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Exploring the Formulation and Approaches for Transdermal Drug Delivery

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Abstract: Transdermal delivery of drugs has become another useful alternative to the traditional dosage modes of oral and injectable doses. Most orally administered drugs are degraded in the gastrointestinal tract or subjected in large amounts to first-pass liver metabolism leading to poor efficacy. Drug delivery through the skin to the patient can be used to avoid these restrictions and enhance patient compliance and adherence to treatment. Nevertheless, good delivery of drugs through the skin is still difficult because of stratum corneum that is a potent barrier against external substances. The review addresses the basic gist of transdermal drug delivery such as the structural arrangement of the skin and the various routes that the drug can permeate. Traditional dosage formulations of patches, creams, gels, and sprays are also discussed and their benefits on practice and restrictions to formulation. The recent developments that include nanocarriers, vesicular systems, nanoemulsions, nanogels, and microneedle technology are also reported as an encouraging strategy to increase permeation and obtain controlled drug release. Taken together, all these advances indicate that transdermal systems have a potential to enhance therapeutic effects and to increase the number of drugs that can be administered through non-invasive methods.

Keywords: *Trandermal, Drug Delivery, Patches, Stratum Corneum, Nanoemulsions.*

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I. INTRODUCTION

Existing methods of drug administration like the oral and the parenteral administration are popular methods of drug administration in clinical practice. The routes however have numerous limitations such as they have large hepatic first-pass metabolism, the drugs can be degraded in the gastrointestinal tracts and there is little control over distribution of the drugs in the body. Due to such difficulties, alternative delivery methods have also been examined to enhance the effectiveness of therapy and adherence to therapy by patients. One of such alternative strategies is transdermal drug delivery (TDD). In this path, drugs enter the stratum corneum and pass to the epidermal and dermal layers below and create either a local or systemic effect. The initial research studies revealed that stratum corneum was the major barrier that controlled transepidermal water loss and restricted the penetration of extraneous materials (He J, 2023).

Transdermal administration has a number of benefits compared to oral administration. It does not enter the bloodstream and is metabolized in the liver during the first pass phase, allows improving the dose schedule and patient adherence, as well as possibly reducing overall adverse events (Xu Q Z. X., 2024). Most orally administered drugs are affected by enzymes or rapidly metabolised and therefore their bioavailability decreases. Also, certain drugs are not stable in acidic gastrointestinal environments and that restricts further their efficacy (Zhang J, 2025).

In order to enter systemic circulation via the skin, a drug needs to traverse several layers such as the epidermis, radical dermis and hypodermis. The most important of these is the stratum corneum which serves as the primary barrier. It is a layer of about 15- 20 μm and it is composed of non-viable keratinized cells, embedded in a structural lipid matrix that limits the diffusion of most molecules (Zhang J B. D., 2025). Consequently, passive permeation can only occur to compounds that have the right physicochemical properties.

Transdermal drug delivery systems are created to deliver sustained and controlled release and reduce the drawbacks of oral and injectable routes (Xu X, 2019). There are a few drugs, despite their advantageous properties, which may be administered via intact skin due to the high barrier properties of stratum corneum. Molecular weight, lipophilicity, solubility, and melting point are crucial drug-related parameters that affect the permeation and thus constitute the significant formulation issues (Ahmed KS, 2020).

Transdermal route is especially beneficial under conditions when the oral administration is inapplicable e.g. vomiting or diarrhea is the case in the sick, as well as, in cases of unconsciousness (Karande P, 2009). It has also been

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thought to be applicable to drugs (that are classified under Biopharmaceutical Classification System into classes II and IV) whereby oral absorption is hindered by poor solubility or permeability (Singh T, 2024). These developments in regulation and effective formulation design, safety assessment and long-acting delivery system have only increased interest in this method.

A perfect combination of transdermal system must be easy to put on and be able to administer the therapeutic dose of the drug at a steady rate in the long run. The stratum corneum is a lipid-based framework, which is commonly referred to as a brick-and-mortar organization of corneocytes and intercellular lipids, and passive diffusion allows unionized molecules below 500 Da in molecular weight and moderate lipophilicity (log P 13).

Even though the conventional adhesive-based systems have been shown to be useful in the delivery of new drugs, they are only useful only to those molecules which satisfy the particular permeability needs. Inactive components of formulation can also have an undesirable effect in some instances, which promotes the necessity of better approaches. As a result, continuous studies are being pursued under the technologies of transdermal advancement that are aimed at improving the level of permeation, overcoming the stratum corneum barrier, and reaching therapeutic drug levels in target tissues (Liu L, 2023).

II. ANATOMICAL STRUCTURE OF THE SKIN

Skin is considered the largest body organ of human body and occupies almost 10 percent of the entire body weight. It acts as a shielding interface in between the internal physiological environment and external environment. Despite the fact that the skin offers a tremendously high surface area to apply drugs to, there is a limitation of effective penetration through the skin layers, which is mainly caused by the stratum corneum (SC) layer that forms the major barrier to transdermal drug delivery. Anatomically, the skin consists of three major layers that include the epidermis, dermis, and hypodermis (Jimenez-Sanchez M, 2025).

In addition to the barrier activity, the skin has a number of other physician functions, such as immune protection, sensory, and protection against mechanical and microbial injury. The intricate structure of the skin constantly controls environmental pressures, variations in temperature and exposure to pathogens. Though skin is a well-experted medium of drug delivery, it is highly structured with tremendous challenges that demand a sophisticated formulation of approaches in order to transport it to the skin (Abd E, 2016).

The epidermis constitutes the outermost layer which is subdivided to form the non-viable and viable regions. The non-viable is stratum corneum, whereas the viable epidermis comprises of separate layers, such as stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale (Phatale V, 2022). The viable epidermis contains cells which are metabolically active and which can be involved in the metabolism of drugs, drug-binding interactions and immune reactions.

Below the epidermis is the dermis which consists of connective tissue, blood vessels, lymphatic and nerve endings. This layer is very important in thermoregulation and nutrient provision. The regulation of body temperature is achieved by the use of processes that include vasodilation, vasoconstriction, and eccrine sweat release that enables the skin to react dynamically to the changes in the environment (McKenna, 2024).

The stratum corneum forms the weakest point in transdermal delivery. It measures about 1020 mm in thickness and can be readily characterised on the basis of the brick-and-mortar model. Corneocytes, as the bricks, and intercellular lipid matrix, as the mortar, are used in this analogy. This is a close-knit lipid, which limits water loss through the trans-epidermis and affects the entry of foreign substances, such as drug substances. Beneath this layer, there is the viable epidermis, which harbors keratinocytes and specialized cells, which include melanocytes, Merkel cells, and Langerhans cells, which are associated with pigmentation, sensual, and immune defense (AL-Japairai KAS, 2020).

Due to this multilayered structure and lipid-enriched barrier, transdermal drug delivery is a complex process that should be carefully considered in relation to drugs and carrier types. Recalling of the anatomy and physiology of the skin is therefore crucial in coming up with effective safe transdermal systems.

- *Mechanism of Transdermal Drug Delivery*

Transportation of drug through the skin is a process that follows specific permeation routes which in totality define how effective the transdermal drug delivery will be. These routes are generally divided into trans-epidermal route and trans-appendageal route. The trans-epidermal route is further split into intracellular and intercellular routes, which all entail the transit by the stratum corneum and passing through the underlying epidermal layers.

Drug molecules go through the corneocytes in the intracellular pathway. Repeated division is necessary between domains of keratin-rich cells and the lipids which are surrounding. Since corneocytes have thick keratin and low water content of water, this pathway presents a great resistance to drug delivery. Consequently, the intracellular pathway through which diffusion takes place is usually limited and ineffective to a wide range of compounds.

On the other hand, intercellular pathway is the diffusion of drug between the lipid matrix that lies between the corneocytes. In this case, the molecules do not penetrate the cell structures instead, they are steered around them. The pathway may avoid cellular obstacles, but in this way, hydrophilic compounds will be challenged by the fact that the intercellular lipids are of a predominantly lipophilic character. The polarity of drugs and their lipid affinity, therefore, have a strong impact on diffusion by this pathway.

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There is an alternative drug entry mechanism, which is the trans-appendageal pathway. This path is by way of penetration through skin appendices, e.g. hair follicles and sweat glands. Although they contribute a small proportion of the total skin area, they could act as point of entry, especially when those huge, solid, or particulate drug carriers are used. The nanocarrier-based systems may also build up in the hair follicles which can become drug reservoirs and allow the gradual release with time (Guo Z, 2025).

The pathway does not ensure good permeation as it is also the physicochemical properties of the drug that affect good permeation and the carrier system design. The penetration efficiency depends on such parameters as the particle size, surface charge, flexibility and deformability. Deformable and flexible nanocarriers have proven to move through small intercellular lipid channels better than hard structures. By comparison, rigid nanoparticles tend to depend more on the appendageal penetration, restricting their dispersion due to population density of the skin appendages that are sparse (Guo Z, 2025).

In general, the overall interaction between skin structure, drug characteristics, as well as formulation design controls the process of transdermal drug permeation. A clear knowledge of such mechanisms is needed in order to optimize drug delivery across the skin barrier to reach consistent therapeutic performance. Figure 1 depicts the different pathways by which penetration takes place by transdermal route.

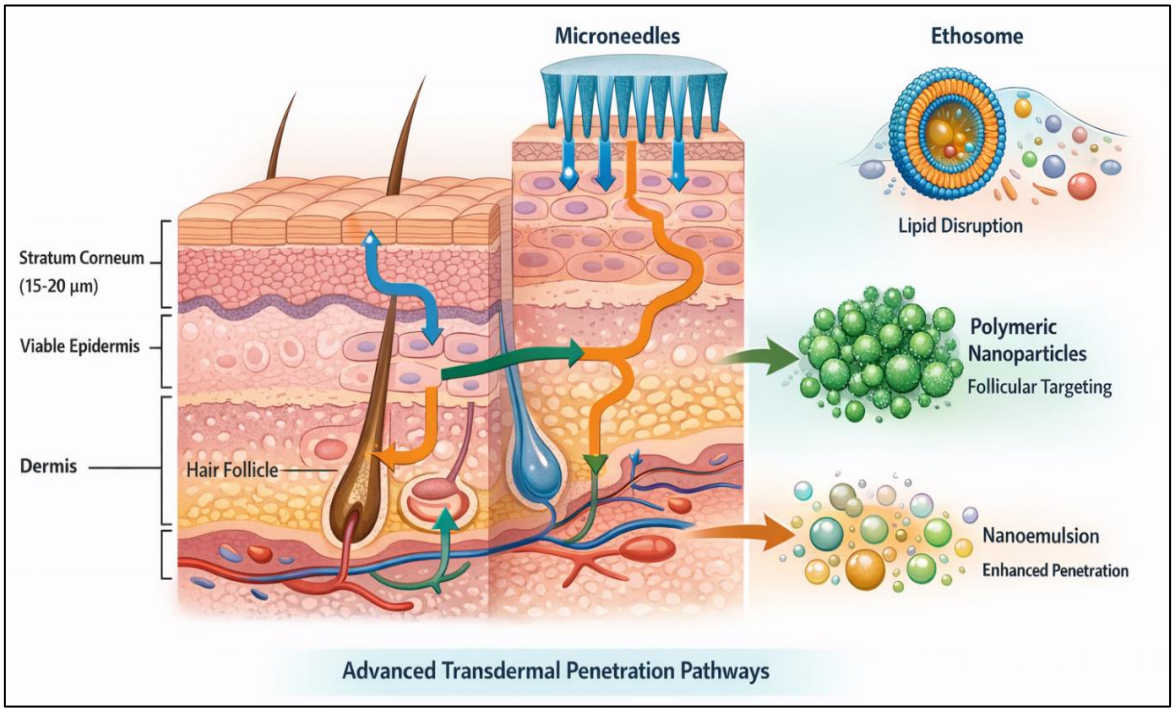

Fig 1 Various Transdermal Penetration Pathways

➢ *Factor Affecting TDDs*

Performance of transdermal drug delivery system is affected by various variables in a manner that is interdependent. Of them, physicochemical properties of the drug are of great significance in deciding the degree of skin permeation. The most significant parameters that influence the diffusion across the stratum corneum are molecular weight. Overall, the molecules with smaller molecular weights are much more mobile across the layers of the skin, but larger molecules are faced with a lot of resistance. In the case of passive permeation, the drugs having a molecular weight less than about 500 Da can be taken as more suitable candidates.

Drug diffusivity of the formulation as well as the skin tissues also contributes significantly in regulating the release behavior. Smaller molecules are more prone to diffusing at a faster rate across polymeric systems and biological membranes leading to high transdermal flux. High molecular weight compounds on the other hand tend to have slower diffusion rates and lower permeation. The significant contact between formulation and skin is another element of the assurance of the successful absorption of drugs through the system of delivery, which is the enhancement of the area of the developed system (Sa'adon S, 2019).

Lipophilicity has a negative effect on drug transport along with other quantities of physicochemical properties such as aqueous solubility, melting point, and degree of ionization, which greatly contribute to drug transport. The average lipophilic molecules tend to be better able to be incorporated in the lipid-rich stratum corneum. Drugs with great hydrophilicity also exhibit poor permeation, therefore, due to low lipid affinity and overly lipophilic compounds are likely to become entrapped in the skin layers and never enter the systemic circulation. Also, compound drugs that are highly melting may exhibit poor solubility in the formulation as well as in the skin lipids, decreasing the total high permeation rate.

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The effectiveness of transdermal systems is also dependent on the components of the formulation. The choice of polymers, adhesives, excipients and penetration enhancers directly play off on the kinetics of drug release as well as drug skin permeability. Appropriate polymeric matrices are able to give structural integrity, as well as control of drug release. Penetration enhancers can cause temporary changes in lipid organization as well as in the stratum corneum, allowing drugs to travel over the barrier more readily.

Other factors such as the skin contribute to more variability in transdermal absorption. The skin depth, level of hydration, age, anatomical location of application, and the general physiological state are some of the parameters affecting drug permeation. Swelling of stratum corneum and increase in intercellular spaces are some of the reasons that result in the increased permeability of the hydrated skin. Variations in the lipid formation and the topography of the skin also generate more differences in the rate of the absorption in the various parts of the body.

All in all, transdermal delivery is reliant on a perfect coordination of the drug characteristics, formulation formulations, and the skin biology. The thorough assessment of all these parameters is extremely important in order to optimize the drug flux and provide uniform therapeutic effect.

III. TRANSDERMAL FORMULATION

➢ *Transdermal Patch*

Some of the clinical benefits indicated by transdermal drug delivery systems include sustained-release of drugs, better adherence by the patient, decreased gastrointestinal side effects and hepatic bypass. Regardless of such advantages, few drugs can be used in such a delivery method as transdermal due to the restrictive nature of the skin (Khatik R, 2025).

A transdermal patch is a medicated system that incorporates an active pharmaceutical substance to enter into the systemic circulation of the skin in a steady rate. Patches are the most popular transdermal dosage form among the existing ones because of their simplicity, convenience, and non-invasiveness. Having been applied, they may be used to release drugs continuously over a long duration lasting between hours and a few days. In case of side effects, the therapy may be discontinued immediately by taking the patch off.

The primary mode of diffusion, caused by a concentration gradient between the formulation and the skin surface, is the primary mode of drug transport through a transdermal patch. In order to ensure a sustained delivery, a fairly high drug load is normally incorporated in the patches. Another that was a successful trial of this method was the nitroglycerin patch that was launched in 1985 and proved the clinical viability of controlled transdermal therapy (Won Fen Wong, 2023).

Transdermal patches have the potential to have better bioavailability than oral dosage forms, as gastrointestinal degradation and hepatic metabolism can be avoided in the former. The concentration of the drug in the system, the area of application, and the skin permeability properties in the location of the placement are among the factors that influence rate of drug release (Andrei Niculae, 2024). The patches are designed structurally; the majority of them have several functional layers that comprise an impermeable base, a primary reservoir or matrix with drugs, an adhesive layer to assure contact with the skin, and a protective coating that is washed off before application (Sharma PK, 2018).

Transdermal patches are especially beneficial where the patient has difficulty in swallowing or he or she is not able to take oral medication. Patches are a cleaner and more convenient form of administration (compared to creams or ointments, which can be greasy and less aesthetically pleasing) (Nalamachu S, 2020). Moreover, drugs last longer when released continuously through patches leading to a relative stability of drug levels in the plasma with minimal variability.

Diffusion based on a polymeric matrix or rate controlling membrane can be used to control the release of drugs based on the design of the patches. The patches can be used to deliver drugs on intact and hairless skin when administered properly, providing a consistent delivery of the drug with low degrees of fluctuations in the systemic levels (Punnel LC, 2021).

The clinical evidence reported demonstrates that transdermal formulations are typically better tolerated than oral therapy and in some examples, can achieve better results than other non-oral delivery methods (Khoury R, 2018). Moreover, the transdermal systems have also demonstrated a good potential in children and those who experience anxiety when it comes to needles. The mentioned qualities have also promoted the study of the applications of self-administered vaccines and home-based immunotherapy (Zasshi, 2019).

On the basis of the structural arrangement, the transdermal patches are more broadly divided into two categories, namely, matrix systems and reservoir systems. The drug is uniformly spread among the layers of polymer in matrix designs. In the reservoir designs, the medicine is put in a separate section and it is discharged via a semi-permeable membrane (Ghosh M, 2025).

➢ *Matrix System*

Transdermal patches that are in the form of matrix are made by percolation or dissolution of the active pharmaceutical ingredient into a polymeric framework. Under this design the polymer is the main constituent that influences the release of the drug. The adhesive layer can be independent or embedded in the drug-bearing matrix depending on the strategy of formulation.

In case of a fully dissolved drug in the polymer, the system results in a homogeneous matrix. When the drug is not dissolved, but it exists in the form of solid particles, then the matrix is said to be heterogeneous. The general rate of release, in both types, is determined by the diffusion of the drug across

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the polymer network. The composition of the polymer, solubility of the drug in the matrix and the thickness of the system all have an effect on the release kinetics.

In matrix systems, pressure-sensitive adhesive is commonly employed to ensure the constant contact of the skin and allow diffusion of drugs. The drug is included directly in some formulations in the form of an adhesive in a drug-adhesive complex. This system eases system architecture and minimizes the use of other structural components.

Typically, matrix patches are prepared by solvent casting techniques wherein the solvent can be distributed uniformly, as well as, controlled film thickness. Many types of polymers and adhesive materials were tested in this respect and they are polyacrylate copolymer (acrylates), polysiloxane (silicones), polyisobutylene, styrene -isoprene -styrene and styrene-block (ethylene -co-butylene)-block-styrene. The choice of such materials is influenced by the compatibility degree with the drug, the mechanical stability, adhesive performance, and the potential to control the drug release (Karve T, 2024).

The relative simplicity of the structure in comparison to the reservoir-based designs is also one of the benefits of the matrix systems. The dosage is also evenly distributed throughout the polymer thus sites chances of dumping the drug. Nonetheless, release of drugs through the systems of matrices can be slowed or fast based on the length of diffusion path, polymer properties, and interactions between drugs and polymers. Thus, it entails that the formulation parameters need to be optimised carefully to obtain a stable and predictable therapeutic performance.

- *Reservoir System*

The reservoir-type transdermal systems have been created to achieve an accurate and controlled drug release period. According to this arrangement, the drug is contained in a separate reservoir compartment that can hold the drug in liquid, gel, or semi solid state. This reservoir will be placed between an impermeable back-layer and semi-permeable membrane which will control the rate of diffusion of drugs to the skin.

The rate controlling membrane is central in ensuring homogeneity in drug delivery. Near-constant release kinetics can be obtained by proper choice of membrane material and thickness. This controlled mode of delivery contributes to the reduction of fluctuations of plasma drug levels and aids to maintain therapeutic activity.

The reservoir systems come in handy especially in chronic diseases that need a long and constant medication level. Constant infusion reduces the hepatic changes in peaks and troughs that can be a result of traditional dosing patterns. This might lead to reduced dose-related adverse effects and the ability of patients to have better symptom control.

The other useful benefit of reservoir systems is that they can be adjusted to fit the needs of the clinical drug release. Drug flux can be altered by altering the composition of the reservoir or the properties of membranes to fulfill certain therapeutic needs. This is flexible and improves patient compliance because it endorses personalized treatment plans (Karthikeyan E, 2024).

But, reservoir systems must be manufactured carefully. Any flaw in the rate controlling membrane can lead to inadvertent fast release of the drug, which is otherwise known as dose dumping. As such, quality assurance needs to be very strict in order to provide safety, consistency, and reliability of such systems.

In general, reservoir-type patches have good delivery of drugs in a sustainable fashion though proper formulation structure and production control should be taken to ensure safety in drug therapy.

- *Ointment and Creams*

Semi-solid dosage forms of topical and transdermal administration have become a useful alternative to oral and injectable routes especially in the treatment of local therapeutic and chronic effects. Systems of passive delivery based on patches, gels, creams, ointments, and sprays are highly used in treating dermatology and transdermal. The effectiveness of these systems in general does not only rely on how the formulation vehicle is made but also the resistance provided by the skin barrier (Matharoo NS, 2023).

Dermal applications Creams and ointments are widely used in dermal applications because of their quickness to use and acceptability by the patient. Recipes that include the elements of hydrophilic action and humectants are also commonly applied to find the solutions to issues linked with dryness of skin, including mild to moderate xerosa cutis. These formulations can increase skin hydration and flexibility of the stratum corneum which can indirectly increase drug permeation (Augustin M, 2025).

Creams are usually a type of biphasic system where two immiscible phases are present where the one phase is suspended through the other. Based on composition, they can be in form of oil-in-water and water-in-oil emulsions. This structural design enables the use of a structure in which both lipophilic and hydrophilic drugs can be accommodated in the creams. Besides their therapeutic use, the cremes are, as a rule, aesthetically good-looking, and such a definition also leads to improved patient compliance (Simoes A, 2019).

Ways in which ointments and creams differ are that the former is normally more hydrophobic and offers an occlusive property on the skin surface. This occlusiveness has the ability to enhance the skin hydration and even enhance drug absorption. Nevertheless, the patient may not like ointments because they are greasy.

To ensure the most positive therapy outcome, semi-solid preparations should reach adequate drug permeation without exercising predictable drug release in the skin layers. The drug is affected by drug properties, there is an interaction between the drug and skin, and compatibility between the

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formulation components and the biological tissues (Simoes A V., 2018).

The success of transdermal delivery using creams and ointments is a result of interacting factors which include, but are not limited to, physicochemical properties of the drug, interactions between the formulation component and skin lipids, and structural integrity of the formulation. Such a combination of these parameters ultimately regulates the drug diffusion across the skin barrier (Jin X, 2022).

- *Gels*

Gel-based formulations have been extensively explored as controlled release and transdermal drugs delivery agents because they have good application characteristics and release capabilities. One of these systems, in situ gels, are an advanced technology whereby formulation is first placed down as a liquid and then gels after being placed in physiological environments. The sol-gel change is dependent on environmental factors, which include temperature, change in pH, ionic concentration, enzyme action, or any other external condition.

The sol-gel transition process enables the formulation to stay at the point of application at a longer time to generate drug residence and assist in prolonged release. Gel formation can be caused by different factors such as temperature variation, pH variation and exposure to ultraviolet light, presence of ions, or electrical influence. After gelation the created network is capable of retaining the drug and enhancing its therapy (Kurniawansyah IS, 2023).

Depending on the purpose of the application in situ gel system can be prepared either via hydrophilic or hydrophobic polymers. These systems belong to particular rheological properties that include elasticity and rigidity which affect the spreadability and retention on skin surface. Gels are usually formed by a mixture of a solvent usually purified water and a gelling material which is usually a polymeric network. Some of the gelling agents used include synthetic polymers, carbomers, and natural polymers, including xanthan gum (Rathore PN, 2025).

Gel formulations have a number of benefits in transdermal therapy. They tend to be non-greasy, non-sticky, being easy to use and are not rejected by patients. Their semi solid form provides a uniform distribution of drugs and a better contact point to the skin surface. Also, the gels can be designed to have the ability to regulate drug delivery and, in that way, improve therapeutic performances and preserve the stability of the formulations.

Through these characteristics, gel-based systems still elicit a great deal of research attention in the area of creating new transdermal drug delivery systems.

- *Spray*

The use of Transdermal spray systems has come up as an alternative that can be used as alternative to traditional dosage forms; patches, Gels and ointments. Such systems are worked to be easy and convenient in drugs application and yet effective in transdermal delivery. Sprays provide flexibility of the dosing and enhance user comfort compared to the conventional semi-solid or adhesive systems.

An average transdermal spray formulation has volatile solvents that are evaporated very quickly after they are left on the skin. After the evaporating of the solvent, a thin film of the drug is left on the corporate skin. This movie enables the drug to be in close contact with the stratum corneum thereby promoting drug diffusion without the need to apply the drug manually. This also enhances patient convenience by the fact that the sprays dry very fast and the fact that there is no residue left on the hands (Mandal UK, 2016).

Sprays do not produce a significant raise in skin hydration, as is produced by occlusive systems by prolonged coverage. This feature can minimize the possible risk of extreme irritation that might be experienced with some adhesive patches or occlusive ointments. Moreover, the dosage may be further altered by simply changing the amount of spray actuations during administration, which means that there is flexibility in the drug administration without having to reformulate the product.

Due to their convenient format, fast drying nature and flexible dosing ability, transdermal sprays are an encouraging system to utilize both in the short-term and the long-term treatment of illness. Their application in formulation design can be further enlarged in the future in the area of transdermal drug, which can contribute to their clinical applications.

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➢ *Advanced Transdermal Drug Delivery Strategies to Overcome Stratum Corneum Barrier*

Table 1 Advanced Transdermal Drug Delivery Strategies to Overcome Stratum Corneum Barrier

Strategy / Technology	Barrier-Overcoming Mechanism	Key Advantages	Limitations	Representative Recent References
Hydrogel-forming microneedles	Swell after insertion, forming aqueous microchannels for sustained diffusion ("poke-and-release")	High drug loading, controlled release, no polymer residue	Requires precise cross-linking control	Donnelly RF et al., 2023; Vora LK et al., 2023; Wang J et al., 2022
Elastic lipid vesicles (Transfersomes)	Extreme deformability enables squeezing through SC lipid channels	Enhanced penetration of macromolecules, systemic delivery	Stability issues	Patel SK et al., 2024; Chen RP et al., 2022
Ethosomes	Ethanol disrupts SC lipids + increases vesicle flexibility	Deep skin penetration, suitable for hydrophilic & lipophilic drugs	Skin irritation at high ethanol %	Dahri M et al., 2023; Bakhrushina EO et al., 2025
Nanoemulsion-based TDDS	Reduced droplet size increases surface area and drug thermodynamic activity	High bioavailability, good physical stability	Surfactant-related toxicity	Preeti et al., 2023; Sah MK et al., 2023
Nanogels	Swellable polymeric network enables sustained release & stimuli responsiveness	High encapsulation efficiency, controlled release	Complex synthesis	Mastella P et al., 2024; Manimaran V et al., 2023
Physical enhancement (iontophoresis MNs)	Electrical force + microchannels + synergistically enhance permeation	Suitable for peptides & proteins	Device dependency	Bakhrushina EO et al., 2025; Guo Z et al., 2025

IV. NOVEL TRANSDERMAL SYSTEM

➢ *Nano-Based Systems*

The use of nanotechnology in transdermal drug delivery has greatly increased the potential to solve the restrictions on the skin barriers. The nano-scale systems are generated through either reducing the size of the drug particles to nano-meter sizing or through the use of the drugs to create system engineered nano-carriers that enhance their stability and penetration. These systems are designed to improve the permeation across the stratum corneum besides facilitating the regulated and slow release of the therapeutic agents (Guo Z, 2025).

Nanoparticles have also elicited a lot of interest as they can enhance absorption of drugs through the skin and their efficacy on a long-term basis. The smaller the size of the particles, the greater surface area created and thus the drug can interact with the skin layers. Nano-formulations also solve the limitation with solubility especially where the drug being used is hydrophobic and thus presents poor diffusion across the biological membranes.

Some hydrophobic molecules like photosensitizers like phthalocyanines and chlorins are prone to aggregation upon physiological conditions and this limits their therapeutic properties. Conversely, hydrophilic medications can have low lipid affinity to the skin layers that are rich in lipids. Nanocarrier platforms like liposomes offer an environment that has the potential to carry both lipophilic and hydrophilic molecules, hence enhancing the stability of the formulations and distribution of the drugs (Guo Z, 2025).

The parameters can be altered (change in particle size, surface charge, carrier composition) to make nano-based systems suitable to increase skin retention, enhance bioavailability, and mitigate systemic toxicity. It is these benefits that have made nanotechnology a significant means of the development of transdermal treatment therapies.

➢ *Nanoemulsion (NE)*

An emulsion is a dispersed system where an immiscible liquid is carried throughout another under the aid of surface-active agents. These amphiphilic molecules bear a hydrophilic and lipophilic part and therefore can stabilize the interface of the two phases. In standard emulsions, post-

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application instability like phase separation can take place. Nevertheless, in case droplet size is minimized to the nanometers, increased kinetic stability can be obtained (Portugal I, 2021).

Nanoemulsions are dispensable entities whose size of droplets usually ranges within the range of 20-200 nm. Depending on how the formulation is designed, they can either be oil-in-water or water-in-oil systems. Since nanoemulsions are characterized by a small size of droplets, they appear thin or colorless and achieve a greater physical stability in contrast to coarse emulsions. They are not thermodynamically stable systems but have the ability to resist aggregation, flocculation and creaming over a long time (Preeti, 2023).

Nanodispersion in nanoemulsions is considered one of the greatest benefits as nanosized droplets increase surface area of the droplets considerably. It is a property that increases the solubilization of drug and improves thermodynamic activity at the interface with the skin, thus increasing the permeation. Nanoemulsions are also found to have desirable zeta potential and stability parameters and contributes in enhancing performance in transdermal application. Stability can vary with periods ranging between several hours to several years depending on the composition and storing conditions (Ujilestari T, 2023).

Due to the tendencies to entrap and shield lipophilic bioactive compounds, nanoemulsions have been extensively studied in pharmaceutical, cosmetic, and biotechnological spheres. They are not only used in the delivery of drugs but have also been applied in food and nutraceutical sectors (Ho TM, 2022).

High-energy or low-energy can be used to prepare nanoemulsions. The mechanical devices that are used in high energy procedures include high-pressure homogenizers, microfluidizers, and ultrasonica systems. The physicochemical processes, that is, phase inversion temperature methods or self-nanoemulsification techniques, are used as a low-energy method (Sah MK, 2023; Kumar M, 2019). The choice of method used in the preparation process is determined by the size of droplets, formulation stability, and scale.

Because of their increased permeation capacity, greater drug solubilization and good stability profile, nanoemulsions are still under investigation as efficient agent in new demand transdermal drug delivery.

- *Nanogels*

Nanogels Nanogels are made of polymeric networks which are cross-linked on the nanoscale and are stable in structure to contain a substantial amount of water or biological fluid. They are ideal vectors to entrap drugs and deliver it in a controlled manner due to their three-dimensional structure and size; they can also be used as vectors to carry low-sized particles. Nanogels have a high surface area and tunable characteristics so that they are becoming highly studied in terms of advanced drug delivery (Manimaran V, 2023).

Such systems can either be made out of synthetic polymers, natural polymers or a mix of both. Cross-linking can be due to covalent bond, but can also be as a result of physical forces like electrostatic bonds and even hydrophobic bonds. The average size of nanogels is about 10 to 100 nm, and this nanoscale size makes nanogels more effective in interacting with biological tissues as well as effective in loading drugs (Vashist A, 2023).

Another remarkable property of nanogels is that they respond to the environmental stimuli. Their swelling can be affected by changes in pH and temperature or ionic strength and can affect the kinetics of drug release. It enables long-term or controlled release of drugs to the body based upon particular physiological realities. Also, the encapsulated drugs are safe because of the protection of the polymer network structure by the interpenetrating network, which minimizes the untimely degradation process and enhances the stability of therapeutic agents (Mastella P, 2024; Wu Y, 2023).

Nanogels have found application in various administration pathways, which have been oral, nasal, pulmonary, ocular, and transdermal. They are also flexible and injectable, which additionally expands their possible uses. Nanogels can also be used to improve the retention of drugs in the skin in transdermal systems, but also to facilitate the diffusion of the drug into the body through the biological barriers.

There are two main strategies that are followed in the preparation of nanogels. The first entails physical assembly of interacting polymers with non covalent interactions. The second technique involves the polymerization reactions that are undertaken in the nonhomogenous environment in order to create cross-linking networks. The monomer composition, cross-link density, reaction temperature, initiator concentration, and reaction time are important parameters that influence the final physicochemical properties, such as particle size, swelling capacity, and drug release behaviour (Rabiee N, 2019).

Due to their versatile characteristics in modifying properties, capacity to carry a great amount of drugs, and stimulus-sensitive properties, nanogels represent a flexible platform in the establishment of improved transdermal drug delivery systems.

- *Vesicular System*

Traditional topical and transdermal formulations may often face certain limitations, such as insufficient penetration past the skin barrier, elimination of the drug from site of application at a rapid rate and difficulty achieving sustained therapeutic concentrations. To overcome these problems, vesicular drug delivery systems have been developed as new carriers that are able to enhance the drug transport through the skin. These systems are typically made with lipid-based nanoscale vesicles that are used to promote higher drug retention and a controlled release (Abu Lila AS, 2025).

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Vesicular carriers based on nanotechnology have shown potential to enhance the outcome of therapies with the lowest possible systemic exposure. By packaging medications in lipid bilayers or aqueous cores, these systems are able to alter the distribution of medications and improve localization in the target location. In addition to the fact that some vesicular platforms have investigated transdermal and topical delivery, some have investigated intranasal administration and enhanced transport across biological barriers such as the blood-brain barrier (Sayyed ME, 2025; Szkudlarek J, 2026).

Elastic vesicular systems have higher deformability than the previously used rigid vesicles. This flexibility allows them to be able to pass through narrow intercellular spaces in the stratum corneum more effectively. Among these carriers, spanlastics have shown increased performance compared with the traditional niosomes in regard to penetration of the skin barrier. Their deformable structure enables them to adapt to microscopic pores and channels which increases drug penetration into deeper layers and prolonged residence time of the drug (Khalil RM, 2025).

Vesicular systems also present benefits such as biocompatibility, lesser toxicity and the ability for sustained release of the drug. These characteristics make it serving as candidates for dermal and transdermal therapeutic use (Hatem S, 2024). However, in spite of potential improvements in cutaneous drug accumulation exerted by conventional vesicles, complete transport across the skin barrier may be limited in some cases. This points to the need for further optimization of the design and formulation strategies for vesicular (Ahmed OAA, 2019).

Overall, vesicular drug delivery systems are a promising strategy for improved transdermal permeation as well as controlled therapeutic performance.

- *Liposomes*

Nano-scale drug carrier has become so important due to compatibility with biological system and increase in effectiveness of drug therapy. Among the several types of vesicles, liposomes are among the most widely studied platforms for the transdermal drug delivery. Their structural similarity to cellular membranes makes them especially suitable to be used for topical and dermal application (Guo J, 2025).

Liposomes consist of spherical vesicles in which phospholipids are predominately organized in bilayers and sometimes stabilized with cholesterol. This bi-layer organization is similar to the lipid organization in the stratum corneum. Due to the nature of liposomes they can entrap water-soluble drugs in their water core and oil-soluble drugs in the lipid bilayer. Amphiphilic molecules can be fitted into the membrane interface whereas charged compounds can associate to the vesicle surface (Zhang P, 2025).

One of the important benefits associated with liposomal systems is flexibility. They can be designed to change drug release patterns, offer targeted delivery and shield sensitive drugs from degradation from environmental factors such as light, pH or oxidation. By virtue of their ability to biodegrade and possess generally biocompatibility characteristics, the liposome is generally thought to have lower systemic toxicity than some of the synthetic carriers. In addition, encapsulation in liposomes can affect the pharmacokinetic behavior, and enhance the overall response to therapy (Souto EB, 2021).

In dermatological applications, liposomal formulations have been shown to increase the drug deposition of the skin layers. Their affinity for keratin in the stratum corneum may be good for penetration and retention. As a result, liposomes have been investigated for the management of a number of skin conditions such as acne, psoriasis, vitiligo, alopecia, scar and melanoma (Choudhury A, 2025; Xu S, 2025).

The components added inside and between the bilayers of liposomes provide a dual-compartment system for the stabilization of water-soluble and lipid-soluble drugs. Vesicles can be made of single or multiple bilayers according to the structure and it affects the capacity of drug loading and releasing (Pasarin D, 2023).

Although conventional liposomes can increase the effectiveness of topical drug delivery, their ability to fully pass through the skin barrier might be limited. To overcome this limitation modified and deformable liposomal systems with penetration enhancers have been developed. These advanced variants, display better interaction with skin lipids and perform significantly better when compared to the traditional liposomal formulations (Cheng YC 2020 Babaie S 2020).

Overall, liposomes remain a central platform when it comes to nano-enabled transdermal drug delivery research due to their flexibility, safety profile and ability to enhance the localization of the drug in the skin.

- *Ethosomes*

Ethosomes are phospholipid-based nanovesicular carriers which are characterized by a relatively elevated concentration of ethanol. In addition to phospholipids and water, they may contain other components such as glycerol, for impurity, in order to increase the flexibility. Ethanol is an important component for changing the characteristics of vesicles by decreasing the size of the particles, adding a charge to its surface, and making the membrane more fluid. These combined effects work towards better penetration of hydrophilic and lipophilic drugs across the skin (Dahri M, 2023).

Ethosomes have been termed often a special version of elastic vesicles. Their higher permeation capability is due to the synergistic dynamic of ethanol and phospholipids. Ethanol reacts with the lipid domains of the stratum corneum and leads to partial disruption and increased fluidity of the lipid bilayers. This change in structure reduces the resistance of the barrier of the skin and makes the chambers within the barriers migrate more deeply (Bakhrushina EO, 2025).

Once ethosomal vesicles permeate throughout the more superficial skin layers, they will possibly fuse with cell

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membranes and release the encapsulated drug. This fusion-based mechanism is responsible for enhanced deposition of drugs within the epidermis and dermis; it may also be responsible for systemic absorption when necessary. Ethosomes were first developed as nano- to micron-sized vesicles consisting of phospholipids mixed with excessive concentrations of ethanol or isopropyl alcohol in an aqueous environment. The ethanol content at such high levels is the main reason why they are responsible for their superior permeation behavior (Mombeiny R, 2021).

The penetration process is typically explained by so-called ethanol effect. Ethanol interacts with the polar head groups of lipid bilayers in the stratum corneum and makes it more pliable and decreases the packing density of lipids that form the skin's outer material. As a result, highly deformable vesicles are created that are capable of migrating through the lipid domains that have been disrupted and to deeper areas of the skin. Additional fusion of vesicle membranes and skin lipids also helps facilitate migration of the drug across the barrier (Antonara L, 2025).

Due to their structural flexibility and capability to boost the drug penetration, ethosomes are regarded as a promising platform for trans-dermal and dermal therapeutic applications.

➢ *Transfersomes*

Transfersomes are very flexible lipid vesicles that have been developed to improve skin barrier drug transport. Unlike conventional liposomes these carriers have amazing deformability as they can squeeze through narrow intercellular spaces of the stratum corneum. Their elastic nature helps deliver smaller molecules as well as larger therapeutic molecules in order to pass through intact skin (Patel SK, 2024).

These vesicles are generally applied in non occlusive conditions. After application, the hydration gradient between the skin surface and the deeper layers of skin is caused by the natural transepidermal water loss. This gradient leads to osmotic forces of transferosomes towards the inside. By reacting to this gradient, transfersomes move in the lipid domains towards areas of water content within the viable epidermis and dermis (Chen RP, 2022).

A defining characteristic of transfersomes is the ability to experience great shape deformation without losing the structural integrity. They are able to traverse pores and channels significantly smaller than their own diameter, quite commonly with no rupture or leakage of encapsulated drug. This adaptability however, is accomplished through incorporation of edge activators, which are surfactants incorporated in optimized concentrations to make the membrane more flexible without affecting the stability of the vesicle (Garg U, 2022).

Because of their superior deformability, transfersomes exhibit better skin penetration than conventional vesicular rigid systems. This makes them especially suitable for the delivery of peptides, macromolecules and drugs with limited passive permeability. Their ability to efficiently pass through the stratum corneum has led to them being an important platform in the continuing advanced transdermal drug delivery research.

➢ *Recent Nano-Enabled Transdermal Systems: Drug Type, Therapeutic Area, and Clinical Relevance*

Table 2 Recent Nano-Enabled Transdermal Systems: Drug Type, Therapeutic Area, and Clinical Relevance

Nano-System	Drug / Payload Type	Therapeutic Application	Key Outcomes	Year	Reference
Liposomal TDDS	Methotrexate	Psoriasis	Enhanced skin retention, reduced systemic toxicity	2025	Zhang P et al., 2025
Ethosomal gel	Anti-inflammatory drug	Chronic wound healing	Increased penetration & healing rate	2021	Mombeiny R et al., 2021
Transfersomal vesicles	Curcumin + Berberine	Neurodegenerative disorders	Improved brain bioavailability	2024	Patel SK et al., 2024
Nanogel TDDS	CNS drugs	Neuro-therapeutics	Sustained release & improved targeting	2024	Mastella P et al., 2024
Nanoemulsion TDDS	Lipophilic APIs	Dermal & systemic delivery	Increased bioavailability	2023	Preeti et al., 2023
Intelligent nanoparticles	Precision therapeutics	Personalized medicine	Controlled & stimuli-responsive delivery	2025	Guo Z et al., 2025
Microneedle-nano hybrid	Biologics	Arthritis / Vaccines	Painless, enhanced systemic delivery	2024–2025	Yao W et al., 2024; Li Y et al., 2025

➢ *Microneedle System*

Different methods have been discussed to enhance drug delivery across the skin such as chemical penetration enhancers, formulation changes and device-aided-strategies. Microneedle technology has been found to be one of the most effective mechanisms of improving the process of drug delivery through transdermal and intradermal means. There is ample evidence in the scholarly and pharmaceutical community about its reliability and therapeutic possibilities.

Microneedles are tiny needles patterns which are usually 25-2000 microns long. These are intended to enter the stratum

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corneum in a least invasive way that does not embrace deep nerve rich tissues hence making the application less painful. Microneedles open microscopic pathways in the skin, successfully bypassing the epidermal barrier that is the main one of drug permeation (Zhao J, 2021).

Microchannels created by microneedles are also temporary and they close automatically once the device has been removed and this helps in reducing the chances of long term tissue reparation or infection. This feature causes the microneedle systems to be less hazardous and more convenient to patients than the regular hypodermic injections.

A number of designs of microneedles have been designed to fit in various therapeutic requirements. These are solid microneedles, hollow microneedles, coated microneedles, dissolving microneedles and hydrogel-forming microneedles. All designs vary in their drug delivery mechanism. As an example, solid microneedles make channels that can be filled by subsequent administration of drugs, hollow microneedles can be used to administer drugs directly into the body and dissolving microneedles can inject the drug directly into biodegradable polymers that dissolve upon insertion.

Micro needle hydrogel based microneedles are more recent developments in this area. When implanted in the skin, these microneedles take up stasis fluid in the skin and swell to create a moist matrix within which the medication diffuses over time. Notably, they are not left in the tissue polymeric residues when removed. This is a swelling-based technology, enabling a drug in the system to be actively released and structurally intact throughout the use (Nguyen HX, 2023).

Biologics like peptides, proteins, vaccines, and nucleic acid-based therapeutics are only some of the types of drugs that microneedle systems have greatly expanded the repertoire of drugs that can be administered transdermally. Their low invasiveness together with the higher dependence of drugs enhances their permeability of better drug delivery to the target body areas make them a potential avenue in future transdermal and intradermal therapies.

➢ *Types of Microneedles*

Microneedles are categorized based on the configuration of structure and mode of delivering drugs. Both forms are developed to penetrate the stratum corneum surface as well as cause less pain and tissue injury. The key ones are solid, coated, dissolving, hollow, and hydrogel-forming microneedles.

- *Solid Microneedles*

Solid microneedles are mostly utilized to produce temporary microchannels on the skin. Micro needle array in this method is inserted on the skin and is removed after pecking the stratum corneum. An example of such a drug formulation is a patch, cream, or gel that is applied on the treated area. The formed microchannels increase diffusion of drugs to deeper layers.

This is what is widely referred to as the poke and patch technique. Micro-needles of solid type are usually made using metals, silicon and powerful polymers. Their design has good mechanical strength and consistent penetration of the skin. Nonetheless, microneedle removals necessitate a second step of the formulation to support the delivery of drugs (Zhao J, 2021).

➢ *Coated Microneedles*

The coated microneedles are composed of solid structures of needles whose outer layers are covered with a thin layer of drug formulation. When inserted in the skin, the coating can be quickly washed off in interstitial fluid with the drug being deposited straight into the epidermis or dermis.

The method can be used to achieve accurate dosing and speed of action. It is also convenient in the case of vaccines and other potent drugs that have small dosages. The primary drawback is the limited loading capacity of the drugs, as the quantity of coated drug is limited without compromising sharpness of the needle and ingestion efficiency (Zhao J, 2021).

➢ *Dissolving Microneedles*

Micro needle drugs are dissolved in biodegradable polymers, such that the polymer is biodegradable and the drug is embedded into the polymers forming the needle structure. Once the microneedles are inserted in the skin, they dissolve and release the drug that is encased in the microneedles.

Such systems also remove the issue of medical wastes that are sharp, since no solid needle is left upon using the system. Micro needles that are dissolved are studied using delivery of peptides and proteins and vaccines. Their functioning relies on finding the optimal compromise of a high minimum mechanical force to insert and a decent drug dissolution rate (Nguyen HX, 2023).

➢ *Hydrogel-Forming Microneedles*

Microelectrolytes such as hydrogel forming microneedles are made of non-soluble cross-linked polymeric material. Rather, they take up interstitial fluid and swell on being inserted into the skin and forms a network of fluid that is hydrated.

The swollen microneedles serve as channels, through which drug molecules in an attached reservoir can diffuse into the hydrogel structure into deeper layers of a skin. This system provides the sustained and controlled release without the polymer tissue residues. More recent developments in the technology of microneedle are Hydrogel-forming microneedles (Nguyen HX, 2023).

➢ *Hollow Microneedles*

Hollow micro needles have a central lumen which allows a liquid drug formulation by means of infusion into the skin. They would work in a similar manner as a conventional hypodermic needle, only at a smaller scale.

This type of design allows administration of greater doses of medication to be controlled and the continuous

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infusion of medication should the need arise. Hollow systems are appropriate when the dose should be delivered accurately, but fabrication is more complicated, and it is possible that it can be obstructed in the lumen (Zhao J, 2021).

- *Hydrogel Systems (with Swelling Microneedles)*

Swellingmicroneedles are engineered to swell post-insertion as opposed to hydrogel-forming systems and operate on the principle that these need to swell. The swelling process increases the contact with the immediate tissue, as well as, facilitates the diffusion of the drug over a longer time.

Such systems also prove valuable in sustained delivery applications where the delaying of the release requires (Nguyen HX, 2023).

V. CONCLUSION

The process of transdermal delivery of the drug has greatly advanced over the decades and it presents a convenient alternative to the traditional oral and injectable methods. Transdermal systems will have an advantage since they avoid gastrointestinal degradation as well as hepatic first-pass metabolism and, therefore, increase bioavailability and patient compliance. The shielding framework of the stratum corneum is however a significant constraint to a large group of medications.

Practical therapeutic advantages of traditional dosage types like patches, creams, gels and sprays are limited to molecules that have favorable physicochemical properties. In order to conquer those constraints, more sophisticated methods such as nanoemulsions, and nanogels, vesicular carriers, liposomes, ethosomes, transfersomes, and microneedle-based systems have been invented.

Nano-enabled systems enhance solubility, stability and skin penetration of drugs whereas, vesicular carriers enhance increased localization and controlled release. The technology of microneedling, specifically, has proven to be the high potential solution concerning a low invasive delivery of macromolecules and biologics.

Even though considerable advancements have already been made, there are still obstacles associated with formulation stability, mass production, safety testing, and drug certification. Further studies and technological advancements are necessary to increase the number of drugs that can be applied through the transdermal route and to make therapeutic systems safe, effective and easy to use by patients.

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