Journal of Pharmaceutical Research and Integrated Medical Sciences (JPRIMS)
ISSN: 3049-1681, Vol.02, Issue No.07, 2025 (pp. 103-116)
AKT PUBLICATION

ORIGINAL ARTICLE https://aktpublication.com/index.php/jprims/index

Transdermal Drug Delivery: Advances In Permeation Enhancers and Microneedles

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Abstract

Transdermal drug delivery systems (TDDS) is a promising method of non-invasive delivery of drug molecules, and it has the following benefits: it avoids first-pass metabolism, minimizes intestinal breakdown and increases patient compliance. The stratum corneum however presents a great obstacle to drug permeation and more so on hydrophilic and high-molecular-weight drugs. More recent developments have then been directed at the inclusion of chemical permeation enhancers (CPEs) which comprise alcohols, fatty acids, terpenes and surfactants that disturb the structure of the lipids, and increases the solubility of the drug in order to enhance permeation. Simultaneously, the so-called microneedle (MN) technologies, which could be solid, coated, hollow, or dissolving, have been developed to generate the temporary microchannels in the skin and allow deep and efficient drug delivery with low discomfort and minimal damage. Effectiveness, safety, and mechanism of both CPEs and MNs were proven in preclinical trials based on rodent and porcine models, where porcine skin was also compared as a translational-friendly model known to mimic the human one. Noteworthy, the formulation of CPEs with microneedles has demonstrated the synergetic phenomenon, by improving the drug flux, extending therapeutic potential, and extending the ability to deliver a broadened range of molecules such as peptides, hormones, and even vaccines. This review summarizes the existing evidence and points at the translational prospects of the above-mentioned technologies, as well as the future directions of clinical application and improvement of formulation in trans-dermal therapies.

Key Words:

History: Transdermal Drug Delivery, Permeation Enhancers, Microneedles, Skin Barrier, Drug Bioavailability, Animal Models, Synergistic Delivery, Non-Invasive Therapeutics.

Received: March, 23,2025

Revised: April, 13,2025

Accepted: May, 27,2025

Published: July 25, 2025

DOI: https://doi.org/10.64063/3049-1681.vol.2.issue7.9

1. INTRODUCTION

The transdermal drug delivery technology in the form of Transdermal drug delivery systems (TDDS) has come up as a non-invasive, patient-friendly method of drug administration compared to other methods like either oral or injectible delivery method. TDDS overcome many of the limitations of current administration styles by directing a drug into the skin, avoiding first-pass hepatic metabolism, increasing therapeutic efficacy and compliance in patients[1]. But the outer layer of the skin the stratum corneum acts as a great barrier and hinders the transdermal movement of most therapeutic agents and most especially on the hydrophilic and compounds of high-molecular-weight. A major breakthrough has encountered the challenge by developing permeation promoters and microneedle technology to alter or circumvent the skin barrier to enable the drug penetration to be effective.

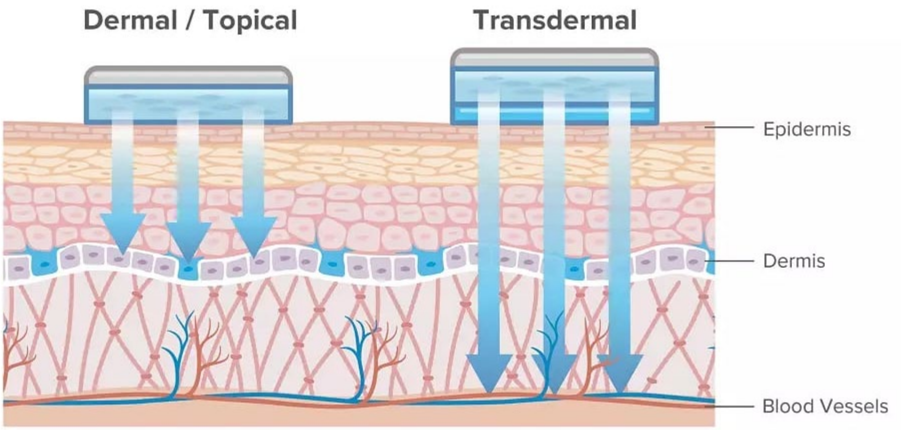

Figure 1: Transdermal drug delivery systems (TDDS)[2]

The permeation enhancers such as alcohols, fatty acids, terpenes and surfactants are used with the basic working behind them that highlights them in breaking down the lipid structure or reshaping the protein in the stratum corneum, eventually increasing the drug solubility and diffusity. In the meantime, microneedles form microchannels in the skin by enabling access to deeper tissues without causing pain or injury to the tissues. Recent developments in research have also aimed at synergistic effects of combining both these two strategies that can lead to increased rate, as well as extent of drug delivery. The review discusses the recent advancements, preclinical testing and translational prospects of permeation enhancers and microneedles in developing the transdermal drug delivery innovation.

1.1.Background Information and Context

During the last few decades, transdermal drug delivery has attracted a lot of attention because of the ability to administer therapeutic agents in the controlled, non-invasive, patient-compliant way. Compared to oral or injectable administration, transdermal systems bypass GI degradation and first-pass effects, and thus they are even more suitable in the case of a chronic disease, as well as long-term treatment. Nevertheless the rationale that poses the greatest restriction is the selective nature of the outermost layer of the skin or stratum corneum, which limits diffusion of most drug molecules. This has seen increased research in methods that help increase transdermal permeability and this has led to application in the use of chemical permeation enhancers (CPEs) and microneedle (MN) technology community.

1.2.Objectives of the Review

The primary objectives of this review are outlined as follows:

- To analyze the role and mechanism of chemical permeation enhancers (CPEs) in transdermal delivery.
- To study the design and function of microneedles (MNs) in enhancing skin permeability.

- To evaluate the translational relevance of animal models for human applications.
- To explore the synergistic effects of combining CPEs with MNs for improved drug delivery.
- To identify current challenges and future directions for clinical translation of these systems.

1.3. Importance of the Topic

As transdermal drug delivery systems with easy-to-use platform are increasingly desired in drug delivery applications, the therapeutic potential and commercial potential of maximizing transdermal drug delivery have become important. Increasing permeability of the skin without affecting skin integrity and safety is a major concern of the pharmaceutical science. The permeation enhancer in combination with microneedles is a state-of-the-art option, which has a potential to broaden the scope of drugs that can be used through transdermal delivery with the inclusion of biologics or vaccines[3]. Further developments in the area of these technologies are not only key in enhancing the current treatment regimes but also to facilitate the administration of new classes of therapeutics that were previously thought to be inappropriate in terms of livery via transdermal routes.

2. PRECLINICAL EVALUATION OF TRANSDERMAL ENHANCERS: INSIGHTS FROM ANIMAL MODELS

In recent years, transdermal drug delivery systems (TDDS) have attracted enormous consideration considering their controlled and non invasive delivery of drugs. One of the most important factors in the development of TDDS technologies is the deployment to date of chemical permeation enhancers (CPEs) to circumvent the barrier nature of the stratum corneum. The preclinical animal studies have been rendered as very crucial to assess the efficacy, safety, and mechanisms of different CPEs so that researchers are able to shortlist the effective ones before advancing into human trials. Such evaluations require rodents (rats and mice); porcine models, and guinea pigs, which are especially preferred due to their similar morphologic skin and lipid composition to human skin.

Table 1: Summary of Key Studies on Skin Permeation Enhancement Techniques

Author(s)	Study	Focus Area	Methodology	Key Findings
Bian, J. (2020)[4]	Skin permeation enhancement using chemical enhancers and	Enhancing skin permeability for drugs and peptides	Doctoral research using experimental setups with polymeric microneedles	Combination of microneedles and chemical enhancers significantly improves skin penetration of

	polymeric microneedles		and chemical enhancers	peptides and hydrophilic drugs
Escobar-Chávezet al. (2024)[5]	Chemical and physical enhancers for transdermal drug delivery	Overview of chemical and physical penetration enhancers	Literature review on transdermal delivery mechanisms and enhancer classes	Both chemical and physical enhancers play complementary roles in facilitating drug permeation; selection depends on drug properties
Gao, Y. et al. (2022)[6]	How physical techniques improve the transdermal permeation of therapeutics: A review	Physical enhancement strategies (e.g., microneedles, ultrasound, iontophoresis)	Comprehensive review of physical transdermal techniques	Physical methods can significantly increase drug delivery efficiency with minimal invasiveness and improved safety
Hmingthansanga, V. et al. (2022)[7]	Improved topical drug delivery: Role of permeation enhancers and advanced approaches	Modern approaches to enhance topical drug delivery	Review integrating both conventional and advanced enhancer technologies	Use of natural enhancers, nanocarriers, and physical methods can greatly optimize skin absorption and therapeutic outcomes

2.1.Key Research Studies

Various benchmark studies have shown the use of the various CPEs in the transdermal drug delivery in the animal models. In one of such studies, ethanol was studied using rat skin as permeation promoter in delivering propranolol hydrochloride, a hydrophilic beta-blocker. It was found that ethanol caused a large increase in drug permeation due to the disturbing of the tightly packed lipid subdomains in the stratum corneum as well as augmenting the solubility of the drug in the skin layers. It is this two-pronged mechanism that renders ethanol an effective remedy to drug with low permeability[8].

Another characteristic instance concerns the oleic acid application on guinea pig skin wherein the ability of inducing microdomain within the lipid bilayers was measured in relation to the local use of a lidocaine that is one of the common anesthetics. Oleic acid elevated the flux of lidocaine through fluidizing the lipid matrix and consequently attaining the diffusion of hydrophilic molecules in the intercellular route.

Another third example is that of d-limonene, a naturally existing terpene which was tested upon porcine skin in the case of permeation of ibuprofen. The research found that d-limonene possesses a capability of reversibly removing stratum corneum lipids and this increases drug permeation inducing no irreversible skin damage. This reversible interaction is especially important to clinical use, where skin integrity over time is important[9].

2.2.Methodologies and Findings

In vitro skin permeation assays most commonly used in most preclinical studies are the Franz diffusion cell system that allows the controlled determination of permeation of drugs through excised skin. In such arrangements, the donor chamber has the mixture of the drug preparation and a chosen CPE and the receptor chamber has a buffer to simulate systemic circulation. The skin hangs in between these chambers and the permeation of drugs is measured as a function of time by sampling the receptor fluid and making analytical quantifications (e.g. HPLC or UV spectrophotometry).

Along with the in vitro procedures, there are in vivo animal studies that allow gaining information on pharmacokinetics, systemic exposure, skin irritation, and toxicity. To illustrate, rat abdominal skin was compared to the case study of different CPEs, namely, ethanol, isopropyl myristate (IPM), and oleic acid, measuring their impact on the percutaneous absorption of diclofenac (anti-inflammatory drug that is non-steroidal). The findings presented clear models of each of the enhancers:

- **Ethanol:** There was better solubility and lipid extraction resulting in better flux.
- **IPM:** Exposed to Keratin Structures in the stratum corneum, enhanced fluidity and permeability.
- **Oleic acid:** Disrupted the lipids and led to a phase separation, which increased the diffusivity.

Remarkably, each of the CPE differed in improvement ratios and activation kinetics, which emphasizes the need to make right enhancer choices, according to the physicochemical characteristics of the drug. Skin irritation testing also revealed that ethanol and oleic acid caused mild erythema in one instance, which is why IPM is a preferable solution when it comes to sensitive skin applications because it is tolerated well by skin[10].

2.3. Critical Evaluation: Strengths and Weaknesses

Strengths

- **Ethical and Cost:** It is ethically and cost effective to use animal models, especially rodents, which can be screened much faster than at an early-phase stage in humans testing several enhancer-drug combinations.
- **Structural Similarity to Human Skin:** The skins of rodents, guinea pigs and pigs bear noteworthy biophysical and biochemical resemblance with regards to human skin especially in regards to the stratum corneum lipid content, stratum thickness, and barrier to permeability, and thus, make reasonable stand-ins.
- **Standardized and Reproducible Systems:** The controlled and reproducible systems of in vitro methods such as Franz diffusion cell present a standardized and reproducible model of comparative analysis of permeation rate of specific models, their flux values and augmentation ratios.
- **Mechanistic Insights:** Preclinical models can also be used to investigate the biophysical processes underlying skin structure, lipid disruption and protein-protein interaction that are elicited by enhancers to aid in rational design of TDDS formulas[11].

Weaknesses

- **Species-Specific Differences:** These have important interspecies differences in percutaneous absorption, enzyme activity and immune response and healing behavior. As an example, rat skin is highly permeable as compared to human skin, which is likely to over-estimate the effectiveness of a CPE and cause low-level clinical translation.
- **Protocol inconsistencies:** Inconsistency in the variation of studies is observed with regard to enhancer concentration, formulation viscosity, vehicle pH, thickness of skin, and occlusion state; this hinders comparability and reproducibility of values.
- **Poor prediction of human irritation:** Although preclinical models are able to identify gross irritation or erythema they may not recapitulate delayed or chronic skin responses seen in humans because of variations in modulation of the immune response and inflammatory pathways.
- **Long-term Assessment Exertion:** A substantial number of the animal studies consider short-term consequences, whereas most TDDS uses mandate long-term or multiple exposures that include a more rigorous assessment of the irritancy building up, recuperation of the barriers, and stimulation capacity.

3. TRANSLATIONAL RELEVANCE: BRIDGING ANIMAL STUDIES TO HUMAN APPLICATIONS

Combinations of permeation enhancer (CPEs) like alcohols, fatty acids, terpenes, and surfactants play an important role in enhancing transdermal drug delivery either by modifying the lipid composition of the stratum corneum or increasing drug solubility. Ethanol, a form of alcohol will break down the hydrogen bonding and release lipids making them more fluid, whereas fatty acids such as oleic acid forms microchannels to enhance diffusion of drugs. Skin irritations requires a formulation (such as) terpenes including d-limonene provide reversible action with little skin damage, and surfactants enhance solubility, although can cause irritation. Recent developments such as nanoemulsions and co-solvent systems have enhanced efficacy of enhancers further with minimization of side effects[12].

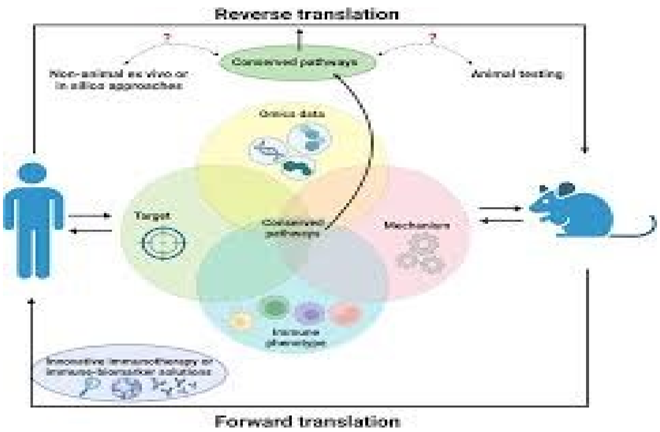

Figure 2: Bidirectional Translation in Drug Development: Forward and Reverse Translational Research Approaches[13]

Microneedle systems (MNs) provide minimally invasive alternative, whereby transient micro channels are formed to push drugs into the dermis. Both polymeric solid and hollow, and coated and soluble MNs have been examined in models of rats, and pigs, and have shown effective penetration with no-bleeding and increased patient compliance. In early testing, the use of rodent models is helpful but the Rodents have a higher skin permeability that may overestimate the results. Human skin which is similar to porcine skin is a more suitable option to predict clinical performance. All in all, both microneedles and optimized enhancers provide a promising and patient-friendly interface towards transdermal treatments**.**

3.1.Permeation Enhancers: Mechanisms and Optimization

CPEs are essential in terms of penetrating through the skin natural barrier, known as the stratum corneum-the bricks and mortar of stratum corneum consists of closely packed corneocytes that are enclosed within a lipid matrix. These additives work by altering the biophysical characteristics of the skin enabling the hydrophilic or high-molecular-weight drugs to pass transdermally through active pharmaceutical ingredients (APIs)[14].

Alcohols, fatty acids, terpenes, and surfactants are the most popular CPEs that have different mode of action:

- **Alcohols:** Promote the penetration mostly by dissolving lipids and destabilizing hydrogen bonding in the stratum corneum. Ethanol has been identified to bring in a rise in lipid fluidity in rat models which has been proved using differential scanning calorimetry (DSC) and Fourier- transform infrared spectroscopy (FTIR), which measure changes in phase transition temperature of lipids and disorder in lipid chains respectively.
- **Fatty acids:** interact with the lipid bilayers by insertion into the stratum corneum and form phase-separated domains or microchannels. These structural perturbations aid in enhanced drug diffusivity particularly those that are hydrophilic and amphiphilic in nature.
- **Terpenes:** Provide reversible, selectivity depotentiation. The supposedly temporary result erupts and extracts stratum corneum lipids, such as D-limonene, which do not have a destructive and lasting effect on the barrier. Terpenes are highly effective and tolerable on the skin as animals studies have revealed.
- **Sodium lauryl sulfate:** Lower surface tension, enhance solubility of drugs, but their applicability in medicine is hampered by the risk of causing irritancy. Therefore, optimization entails the trade-off between enhancement effect and cytotoxicity.

The selection and concentration of enhancers should be narrowed down depending on the properties of drugs and also on the formulation needs. The usefulness of CPEs is further enhanced by new formulations that include co-solvent system, nanoemulsions systems, and lipid-based delivery systems, which reduce the potential irritation effects[15].

3.2.Microneedle-Assisted Delivery: Design and Functionality

Microneedle arrays (MNs) are micro-projection devices that are minimally invasive systems that mechanically penetrate stratum corneum to form transient, aqueous delivery apertures of drug penetration into viable epidermis and dermis. MNs also have the potential to be used self-administered, and they cause no pain, which is an advantage over the old-fashioned hypodermic needles; they also exhibit good patient compliance, which makes them particularly promising when dealing with long-term or chronic diseases, as well as vaccinations.

These microneedles are classified according to the construction and operation:

- **Solid MNs:** These are usually made of metals or silicon and these are placed on the skin to puncture small holes termed as micropores and this is subsequently followed by a patch containing drug or drug formulation. According to the investigations in the rat skin and pig skin, solid MNs cause an increment in the permeability of the skin without damage to the tissues or serious bleeding.

- **Hollow MNs:** These MNs enable injection of liquid formulations of drugs in the dermal layer directly. They give accuracy in dose, but it is necessary that flow rate and backpressure be carefully maintained[16].
- **Coated MNs:** The drugs are coated on the surface of the needle and upon insertion on the skin, they are delivered. Coating uniformity and the loading of the drug are very significant to achieve reproducibility.
- **Dissolving MNs:** These are machined using polymers that are biodegradable such as polyvinylpyrrolidone (PVP), polylactic acid (PLA) or hyaluronic acid. During insertion, these MNs dissolve liberating the drug that is embedded in the matrix. Dissolving MNs dissolve very fast, appropriately deliver drugs up to the dermis and leave little waste in the animal models.

Mechanical testing validates that microneedles may reliably penetrate the stratum corneum without bleeding, or other long-term skin damage, a property that renders them suitable to repeated or chronic applications, e.g. in insulin delivery or hormone replacement therapy[17].

3.3.Comparative Efficacy and Safety in Animal Models

The performance, safety, and scalability of chemical enhancers and microneedles in transdermal application cannot be given a go-ahead without preclinical animal models. Nevertheless, the predictive value of such models is being influenced by similarity to human skin in anatomical and physiological terms.

Rodent Models (Rats and Mice)

- **Pros:** Cheap, genetically uniform and high throughput screenable**.**
- **Use:** Popularly applied to evaluate CPEs and microneedle permeation kinetics, irritation, and tissue response to the local tissue.
- **Limitation:** That due to thinner epidermis and increased density of the follicles, there may seem to be an overestimation of the permeation rates. They also have a different immune and healing system when compared to humans.

Example: Rat studies in which dissolving MNs were used illustrated quick absorption of low-molecular-weight drugs into the systemic circulation, but those studies necessitated scaling to administration in humans because the dermal drug absorption occurred faster in rodents than in humans[18].

Porcine Models (Mini-Pigs)

- **Pros:** Porcine skin (especially Back or ear) is comparable closely to human skin in thickness, lipid profile, collagenous production and immune profile.

- **Application**: Mini-pigs are also employed in longitudinal studies to determine drug depot formation, drug kinetics release, and immunogenicity particularly during vaccine delivery or biologics delivery.
- **Example:** Neutralizing MNs administering vaccination into pigs produced continued antigen release, reduced inflammatory reaction, and little skin injury, which is quite similar to the effect projected in the human body.

Translational Insight: Although rodents are excellent research tools against the outcomes of study that requires mechanistic processes and short-term outcomes, in situations where researchers are more interested in a long-term and complicated research model, porcine models are superior predictors of the human efficacy and safety (particularly in the application of devices to be administered over a prolonged period or complex molecules as they relate to human beings)[19].

4. SYNERGISTIC APPROACHES: COMBINING PERMEATION ENHANCERS WITH MICRONEEDLES

Use of chemical permeation enhancers (cCPEs) in combination with the microneedle (MN) technology is one of the potential approaches towards surmounting the formidable barrier role played by a stratum corneum towards transdermal delivery of the drug[20]. Combining all these methods will not give the advantage of the other methods as a specific set, but they produce a synergistic effect, meaning that it will allow the drug to penetrate, gain better bioavailability, and deliver more efficiently, a wider variety of pharmacological agents, and not only small-molecule drugs but also macromolecules and hydrophilic types of drugs.

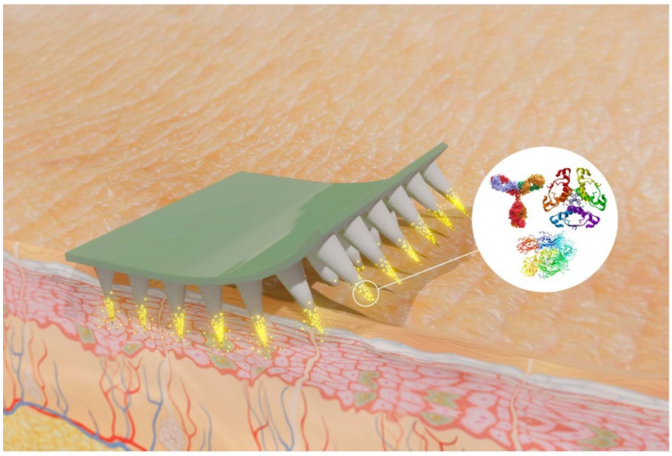

Figure 3: Microneedles[21]

The micro-needles (solid, coated, dissolving, and hollow) operate by making microchannels in the stratum corneum without penetrating the pain-sensing nerve. These microchannels greatly minimize the diffusional resistance of drugs thus increasing skin permeability. The microchannels formed with the help of MNs, however, close after a few hours as a result of skin repair process. In this case, CPEs are of great concern: if used alongside with microneedles, permeation enhancers can make microchannels stay longer open and break down lipid membranes to continue and increase drug delivery.

To illustrate, experiments where rats have been used to study the effects of adding insulin to their bodies have revealed that reapplying ethanol or oleic acid after placing MN could help in ensuring elevated levels of drugs in the plasma than would be possible with each of the two means of administration separately. The ethanol is used to solubilize the drug and enhance the capacity of the drug to partition in the skin and oleic acid to alter the lipid structure in and around the microchannels formed thereby enabling deeper diffusion. This taken together with dual mode approach will provide faster onset of action and maintenance of therapeutic levels- which is advantageous especially in drugs with small therapeutic windows and rapidly metabolized drugs.

The other important ability of this mix is that of dose flexibility, and patient compliance. In dissolvable MN patches containing drugs with low permeability, such as naltrexone or hydrophilic peptides, co-formulating with terpenes including menthol or d-limonene has resulted in a much higher transdermal flux in porcine and cadaver human skins models. Terpenes follow the path of residual lipid domains and intercellular pathways to facilitate, together with the physical disruptor of the microneedles, both pathways of transcellular and paracellular routes[22].

5. DISCUSSION

Chemical permeation enhancers (CPEs) and microneedles (MNs) have also been shown to have a potent combination that is able to penetrate through the skin barrier, amplified drug fluxes and effective transdermal delivers on difficult to deliver molecules such as peptides and vaccines. This synergistic model enhances bioavailability, favor self-administration, and corroborate the aims of personalized medicine. Clinical translation will need, however, standardized protocol, long safety term data, and additional human testings. Smart materials and integrated delivery system are the areas that should be viewed further to improve efficacy, safety and patient adherence in real world applications[23].

5.2.Interpretation and Analysis of Findings

Chemical permeation enhancers (CPEs) and microneedle (MN) systems have been found to be quite promising in breaking the skin barrier phenomenon, since many preclinical investigations have revealed this development. CPEs (ethanol, oleic acid and d-limonene) promote drug permeation by altering or destabilising the lipid matrix of the stratum corneum, whereas MNs generate temporary microchannels allowing more penetration of drugs. The combination of these methods shows synergistic tendencies in enhancing several effects, the MNs allow immediate drug entrance, and the CPEs allow additional prolonged drug passage as well as improved drug flux, drug bioavailability, and sustained therapeutic response, especially of macromolecular and hydrophilic drugs.

5.3.Implications and Significance

Such synergistic approach considerably expands the realm of transdermal drug administration, allowing to deliver such drugs as peptides, hormones, and even vaccines that are usually injected. MNs are non-invasive and the pain-free condition of CPEs optimized enables improvement in patient compliance, facilitate self-administration, and fit the ongoing personalized and wearable medicine initiatives. It also opens the doors of chronic care, pain management, and remote care, particularly low-resource environments, through effective and friendly platforms of delivering care[24].

5.4.Highlight Gaps and Future Research Directions

There are a few challenges that have to be overcome so that successful clinical translation is attained in spite of such developments. There is need to standardize the protocols in preclinical so as to attain reproducibility and regulatory compliance. The current long term data on cumulative skin effects and immune related responses of the Cumulative skin effect and immune response are limited therefore chronic use studies on the cumulative Skin effect and immune diligence should be considered. Besides, there are urgent needs to increase the clinical investigations (human subjects) to confirm the results of animal studies. The alternative avenues involving smart, responsive materials and integrated systems in order to further optimize and personalize the transdermal drug delivery systems should also be investigated in future[25].

6. CONCLUSION

The combination of chemical permeation enhancers (CPEs) and microneedle (MN) technologies in transdermal drug delivery has taken a novel level of approach, where the alternative process can be deemed viable, non-invasive, efficient, and patient-compliant. The CPEs alter the lipid structure and increase drug penetrability in the stratum corneum sufficiently to permit diffusion of the therapeutics through the skin barrier. Microneedles make microscopic holes in skin respectively penetrating directly into deeper levels without any feeling of pain. The combination of these two technologies translates into increased early drug penetration and permeation prolongation of drugs, which optimize drugs flux, system absorption, and effective improvement of the system pharmacotherapy. This method is also especially advantageous to hydrophilic, high-molecular-weight medications, biologics and vaccines that have typically been recalcitrant to transdermal administration. More studies are warranted to harmonize practices and assess the long-term safety and to formulate preparations more suitable to various individuals.

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