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Approach on Transdermal Drug Delivery System

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Abstract

Transdermal therapeutic systems are defined as self-contained,self-discrete dosage forms,which when applied to the intact skin deliver the drug at a controlled rate to the systemic circulation. simple patch that you simply stick onto your skin like an adhesive bandage, that utilize passive diffusion of medicine across the skin because the delivery mechanism. Transdermal drug delivery offers controlled release of the drug into the patient, it allows a gradual blood level profile, leading to reduced general aspect effects and, sometimes, improved effectuality over different indefinite quantity kind. TDDS might be applicable in not solely prescription drugs but also in the skin care industry, including cosmetics. as a result of this methodology primarily involves local administration, it can prevent local build-up in drug concentration and nonspecific delivery to tissues not targeted by the drug.

Key Words: Transdermal drug delivery system, Topical, Skin, Design.

Introduction

Drug delivery system (DDS) may be a generic term for a series of chemical science technologies that may management delivery and unleash of pharmacologically active substances into cells, tissues and organs, such these active substances might exert best effects.[1, 2] In different words, DS covers the routes of administration and drug formulations that with efficiency deliver the drug to maximise therapeutic effectuality whereas minimizing any aspect impact.[3–5]Depending on the delivery route, there are many types of administration modalities, such as oral administration, transdermal administration, lung inhalation, mucosal administration, and intravenous injection. so the transdermal drug delivery system (TDDS) represents an attractive approach

TDDS has become one in all the foremost wide investigated routes of non-invasive drug delivery into the body through the skin, not like conventionally used direct administration

Routes that build use of needle-based injections has considerably influenced the delivery of assorted therapeutic agents, particularly in pain management, secretion medical care, and treatment of diseases of the vessel and central

nervous systems.[6–9]TDDS does not involve passage through the gastrointestinal tract; so, there's no loss because of first-pass metabolism, and medicines will be delivered while not interference from pH scale, enzymes, and enteric microorganism.In addition, TDDS will be wont to management drug unleash in keeping with usage restrictions, thereby contributive to the high persistence of this methodology. most significantly, because TDDS may be a noninvasive administration methodology and involves nominal pain and burden on the patient, medication will be safely and handily administered to youngsters or the aged.[10–12]

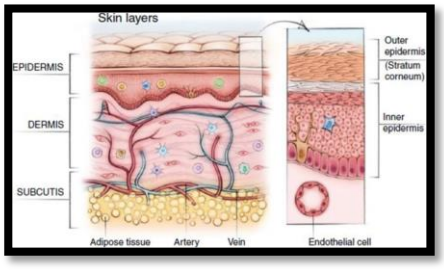

Fig- Structure of Skin

Factors Affecting Percutaneous Absorption-

Not all drug substances are appropriate for transdermal delivery. Among the factors playing a part in percutaneous absorption are the physical and chemical properties of the drug, together with its relative molecular mass,olubility, partitioning constant and equilibrium constant (pKa), the character of the carrier vehicle, and also the condition of the skin. though general statements applicable to any or all doable mixtures of drug, vehicle, and skin condition square measure tough to draw, most analysis findings is also summarized as follows. [13,22]

1. 1. Drug concentration is a very important issue. Generally, the quantity of drug percutaneously absorbed per unit of area per interval will increase with a rise within the concentration of the drug within the TDDS.

2. The larger the world of application (the larger the TDDS), the additional drug is absorbed.

3. The drug ought to have a larger chemical science attraction to the skin than to the vehicle in order that the drug can leave the vehicle in favor of the skin. Some solubility of the drug in each lipide and water is believed be essential for effective body covering absorption.In essence, the aqueous solubility of a drug predict the concentration presented to the absorption site, an the partition coefficient influences the rate of transport across the absorption site. Generally, drugs penetrate the skin better in their unionized form. Nonpolar drugstend to cross the cell barrier through the lipid-rich regions (transcellular route), whereas the polar drugs favor transport between cells (intercellular route) . For example, erythromycin base demonstrates better percutaneous absorption than does erythromycin ethyl succinate.

4. Drugs with molecular weights of 100 to 800 and adequate lipid and aqueous solubility will permeate skin. The ideal molecular weight of a drug for transdermal drug delivery is believed to be 400 or less.

5. association of the skin usually favors body covering absorption. The TDDS acts as an occlusive wet barrier through that sweat cannot pass, increasing skin association.

6. Percutaneous absorption appears to be greater when the TDDS is applied to a site with a thin horny layer than with a thick one.

7. Generally, the longer the medicated application is permitted to remain in contact with the skin, the greater is the total drug absorption. These general statements apply to skin within the normal state. Skin that is abraded or cut permits drugs to gain direct access to the subcutaneous tissues and the capillary network, defeating the role of the TDDS.

Percutaneous Absorption Enhancers

Percutaneous Absorption Enhancers There is nice interest among pharmaceutical scientists to develop chemical permeation enhancers and physical strategies which will increase transdermic absorption of therapeutic agents.

Chemical Enhancers By definition, a chemical skin penetration enhancer increases skin permeability by reversibly damaging or altering the physicochemical nature of the stratum corneum to reduce its diffusional resistance.[23] Among the alterations area increased hydration of the stratum corneum, a modification within the structure of the lipids and lipoproteins in the intercellular channels through solvent action or denaturation, or both.[24-28]

Some medication having inherent capability to permeate the skin while not chemical enhancers. However, once this is often not the case, chemical permeation enhancers might render chemical permeation enhancers may render an otherwise impenetrable substance useful in transdermal drug delivery. More than 275 chemical compounds have been cited within literature as skin penetration enhancers; they include acetone, azone, dimethylacetamide, dimethylformamide, dimethyl sulfoxide, ethanol, oleic acid, polyethylene glycol, propylene glycol, and sodium lauryl sulphate. The choice of a permeation enhancer should be based not only on its efficacy in enhancing skin permeation but also on its dermal toxicity (low) and its physicochemical and biologic compatibility with the system's other components.[28]

Iontophoresis and Sonophoresis

In addition to chemical means, some physical methods are being used to enhance transdermal drug delivery and penetration, namely, iontophoresis and sonophoresis. *Iontophoresis* is delivery of a charged chemical compound across the skin membrane using an electrical field. A number of drugs have been the subject of iontophoretic studies; they include lidocaine dexamethasone; amino acids, peptides, and insulin verapamil and propranolol . There is particular interest to develop alternative routes for delivery of biologically active peptides. At present, these agents are delivered by injection because of their rapid metabolism and poor absorption after oral delivery. They are also poorly absorbed by the transdermal route because of their large molecular size and ionic character and the general impenetrability of the skin. However, iontophoresis-enhanced transdermal delivery has shown some promise as a means of peptide and protein administration. *Sonophoresis*, or high-frequency ultrasound, is also being studied as a means to enhance transdermal drug delivery.Among the agents examined are hydrocortisone,lidocaine, and salicylic acid in such formulations as gels, creams, and lotions. It is thought that high-frequency ultrasound can influence the integrity of the stratum corneum and thus affect its penetrability. [17,26]

Percutaneous Absorption Models-

Skin permeability and percutaneous absorption have been the subject of numerous studies to define the underlying principles and to optimize transdermal drug delivery. Although many experimental methods an models have been used, they tend to fall into one of two categories, in vivo or in vitro.

In Vivo Studies

In vivo skin penetration studies may be undertaken for one or more of the following purposes

1. To verify and quantify the cutaneous bioavailability of a topically applied drug

2. To verify and quantify the systemic bioavailability of a transdermal drug

3. To establish bioequivalence of different topical formulations of the same drug substance

4. To determine the incidence and degree of systemic toxicologic risk following topical application of a specific drug or drug product

5. To relate resultant blood levels of drug in human to systemic therapeutic effects The most relevant studies are performed in humans; however, animal models may be used insofar as they may be effective as predictors of human response. Animal models include the weanling pig, rhesus monkey, and hairless mouse or rat.[29,30] Biologic samples used in drug penetration and drug absorption studies include skin sections, venous blood from the application site, blood from the systemic circulation, and excreta (urine, feces, and expired air)[29,33]

In Vitro Studies

Skin permeation may be tested in vitro using various skin tissues (human or animal whole skin, dermis, or epidermis) in a diffusion cell . In vitro penetration studies using human skin are limited because of difficulties of procurement, storage, expense, and variation in permeation . Excised animal skins may also vary in quality and permeation. Animal skins are much more permeable than human skin. One alternative that has been shown to be effective is shed snakeskin (*Elaphe obsoleta*, black rat snake), which is nonliving, pure stratum corneum, hairless, and similar to human skin but slightly less permeable.[34,35]Also, the product Living Skin Equivalent Testskin (Organogenesis,Inc.) was developed as an alternative for dermal absorption studies. The material is an organotypic coculture of human dermal fibroblasts in a collagen-containing matrix and a stratified epidermis composed of human epidermal keratinocytes. The material may be used in cell culture studies or in standard diffusion cells. Diffusion cell systems are employed in vitro to quantify the release rates of drugs from topical preparations. In these systems, skin membranes or synthetic membranes may be employed as barriers to the flow of drug and vehicle to simulate the biologic system.

1 Typical side-by-side diffusion cell

2 Typical Franz diffusion cell

3 Microdiffusion cell

The typical diffusion cell two chambers, one on each side of the test diffusion membrane (Figs. 1 to 3). A temperature-controlled solution of the drug is placed in one chamber and a receptor solution in the other chamber. When skin is used as the test membrane, it separates the two solutions. Drug diffusion through the skin may be determined by periodic sampling and assay of the drug content in the receptor solution. The skin may also be analyzed for drug content to show permeation rates and/ or retention in the skin .

The *United States Pharmacopeia* (USP) describes the apparatus and procedure to determine dissolution (release) of medication from a transdermal delivery system and provides an acceptance table to which the product must conform to meet the monograph standard for a given article (33). Commercial systems use transdermal diffusion cells and automatic sampling systems to determine the release rates of drugs from transdermal systems (34). In USP 35/NF 30, there were two official transdermal systems, that is, clonidine and nicotine.

Design Features of Transdermal Drug Delivery Systems

TDDSs (also often called transdermal patches) are designed to support the passage of drug substances from the surface of the skin through its various layers and into the systemic circulation. Examples of the configuration and composition of TDDSs are described in the text Technically, TDDSs may be categorized into two types, monolithic and membrane-controlled systems. Monolithic systems incorporate a drug matrix layer between the backing and the frontal layers. The drug matrix layer is composed of a polymeric material in which the drug is dispersed. The polymer matrix controls the rate at which the drug is released for percutaneous absorption. The matrix may be of two types, either with or without an excess of drug with regard to its equilibrium solubility and steady-state concentration gradient at the stratum corneum. In types having no excess, drug is available to maintain the saturation of the stratum corneum only as long as the level of drug in the device exceeds the solubility limit of the stratum corneum. As the concentration of drug in the device diminishes below the skin's saturation limit, the transport of drug from device to skin declines . In systems with excess drug in the matrix, a drug reserve is present to ensure continued saturation at the stratum corneum. In these instances, the rate of drug decline is less than in the type having no reserve. In the preparation of monolithic systems, the drug and the polymer are dissolved or blended together, cast as the matrix, and dried

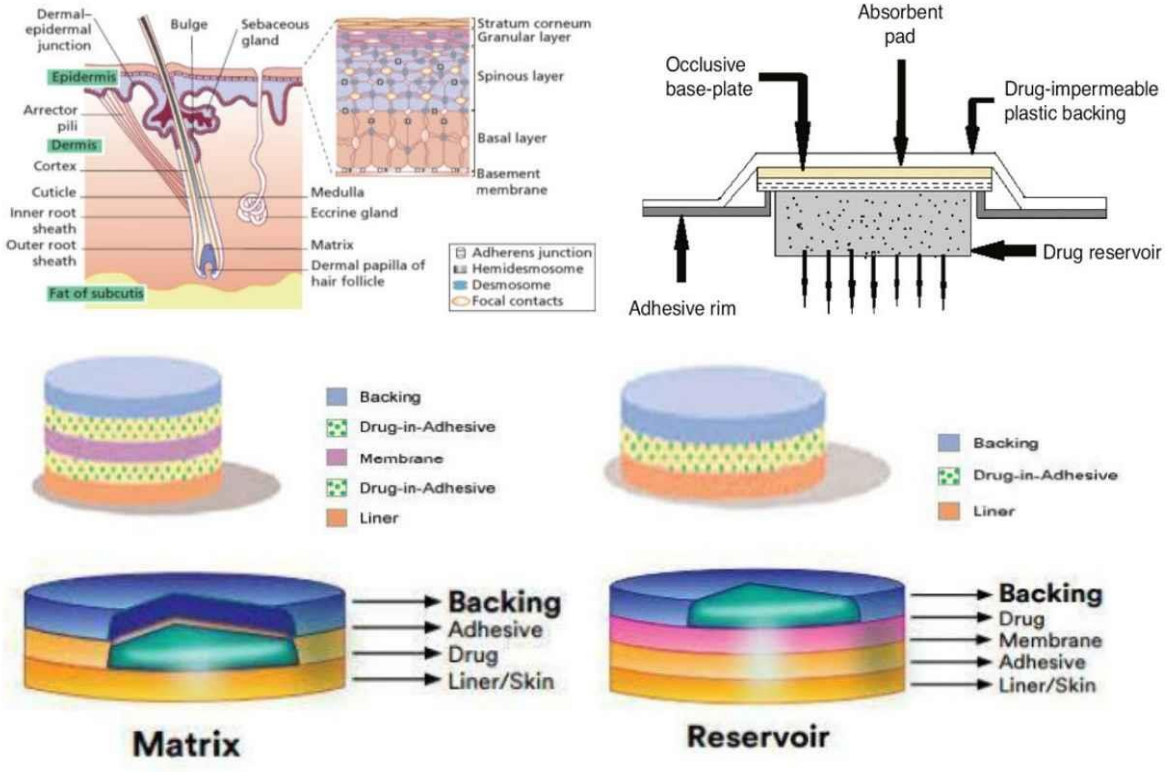

Fig - Design Features of Transdermal Drug Delivery Systems

The gelled matrix may be produced in sheet or cylindrical form with individual dosage units cut and assembled between the backing and frontal layers. Most TDDSs are designed to contain an excess of drug and thus have drug-releasing capacity beyond the time frame recommended for replacement. This ensures continuous drug availability and absorption as used TDDSs are replaced on schedule with fresh ones. Membrane-controlled transdermal systems are designed to contain a drug reservoir,or pouch, usually in liquid or gel form; a rate-controlling membrane; and backing, adhesive, and protecting layers Transderm-Nitro (Summit) and Transderm Scop (Baxter) are examples of this technology. Membrane controlled systems have the advantage over monolithic systems in that as long as the drug solution in the reservoir remains saturated, the release rate of drug through the controlling membrane remains constant. If the drug is delivered to the stratum corneum at a rate less than the absorption capacity, the *device* is the controlling factor; if the drug is delivered to the skin area to saturation, the *skin* is the controlling factor. Thus, the rate of drug transport in all TDDSs, monolithic and membrane, is controlled by either artificial or natural (skin) membranes.[21,35]

TDDSs may be constructed of a number of layers, including

(*a*) an occlusive backing membrane to protect the system from environmental entry and from loss of drug from the system or moisture from the skin;

(*b*) a drug reservoir or matrix system to store and release the drug at the skin site;

(*c*)a release liner, which is removed before application and enables drug release; and

(*d*) an adhesive layer to maintain contact with the skin after application. Two types of adhesive layers, the peripheral adhesive and the face adhesive can be used. The peripheral adhesive contains adhesive The backing layer must be occlusive to retain skin moisture and hydrate the site of application, enabling increased drug penetration. Preferred backing materials are approximately 2 to 3 mm thick and have a low moisture vapor transmission rate, less than about 20 g/m2 in 24 hours .[36]

Transparentor pigmented films of polypropylene, polyethylene, and polyolefin are in use in TDDSs as backing liners. The adhesive layer must be pressure sensitive, providing the ability to adhere to the skin with minimal pressure and remain in place for the intended period of wear. The adhesive should be nonirritating, allow easy peel-off after use, permit unimpeded drug flux to the skin, and be compatible with all other system components. The adhesive material is usually safety tested for skin compatibility, including tests for irritation, sensitivity, and cytotoxicity [37]. In some TDDSs, the adhesive layer contains the drug. Polybutyl acrylate is commonly used as the adhesive in TDDSs. The drug release membranes are commonly made of polyethylene, with microporous structures of varying pore sizes to fit the desired specifications of the particular transdermal system.

Included among the design objectives of are the following

1. Deliver the drug to the skin for percutaneous absorption at therapeutic levels at an optimal rate
2. Contain medicinal agents having the necessary physicochemical characteristics torelease from the system and partition into the stratum corneum
3. Occlude the skin to ensure one-way flux of the drug into the stratum corneum
4. Have a therapeutic advantage over other dosage forms and drug delivery systems
5. Not irritate or sensitize the skin

6. Adhere well to the patient's skin and have size, appearance, and site placement that encourage acceptance.

Advantages of transdermal drug delivery: [36-40]

Transdermal drug delivery enables the avoidance of gastrointestinal absorption with its associated pitfalls of enzymatic and pH associated deactivation.

1. Avoidance of first pass metabolism.
2. The lack of peaks in plasma concentration can reduce the risk of side effects, thus drugs that require relatively consistent plasma levels are very good candidate for transdermal drug delivery.
3. As a substitute for oral route.
4. The patch also permit constant dosing rather than the peaks and valley in medication level associated with orally administered medication.
5. Rapid notifications of medication in the event of emergency as well as the capacity to terminate drug effects rapidly via patch removal.
6. Avoidance of gastro intestinal incompatibility.
7. Convenience especially notable in patches that require only once weekly application, such a simple dosing regimen can aid in patient adherence to drug therapy.
8. Minimizing undesirable side effects.
9. Provide utilization of drug with short biological half lives, narrow therapeutic window.
10. Avoiding in drug fluctuation drug levels.
11. Inter and intra patient variation.
12. Termination of therapy is easy at any point of time.
13. Provide suitability for self administration.
14. They are non invasive, avoiding the inconvenience of parentral therapy.
15. The activity of drugs having a short half life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
16. It is of great advantages in patients who are nauseated or unconscious.
17. Transdermal patches are better way to deliver substances that are broken down by the stomach aids, not well absorbed from the gut, or extensively degraded by the liver.
18. Transdermal patches are cost effective.

Disadvantages of transdermal drug delivery: [37,38,40]

1. Transdermal drug delivery system cannot deliver ionic drugs.
2. It cannot achieve high drug levels in blood.
3. It cannot develop for drugs of large molecular size.
4. It cannot deliver drugs in a pulsatile fashion.
5. It cannot develop if drug or formulation causes irritation to skin.
6. Possibility of local irritation at site of application.
7. May cause allergic reaction.

8. Sufficient aqueous and lipid solubility, a log P (octanol/ water) between 1 and 3 is required for permeate to transverse stratum corneum and underlying aqueous layer.
9. Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's impermeability.
10. Long time adherence is difficult.

1 Transdermal Scopolamine -

Transdermal scopolamine was the first TDDS to receive FDA approval. Scopolamine, a belladonna alkaloid, is used to prevent travel-related motion sickness and the nausea and vomiting that result from the use of certain anesthetics and analgesics used in surgery. The Transderm Scop system is a circular flat patch 0.2 mm thick and 2.5 cm2 in area. The TDDS contains 1.5 mg of scopolamine and is designed to deliver approximately 1 mg of scopolamine at an approximately constant rate to the systemic circulation over the 3-day lifetime of the system. An initial priming dose of 200 mg of scopolamine in the adhesive layer of the system saturates the skin binding sites and rapidly brings the plasma concentration to the required steady-state level. The continuous release of scopolamine through the rate-controlling microporous membrane maintains the plasma level constant. The rate of release is less than the skin's capability for absorption, so the membrane, not the skin, controls the delivery of the drug into the circulation. The patch is worn in a hairless area behind the ear. Because of the small size of the patch, the system is unobtrusive, convenient, and well accepted by the patient. The TDDS is applied at least 4 hours before the antinausea effect is required. Only one disk should be worn at a time and may be kept in place for up to 3 days. If continued treatment is required, a fresh disk is placed behind the other ear and the other removed. The most common side effects are dryness of the mouth and drowsiness. Particularly in the geriatric population, use also may interfere with orientation, cognition, and memory. The TDDS is not intended for use in children and should be used with caution during pregnancy.[41]

Transdermal Nitroglycerin-

A number of nitroglycerin-containing TDDSs have been developed, including Minitran (3 M Pharmaceuticals), Nitro-Dur (Key),Transderm-Nitro (Summit), and Nitrodisc (Roberts). The design of each of these systems is briefly described in Table 1 Each of these products maintains nitroglycerin drug delivery for 24 hours after application. Tolerance, however, is a major factor limiting the effectiveness of these systems when used continuously for more than 12 hours per day. Hence, an appropriate dosing schedule would include a daily "patch on" period of 12 to 14 hours and a "patch off" period of 10 to 12 hours.

Nitroglycerin is used widely in the prophylactic treatment of angina. It has a relatively low dose, short plasma half-life, high peak plasma levels, and inherent side effects when taken sublingually, a popular route. It is rapidly metabolized by the liver when taken orally; this first-pass effect is bypassed by the transdermal route. The various nitroglycerin TDDSs control the rate of drug delivery through a membrane When a TDDS is applied to the skin, nitroglycerin is absorbed continuously, resulting in active drug reaching the target organs (heart, extremities) before inactivation by the liver. Only a portion of the total nitroglycerin in the system is delivered over the usual 24-hour

use period; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. For example, in the Deponit TDDS (UCB), only 15% of the nitroglycerin content is delivered after 12 hours of use The rate of drug release depends on the system. In the Transderm-Nitro system, nitroglycerin 0.02 mg is delivered per hour for every square centimeter of patch, whereas in the Deponit system, each square centimeter delivers approximately 0.013 mg of nitroglycerin per hour [42,43].

The Nitro-Dur matrix is in a highly kinetic equilibrium state [44]. Dissolved nitroglycerin molecules are constantly exchanging with adsorbed nitroglycerin molecules bound to the surfaces of the suspended lactose crystals. Sufficient nitroglycerin is adsorbed to the lactose in each matrix to maintain nitroglycerin in the fluid phase (aqueous glycerol) at a stable but saturated level (5 mg nitroglycerin/ cm2 matrix). When the matrix is applied to the skin, nitroglycerin molecules migrate by diffusion from solution in the matrix to solution in the skin. To make up for the molecules lost to the body, the equilibrium in the matrix shifts such that more molecules of nitroglycerin leave the crystals than are adsorbed from solution. When balance is restored, the solution is again saturated. Thus, the crystals of lactose act as a reservoir of drug to maintain drug saturation in the fluid phase. The Nitro-Dur matrix in turn acts as a saturated reservoir for diffusive drug input through the skin [44].

Generally, these TDDSs are placed on the chest, back, upper arms, or shoulders. The site should be free of hair, clean, and dry so that the patch adheres without difficulty. The use of the extremities below the knee or elbow is discouraged, as are the areas that are abraded or have lesions or cuts. The patient should understand that physical exercise and elevated ambient temperatures, such as in a sauna, may increase the absorption of nitroglycerin.

Conclusion –

Looking to the future, it is likely that first-generation patch technology will continue to be used for delivery of small-molecule drugs with the right set of properties and especially those drugs that are currently administered orally and by injection that are coming off patent. Second-generation chemical enhancers should find continued use as formulation excipients in topical dermatological creams and ointments and some systemic patches for small-molecule drugs. They will probably have little impact on delivery of hydrophilic drugs and macromolecules, because the most effective chemical enhancers generally diffuse out of the stratum corneum and irritate deeper tissue. Targeted, third-generation combinations of chemical enhancers and biochemical approaches offer strategies for more targeted enhancement, but are still in the early stages of development.

Second-generation physical enhancement using iontophoresis has already lead to changes in the clinic, especially for rapid, localized delivery to the skin. Its electronic control over delivery rates gives iontophoresis a special property that can be exploited for patient-controlled dosing and other complex delivery profiles. Likewise, noncavitational ultrasound has found use in transdermal delivery of anti-inflammatories in physical therapy, but does not appear suitable for delivery of large compounds.

Overall, transdermal drug delivery offers compelling opportunities to address the low bioavailability of many oral drugs, the pain and inconvenience of injections, and the limited controlled-release options of both. Building off the successes of first-generation transdermal patches, second-generation chemical enhancers and iontophoresis are

expanding delivery capabilities for small molecules, whereas third-generation physical enhancers (including ultrasound, thermal ablation and microneedles)

could enable transdermal delivery of macromolecules and vaccines. These scientific and technological advances that enable targeted disruption of stratum corneum while protecting deeper tissues have brought the field to a new level of capabilities that position transdermal drug delivery for an increasingly widespread impact on medicine.

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