid-aqueous structure, molecules must partition into the lipid bilayers and then diffuse inward. This longer and more complex pathway is particularly favorable for uncharged, lipophilic drugs, as water molecules would face significantly greater resistance while traveling through this route.[11]

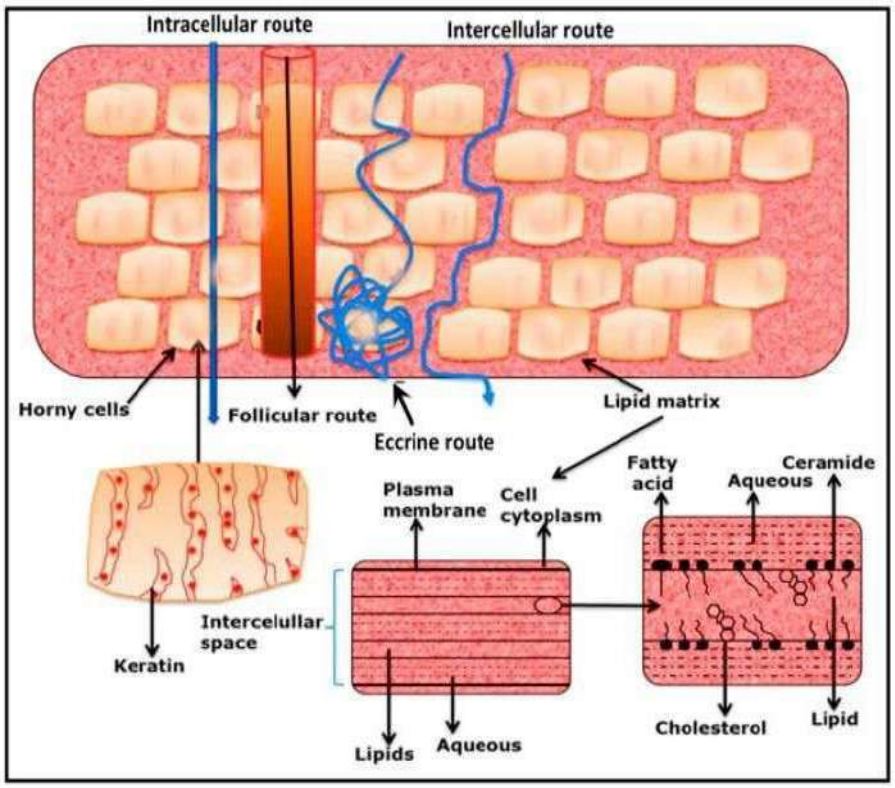

Figure 1: various routes of drug permeation

PERMEATION ENHANCERS:

The skin is considered an attractive route for drug administration because of its accessibility,

noninvasiveness, and ability to provide sustained therapy. The main goal of research over the last few decades has been to create systems that effectively deliver medications into and across the skin. In cases where a drug exhibits good skin permeability, its absorption can be regulated by controlling its release rate from the delivery system. Conversely, for drugs with poor permeability, the incorporation of suitable penetration enhancers is essential to facilitate their passage through the skin.[1] One of the most extensively researched methods for getting around the stratum corneum's natural barrier qualities is penetration enhancement. Although these substances are typically pharmacologically inert, they have the ability to momentarily interact with the stratum corneum's lipid domains, causing reversible fluidization structural disruption. By reducing the resistance of the skin to molecular diffusion, they enhance the transport of therapeutic agents without causing permanent damage to the skin. This approach has enabled the development of more effective transdermal systems capable of delivering a broader range of drugs that would otherwise be restricted by the impermeability of the skin.[12]

Ideal Characteristics of Permeation Enhancers:-

1. They should be pharmacologically inactive, nontoxic, nonirritating, and nonallergenic.
2. It must be compatible with both drugs and formulation excipients.
3. It should not exhibit any pharmacological effects within the body.
4. It need to be cosmetically acceptable for patient compliance.
5. It should be free from odor, taste, and color.
6. Must ensure unidirectional transport, stop the loss of endogenous substances, and make it easier for therapeutic agents to enter the body.
7. They should possess both chemical and physical stability.
8. It must provide a predictable, consistent, and reproducible duration of action.
9. It should exhibit good solvent properties to enhance drug solubility.

1. Physical Enhancers :-

Electrophoresis:

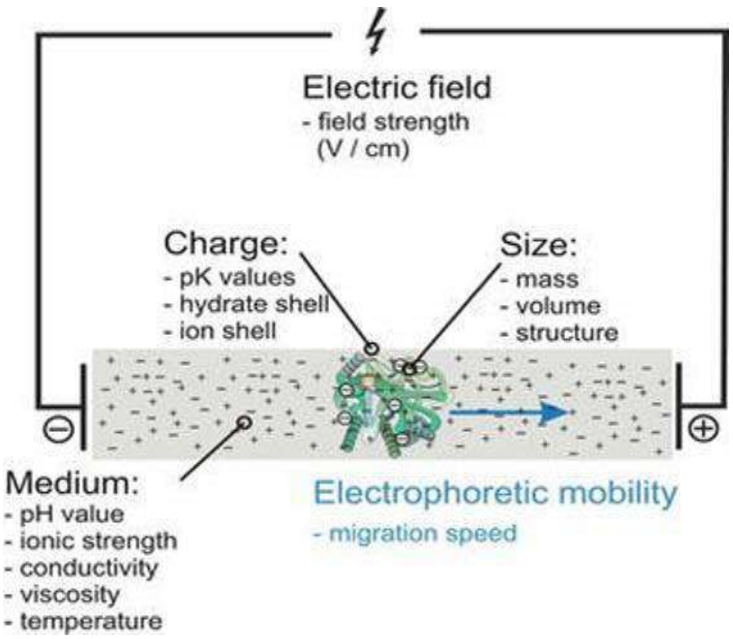

Figure 2: Electrophoresis action in drug solution

Short high-voltage pulses (5–500 V) are used in transdermal drug delivery electrophoresis to temporarily open micropores in the stratum corneum, improving drug permeability in a localized and noninvasive way (fig.2). Consistent drug delivery, possible cellular harm, and unstable drug degradation are among the drawbacks.[14]

Sonophoresis:-

Sonophoresis (high-frequency ultrasound) enhances transdermal drug delivery noninvasively by disrupting stratum corneum lipids**,** generating heat, and inducing cavitation, improving diffusion and patient compliance. Its exact mechanism is still unclear, and further research is needed to optimize device design, standardize protocols, and reduce adverse effects (fig. 3).[15]

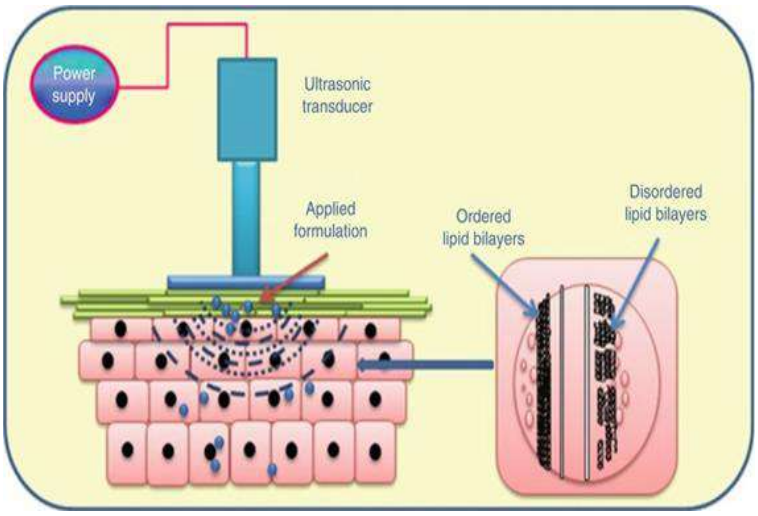

Figure 3: Sonophoresis enhancing permeation

Iontophoresis:-

A mild electrical current is used in iontophoresis, a noninvasive transdermal drug delivery method,

to push ionized drug molecules through the skin (fig.4). It was introduced in 1903 and is usually applied using Ag/AgCl electrodes at 0.2–1 mA/cm². Its efficacy is dependent on electrical parameters (current density, duration) and drug properties (polarity, valency, mobility).[16]

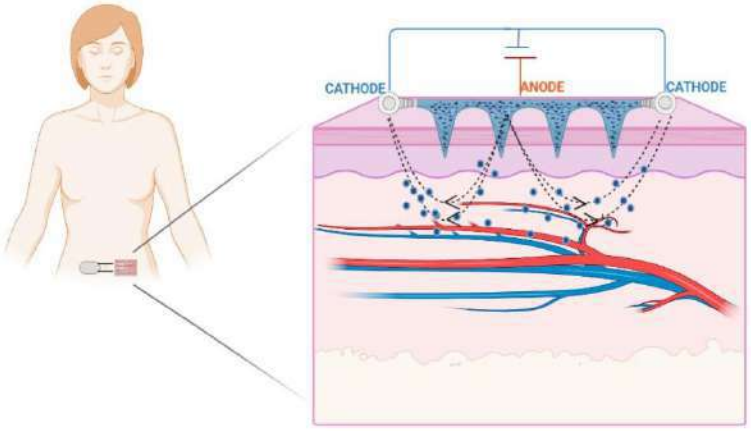

Figure 4: Action of Ionotophoresis

Microneedles:-

By puncturing the stratum corneum with microscopic projections, large molecules can enter the vascular-rich dermis without harming blood capillaries and while still stimulating nerve fibres.[17]

Microneedles are classified on drug delivery system (fig.5):-

- **Solid Microneedles:-** Drugs, such as antihypertensive drugs, are delivered into the dermis by microneedles using a "poke and patch" technique.[18]
- **Coating Microneedle:-** They employ the "coat and poke" strategy.[18]
- **Hollow Microneedles:-** These microneedles use pressure-driven liquid formulations to deliver medications, much like hypodermic needles.[18]
- **Dissolving Microneedle:-** These microneedles are composed of biodegradable substances like sugars or polymers and operate by the "poke and flow" technique.[19]
- **Hollow Microneedles:-** These microneedles use pressure-driven liquid formulations to deliver medications, much like hypodermic needles.[18]

Skin disorders like cancer, warts, dermatitis, and psoriasis, as well as eye disorders like macular degeneration, uveitis, and glaucoma, are treated with microneedles.[21] Small medication dosages, intricate production, storage difficulties, and the possibility of tissue inflammation or needle breakage beneath the skin are some of the limitations.[20]

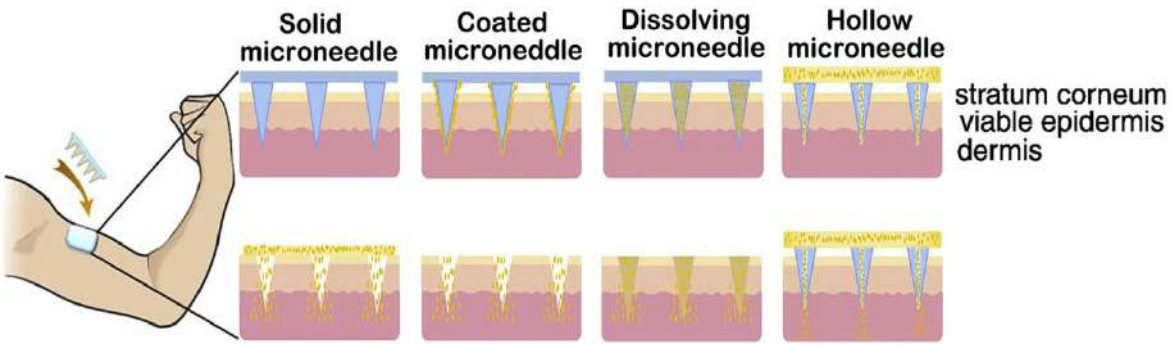

Figure 5: Application of Microneedle

2. **Chemical Enhancers:-**

Water: -

When it comes to transdermal drug delivery, water is a traditional penetration enhancer. In order to facilitate polar permeates, the stratum corneum (SC) contains 15–20% water in two forms: bound water (25–30%) and free/residual water.[22] By improving lipid fluidity, water can improve lipophilic drug delivery and preserve SC elasticity.[23] For instance, shaved mouse skin exhibits a 50-fold increase in permeability, making it an unreliable model for hydration studies. Its effects differ depending on the species.[22]

Alcohols:-

Alcohols, which are also frequently used as co-solvents and water, are the most widely used CPEs in transdermal drug delivery. Alcohols are categorized as short-chain solvents and can remove SC lipids when used at optimal concentrations for prolonged periods of time.[24] Using the human skin sandwich flap model, it was discovered that ethanol improved oestradiol penetration; saturated ethanol solutions showed a greater flux across viable human skin.[25] Approved in 1991, Janssen's Duragesic fentanyl patch continuously delivers fentanyl for 72 hours via a rate-limiting membrane. With drug release proportionate to patch size and alcohol (0.1 ml/10 cm2) as a penetration enhancer, it is available in five strengths (12–100 µg/h).[26] When PEVs were used, the all-skin permeation experiments showed intact PEV penetration through the pig skin and improved delivery of diclofenac (both acid and sodium salt) to and through the skin (especially when compared to the commercial gel). These studies thus show that PEVs are better at enhancing the ex vivo drug transport of diclofenac in both forms.[27]

Sulfoxides:-

The most widely used sulfoxide penetration enhancer is dimethylsulfoxide (DMSO). By changing the intercellular keratin from α helical to β sheet, DMSO generates its enhancement activity.[28] According to studies, 15–30% of applied DMSO metabolizes in vivo while penetrating human skin in vitro in 2 hours. DMSO showed higher penetration for corticosteroids such as hydrocortisone, triamcinolone acetonide, and fluocinolone acetonide when compared to 95% alcohol.[29] According to a bepridil comparison study, only DMSO, at 50% concentration, demonstrated true penetration enhancement among ethanol, DMF, and DMSO. Analogues such as DMF, DMAC, and DCMS were investigated because of the negative effects of DMSO.[30] While DCMS acts reversibly and exhibits a strong enhancement for hydrophilic drugs but a limited effect on hydrophobic ones, DMF irreversibly damages skin membranes.[28]

Azones :-

Azone, a cyclic amide–alkyl sulfoxide derivative, is highly hydrophobic, low-irritant, and soluble in most organic solvents. Used at 1–3%, it enhances permeation by interacting with stratum corneum lipids, likely forming a separate phase in a 'soup spoon' conformation.[31] According to Hadgraft et al., azone can combine with anionic medications to form ion pairs, which will increase penetration.[32] Azone and salicylic acid work in concert to improve permeation and imaging depth, according to studies employing optical coherence tomography(OCT) and diffuse reflectance spectroscopy(DRS).[33] Greater drug retention in the epidermis and dermis was observed upon topical administration of celecoxib with Azone as an enhancer, suggesting a localised effect.[31]

Surfactant:-

By interacting with epidermal proteins, anionic surfactants such as SLS increase the number of anionic sites and improve hydration. SLS increases the water content of the tissue, which promotes skin hydration, according to a DSC study. Longer carbon chains increase surfactant irritation, with the C12 analogue of SLS exhibiting the strongest reaction.[34] SLS was the most successful in comparative studies. A great deal of work has been done in the past few decades to create biosurfactants that are naturally produced by microorganisms when they are cultivated on oily or water-miscible substrates. In transdermal delivery, microbial biosurfactants—primarily glycolipids (such as rhamnolipids, trehalolipids, sophorolipids, and MEL) and lipopeptides (such as surfactin, iturin, and fengycin)—act as permeation enhancers. It has been demonstrated that they enhance the skin transport of medications such as lignans, insulin, hydrocortisone, acyclovir, oestradiol, and lactoferrin.[35]

Terpenes:-

Terpenes (such as 1, 8-cineole, menthol, and menthone), which are classified as GRAS and are thought to be safer natural CPEs, improve both hydrophobic and hydrophilic drug penetration at low concentrations by breaking down hydrogen bonds in the lipid bilayer and stratum corneum intercellular lipids.[35] 1,8-cineole, limonene, D-limonene, carveol, carvone, pulegone, nerolidol, L-menthol, and menthone are examples of common terpene enhancers. Interestingly, 1,8-cineole from eucalyptus oil has been tested to improve 5-fluorouracil and estradiol's penetration through human skin.[36]

3. Nanotechnology methods:-

Nanoemulsion and Microemulsion:-

Oil-in-water, water-in-oil or bicontinuous systems with nanometer-sized droplets stabilised by surfactants are known as Nanoemulsions. In a similar vein, surfactant films stabilise oil-water systems known as microemulsions.[37] Skin irritation caused by high surfactant levels (>20%) in microemulsions has sparked interest in natural or low-surfactant substitutes. For example, nifedipine's transdermal delivery was successfully improved by an oil-in-water microemulsion containing oleic acid and reduced surfactant.[38] All-trans retinoic acid's solubility, stability, and transdermal penetration were improved by a surfactant-free microemulsion containing n-propanol and eucalyptus oil. It demonstrated greater solubility than water or other microemulsions and improved absorption rate.[39]

Ethosomes:-

A particular kind of transferosome known as ethosomes is identified by having higher ethanol content in their makeup. With sinapic acid

penetration of 66.5 µg/cm² compared to 53.2 µg/cm² and 12.3 µg/cm² from transferosomal and plain hydrogels, respectively, ethersomes demonstrated superior transdermal delivery over transferosomes. This is because the vesicle's flexibility and ethanol content allow for deeper stratum corneum penetration.[41]

Liposomes:-

There are two types of glycerophospholipids: natural and synthetic. Natural glycerophospholipids such as phosphatidic acid (PA), phosphatidylethanolamine (PEA), phosphatidylcholine (PC), phosphatidylglycerol (PG), phosphatidylinositol (PI), and phosphatidylserine (PS) are examples.[40] Thin-film hydration, reverse-phase evaporation, solvent injection, detergent removal, dehydration–rehydration, pH jump, colloidal particle hydration, and freeze–thaw are some techniques that can be used to create liposomes. The short half-life, quick clearance, and plasma instability of conventional liposomes have prompted the creation of more sophisticated varieties, including stealth, PEGylated, and ligand-modified liposomes.[41]

Solid lipid Nanoparticles(SLN):-

Aqueous colloidal carriers composed of solid biodegradable lipids are known as solid lipid nanoparticles (SLNs). They have drawn interest because, in contrast to more traditional carriers like emulsions, liposomes, and polymeric particles, they can increase solubility and oral bioavailability.[42] The in-situ penetration of SLN loaded with nebivolol (NBV) and its commercial tablet formulation used to treat hypertension were compared and examined in a study. For this purpose, in-situ permeation studies were conducted using the Single-Pass Intestinal Perfusion (SPIP) method. SLNs alone can be used as a permeation enhancer in oral drug delivery, and PEG-modified SLN can be used to improve oral absorption of NBV. Metoprolol tartrate was employed as a high permeability reference compound in perfusion studies to compare the permeability coefficients of NBV in tablets and pure NBV.[43]

Hybrid approaches:-

A minimally invasive technique for improving the intradermal and transdermal delivery of medications, bioactive compounds, and nanoparticles is ultrasonic treatment (sonophoresis/ phonophoresis). It pushes particles deeper without causing damage by creating cavitation in sweat glands and hair follicles using frequencies higher than 0.7 MHz. It can be used in conjunction with chemical enhancers to improve outcomes and prolongs skin permeability, allowing for stepwise drug or vaccine delivery.[44]

Table 1: Mechanism of Permeation Enhancers

Mechanistic Comparison of Different Permeation Enhancers in Transdermal Drug Delivery Systems (TDDS):

Type of Enhancer	Mechanism of Action	Key Features
Chemical enhancers (e.g., water, alcohol, surfactants, terpenes, azones, sulfoxides)	Improve drug partitioning into the skin, increase skin hydration, and disturb lipid packing in the stratum corneum.	Simple, widely used, may cause irritation with prolonged use
Physical enhancers		
Electrophoresis	Lipid bilayers are broken up by brief, high-voltage pulses, creating temporary pores.	Reversible effect, effective for macromolecules.

Sonophoresis (ultrasound)	Cavitation improves fluid flow through glands and follicles by forming microchannels.	Temporary, non-invasive permeability increase.
Iontophoresis	Drives charged molecules across skin using a low electrical current.	Controlled administration that works well with ionized medications.
Microneedles	Make pores at the micron scale to avoid the stratum corneum.	Direct drug entry is not the best option for antifungal therapy, but it is minimally invasive.
Nanotechnology methods (Nanoemulsion and Microemulsion, liposomes, ethosomes)	Enter through follicular targeting, fusion with skin lipids, and fluidization of stratum corneum lipids.	Enhanced stability, solubility, and controlled release.

CURRENT AND NEXT-GENERATION TECHNOLOGIES: -

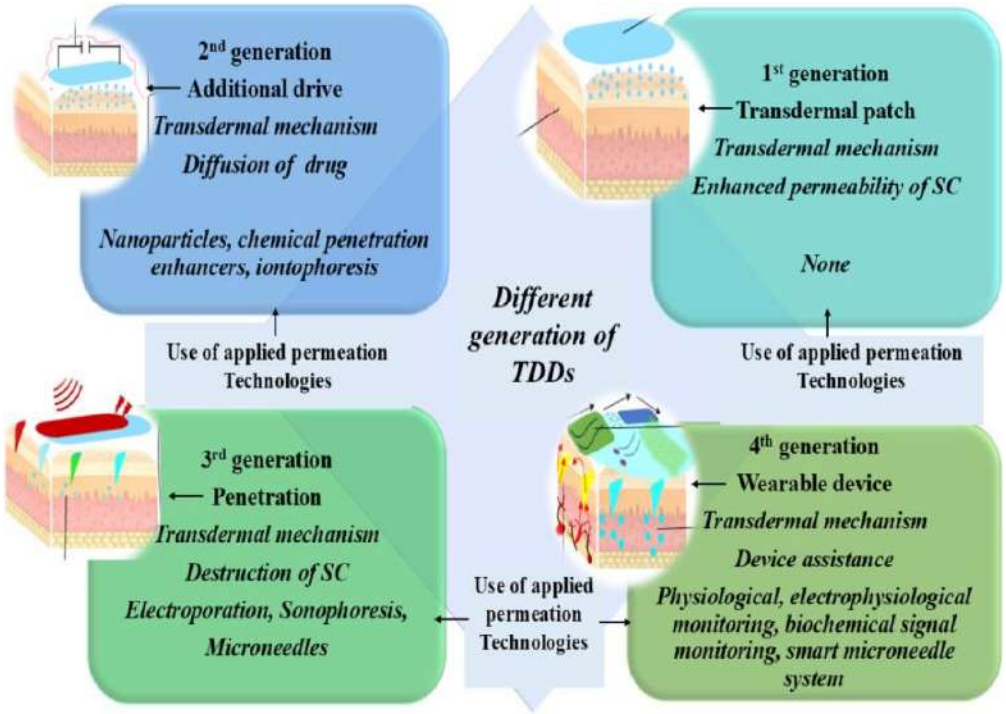

Figure 6: Current and Next-Generation Technologies

Smart hydrogel: -

Smart hydrogels are three-dimensional networks of hydrophilic polymers that change their swelling, permeability, or drug release characteristics in response to external stimuli like pH, temperature, light, magnetic fields, and biomolecule concentration.[45] These materials' ability to adjust to changing environmental conditions allows for programmable release profiles and improves the accuracy of drug delivery.

Example and advancements: -

- Particularly promising for TDDS are chitosan-based smart hydrogels, which show sensitivity to pH, temperature, ion concentration, and other stimuli. Safe and efficient delivery is made possible by their biocompatibility, non-toxicity, and biodegradability.[46]

- Drug adherence can be managed, drug integrity can be preserved, multiple drugs can be delivered, and biosensors can be integrated for real-time feedback using creative hydrogel formulations.[46]

- There are now commercial hydrogel products for transdermal application that provide controlled, prolonged drug release for a variety of medications while reducing side effects and optimizing skin hydration.[47]

Bioinspired Enhancers:-

Bioinspired enhancers in transdermal drug delivery systems (TDDS) are materials and molecules, often mimicking natural structures or biological processes, designed to improve skin permeability, safety, and drug delivery efficacy.[48] In order to interact with the stratum corneum (the skin barrier) without causing undue harm or irritation, bioinspired enhancers use natural mechanisms like lipid structures, adhesive proteins, or enzymatic activities.[35]

Examples in transdermal drug delivery system :-

- Bioinspired Microneedles: These tools increase drug and vaccine delivery while reducing skin trauma by painlessly avoiding the skin barrier by imitating natural structures (such as insect stingers or porcupine quills).[48]

- Biosurfactants: Biosurfactants, which come from microorganisms or plants, work as mild penetration enhancers by interacting with the lipids in the skin to promote drug absorption while preserving biocompatibility.[35]

- Ceramides: By altering the lipid packing density in the skin, modified or natural ceramides that mimic the lipid composition of human skin act as enhancers, increasing the flow of medications through the stratum corneum.[49]

AI –driven formulation optimization:-

AI-driven formulation optimization in transdermal drug delivery systems (TDDS) uses advanced machine learning and computational models to accelerate, personalize, and improve the design of TDDS products for both patient and drug-specific needs.[50]

Key Technologies:-

- Predictive Modeling and Ingredient Selection: Molecular features and skin permeability data are used by AI models such as DNN, ANN, SVM, and ensemble methods to predict appropriate drug molecules and excipients for transdermal delivery.

- Formulation Optimization: For optimal absorption, stability, and skin compatibility, machine learning rapidly optimizes drug-release layers, polymers, and penetration enhancers.

- Personalized Patches: By utilizing patient-specific data to customize patch formulations and delivery profiles, AI makes personalized TDDS possible.

- Smart Patches and Feedback Controls: AI sensors offer automatic drug delivery adjustments based on ongoing feedback and real-time monitoring.

- Stimulation and Prototyping: By simulating drug release, adhesion, microneedle penetration, and in vivo performance, AI modeling tools such as COMSOL and BioSIM reduce development time and expenses.

- Accelerating Regulatory Approval and Clinical Trials: By forecasting stability, adverse effects, and long-term performance, AI speeds up trial design while cutting expenses and time to market.

Through speed, accuracy, and adaptability, AI-driven formulation optimization is revolutionizing TDDS development and offering more sophisticated drug regimens and safer, more effective therapies customized for each patient.[50]

SAFETY, BIOCOMPATIBILITY AND REGULATORY TRENDS:-

Transdermal drug delivery systems (TDDS) now prioritize safety, biocompatibility, and regulatory compliance, particularly as new technologies and permeation enhancers are developed to open up new avenues for skin-based therapies.

Safety and biocompatibility:

- In order to lessen allergies, sensitization, and irritation, modern TDDS employ sophisticated permeation enhancers (hydrogels, nanocarrier, and bioinspired) that have undergone safety testing.[1]

- All TDDS ingredients must be inert, non-toxic, non-irritating, free of contaminants, and stable for prolonged skin contact in order to be considered biocompatible.[1,51]

- With a preference for biodegradable and skin-mimetic ingredients, new TDDS materials (hydrogels, nanocarriers, and polymers) are made to improve penetration while remaining gentle.[51]

Regulatory Trends:

- TDDS are categorized as combination products by regulators such as the US FDA, which mandate adherence to both drug (efficacy, dosing, purity) and device (design, quality) standards.[52]

- In order to comply with regulations, the drug and permeation enhancers must undergo extensive testing, validation, and documentation that addresses stability, dose uniformity, material compatibility, and manufacturing consistency.[52]

- In order to demonstrate efficient drug delivery without impairing barrier function or patient safety, skin-contact materials used in TDDS must pass ISO 10993 biocompatibility and safety tests.[52]

- Smart delivery system adoption, quicker approval for sustainable TDDS, and quick clearance of products with biocompatible, proven enhancers are some recent trends.[52]

- For new enhancers or delivery matrices, manufacturers need to guarantee cleanroom production, validated procedures, safe packaging, and thorough clinical data.[52]

CLINICAL AND TRANSLATIONAL DEVELOPMENTS:-

Table 2: Case study and clinical Outcomes

Technology Area	Case Study Description	Key Outcomes/Benefits	References

Smart hydrogels	A conductive smart hydrogel patch that combines controlled drug release and glucose monitoring for diabetic foot ulcers	Electronic controlled drug release, angiogenesis promotion, antimicrobial activity, and real-time wound monitoring.	53, 54
	VEGF-mimicking peptides in 3D-printed GelMA hydrogels for tissue regeneration	Enhanced cellular growth and adaptable medication release.	54
Bioinspired Enhancers	Hydrogel patches with tetrapeptides and adhesive peptides inspired by mussels for extended skin adherence	Increased biocompatibility, prolonged drug release, and improved tissue adhesion.	53
AI Driven Optimization	AI-based modelling of drug, polymer, and enhancer combinations to quickly choose the best TDDS formulations	Shorter development time, customised patch design, increased effectiveness, and better skin retention.	47

The (table 2) summarizes case studies illustrating recent clinical and translational developments on smart hydrogels, bioinspired enhancers, and AI-driven formulation optimization as emerging approaches in TDDS skin permeation.

FUTURE PERSPECTIVES AND RESEARCH OPPORTUNITIES:-

Table 3: Future Perspectives and Opportunities

Area	Description	Research Opportunities and Trends
Advanced Penetration Enhancers	In order to improve permeation safely, novel chemical and physical enhancers temporarily and reversibly modulate the skin barrier.	New classes of terpenes, amino acid-based enhancers, and fatty acid derivatives; combining physical techniques (microneedles, sonophoresis, and iontophoresis) with chemical enhancers.
Personalized and Precision Medicine	For maximum effectiveness and safety, patch formulations are tailored to each patient's unique skin type, genetics, and disease characteristics.	Personalized TDDS using proteomics and genomics; AI-driven formulation optimization; and smart patches that adjust dosage in real time.
Advanced Carrier Technologies	For better drug stability, targeting, and controlled release, lipid-based systems, microemulsions, polymers, and nanocarriers are optimised.	Investigation of environmentally friendly, biodegradable materials; application of nanotechnology for the delivery of biologics and big molecules
Regulatory and Sustainability Trends	Simplified procedures for approving innovative TDDS, with a greater emphasis on environmental impact, safety, and biocompatibility by regulators.	Standardization of testing for new permeation enhancers; improved post-market surveillance; and the development of green chemistry techniques.
Clinical Translation Expansion	Expansion into novel therapeutic domains, such as cancer immunotherapy, neurological conditions, chronic illnesses, and vaccine delivery.	Comprehensive clinical trials for new TDDS technologies; empirical research; combination treatments with enhanced efficacy.

By improving skin penetration and putting safety and patient-specific medication first, TDDS has the potential to completely transform drug delivery. New treatment options are being made possible by advancements in responsive systems, AI-designed formulations, and smart enhancers. Faster translation from lab to clinic is made possible by regulatory support and sustainable development, which makes TDDS an essential component of future tailored healthcare and targeted treatment solutions (table 3).

CONCLUSION: -

Noninvasiveness, controlled and sustained release, increased bioavailability, and better patient compliance are just a few of the noteworthy benefits that transdermal drug delivery systems (TDDS) offer, solidifying their position as a revolutionary approach to drug administration. The stratum corneum is a formidable barrier that has been successfully overcome by advances in skin permeation enhancers, including chemical agents, physical techniques, smart hydrogels, and bioinspired materials. This has increased the range of drugs that can be treated with TDDS, including biologics and macromolecules.
By enabling quick prediction and improvement of the best drug-excipient combinations suited to each patient's requirements, the incorporation of artificial intelligence-driven formulation optimization has further sped up the development of individualized and effective transdermal therapies. Furthermore, new clinical and translational studies confirm the safety, effectiveness, and usefulness of these cutting-edge TDDS technologies in the treatment of a range of ailments, from vaccine delivery to chronic illnesses. To successfully translate these innovative systems into broad clinical use, strict attention to biocompatibility, safety, and compliance with changing regulatory standards is still essential. Multi-responsive smart delivery platforms, eco-friendly materials, and the smooth integration of digital health technologies should all be investigated further in future studies as they have the potential to establish TDDS as a cutting-edge field in precision medicine and targeted drug delivery.

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