# EMERGING TECHNOLOGIES IN TRANSDERMAL DRUG DELIVERY

**Divneet Kaur, Shivan Jha, Dr. Puja Gulati, Rajesh Kumar*,**
School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab

**ABSTRACT**

Transdermal drug delivery systems (TDDS) have emerged as a promising alternative to conventional drug delivery methods, offering numerous advantages such as improved patient compliance, controlled drug release, and the avoidance of first-pass metabolism. Recent advancements in material science, nanotechnology, and biomedical engineering have significantly enhanced the efficacy and versatility of transdermal systems. This review highlights emerging technologies in TDDS, including microneedle arrays, iontophoresis, sonophoresis, and the incorporation of nanocarriers such as liposomes, ethosomes, and nanoparticles. These innovations aim to address challenges like limited drug permeability, variability in skin absorption, and the delivery of macromolecules such as proteins and peptides. Furthermore, the integration of smart technologies, such as wearable transdermal patches equipped with sensors for real-time monitoring and feedback, is reshaping the landscape of personalized medicine. The convergence of these technologies holds great promise for expanding the scope of transdermal delivery to a broader range of therapeutic agents, paving the way for safer, more efficient, and patient-centric drug administration systems.

**Keywords:** Transdermal drug delivery systems, microneedles, iontophoresis, sonophoresis, nanocarriers and biocompatible materials.

## INTRODUCTION

Transdermal drug delivery systems (TDDS) represent a rapidly evolving domain in pharmaceutical sciences, offering an effective and non-invasive method for systemic drug administration through the skin. TDDS circumvents challenges associated with oral and parenteral delivery methods, including poor bioavailability, first-pass metabolism, and patient non-compliance due to invasive procedures[1]. By facilitating controlled drug release, transdermal systems improve therapeutic outcomes and minimize adverse effects.

The skin, as the largest organ of the body, provides a vast and accessible surface for drug delivery. However, its primary function as a protective barrier limits the permeability of most drugs, particularly hydrophilic and large-molecule compounds[2]. Addressing this limitation, emerging technologies such as microneedles, iontophoresis, and sonophoresis are revolutionizing TDDS. Microneedles create micro-channels in the stratum corneum, allowing for enhanced drug penetration without causing significant pain or discomfort[3]. Iontophoresis and sonophoresis leverage electrical and ultrasonic energy, respectively, to facilitate the movement of drugs across the skin[4].

Nanotechnology has further expanded the scope of TDDS by introducing nanocarriers like liposomes, nanoparticles, and ethosomes, which enhance drug stability, solubility, and skin permeability[5]. Recent advancements in biomaterials have also led to the development of wearable and responsive transdermal patches that integrate sensors for real-time monitoring, offering a step toward personalized medicine[6].

This article explores the current advancements and future potential of transdermal drug delivery technologies. It also examines the challenges and opportunities in expanding TDDS applications to complex therapeutic agents, including proteins, peptides, and vaccines, to meet the growing demands of modern healthcare.

### Drug Delivery Routes Across Human Skin

Drug molecules can penetrate the skin through three main pathways:

1. **Sweat ducts**
2. **Hair follicles**
3. **Sebaceous glands**

Alternatively, they may cross directly through the stratum corneum, the outermost layer of the epidermis.

The stratum corneum, the outermost layer of the epidermis, is primarily made up of large, flat, polyhedral cells known as corneocytes. These cells, originating from the stratum granulosum, are essentially dead and lack nuclei. They are filled with keratin and encased in a tough, proteinaceous envelope. This layer is constantly renewed as new cells ascend from the stratum basale, while older cells are shed from the surface, a process occurring in the stratum disjunctum.

Structurally, the stratum corneum is composed of 10 to 15 layers of corneocytes, with its thickness ranging from 10–15 micrometers (μm) in a dry state to about 40 μm when hydrated. It is often described using the "brick and mortar" model, where corneocytes represent the "bricks" and are embedded within a "mortar" formed by intercellular lipids. This lipid matrix includes ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulfate, and sterol or wax esters. These lipids are produced by keratinocytes in the middle to upper layers of the stratum granulosum and are delivered into the extracellular space via lamellar bodies. After secretion, the lipids organize into structured lamellae, forming lipid bilayers that

differ significantly in phase behavior from conventional biological membranes.

Water plays a vital role in preserving the stratum corneum's function by acting as a plasticizer, preventing cracks and facilitating the formation of natural moisturizing factors (NMFs), which help maintain skin flexibility and hydration.

When evaluating transdermal drug delivery, understanding the physicochemical characteristics of both the drug and its formulation vehicle is key to identifying the most effective penetration route. The transcellular pathway involves the drug passing directly through corneocytes, requiring it to alternate between hydrophilic and lipophilic environments as it traverses approximately 4 to 20 lipid layers. This path presents significant resistance to most molecules. As a result, the intercellular route, which allows drugs to navigate between the corneocytes through the lipid matrix, is considered the dominant mechanism for drug penetration through the stratum corneum due to its relatively lower resistance.

**Advantages and Disadvantages of Transdermal Drug Delivery**

Advantages

1. **Convenient and Simple Dosing Regimen –** Requires only a **once-weekly** application, improving **patient adherence** to therapy.
2. **Alternative for Oral Administration –** Suitable for patients who **cannot tolerate oral medications**, such as those experiencing nausea or unconsciousness.
3. **Reduced Gastrointestinal Side Effects –** Avoids **direct irritation** of the **stomach and intestines**, making it ideal for drugs that cause **gastrointestinal discomfor**t.
4. **Avoidance of First-Pass Metabolism –** Bypasses **hepatic metabolism,** improving the bioavailability of drugs that are metabolized in the liver.
5. **Ideal for Drugs with Consistent Plasma Levels –** Ensures steady drug release, making it effective for medications requiring **long-term systemic delivery.**
6. **Useful for Drugs Degraded by the Gastrointestinal System –** Suitable for compounds susceptible to **enzymatic degradation** or **acidic environments** in the stomach.
7. **Minimized Risk of Infection –** Unlike **injections**, transdermal drug delivery **does not require needles,** reducing the risk of infection.

**Disadvantages**

1. **Local Skin Reactions:** Some individuals may experience skin irritation, such as redness, itching, or mild swelling. These reactions are often caused by the drug itself, the adhesive used to hold the patch in place, or other ingredients in the formulation.
2. **Size Restrictions of Drug Molecules:** Only drugs with relatively small molecular sizes, typically under 500 Daltons can efficiently penetrate the skin's outer barrier, limiting the range of medications suitable for this route.
3. **Solubility Requirements:** For effective absorption, a drug must have a balanced solubility in both water and lipids. Ideally, the drug's partition coefficient (log P) should be between 1 and 3 to move through both the oily stratum corneum and the water-rich inner layers.
4. **Risk of Contact Dermatitis:** Extended use of patches can sometimes cause allergic or inflammatory reactions due to continuous contact with the skin, particularly from adhesives or active substances.
5. **Limited Drug Compatibility:** Not all drugs can be delivered through the skin. Molecules that are too large, too hydrophilic, or not potent enough often fail to achieve therapeutic levels when applied transdermally.

**Table 1: Ideal properties of transdermal drug delivery system 11**

| S. No. | Properties | Range |
|---|---|---|
| 1 | Shelf life | Should be up to 2.5 years |
| 2 | Patch size | Should be less than 40 $cm^2$ |
| 3 | Dose frequency | Once a daily - once a week |
| 4 | Appearance | Should be clear or white color |
| 5 | Packaging properties | Should be easily removable of release liner |
| 6 | Skin reaction | Should be non-irritating |
| 7 | Release Properties | Should have consistent pharmacokinetic and pharmacodynamic profiles over time |
| 8 | Packaging properties | Should be easily removable of release liner (Duplicate) |

**Table 2: Ideal properties of drug for TDDS 11, 12**

| S. No. | Parameter | Properties |
|---|---|---|
| 1 | Dose | Should be low |
| 2 | Half-life (hr) | Should be 10 or less |
| 3 | Molecular weight | Should be less than 500 |
| 4 | Partition coefficient (Log P) | Octanol-water between –1 and 3 |
| 5 | Skin permeability coefficient | Should be less than $0.5 \times 10^{-3}$ cm/hr |
| 6 | Skin reaction | Should be non-irritating |
| 7 | Oral bioavailability | Should be low |
| 8 | Therapeutic index | Should be low |
| 9 | Concentration | Minute |
| 10 | pH of saturated aqueous solubility | 5-9 |
| 11 | Dose deliverable | <10 mg/day |

**Methods for Enhancing Transdermal Drug Delivery**

Several innovative strategies have been developed to improve transdermal drug delivery by overcoming the skin's natural barrier properties. One such method is the prodrug approach, where the drug molecule is chemically modified to enhance its lipid solubility and skin permeability. Once it penetrates into the deeper layers, enzymes such as esterases convert it back into its active form. This strategy has notably improved the skin absorption of compounds like NSAIDs and opioids. Another effective technique involves the use of eutectic systems, which are mixtures of two or more components that melt at a lower temperature than their individual counterparts. The reduced melting point increases the drug's solubility within skin lipids, enhancing its penetration. A well-known example is EMLA cream, a eutectic mixture of lidocaine and prilocaine, used for localized anesthesia.

Liposomes are another promising vehicle, consisting of lipid bilayers that encapsulate drugs and facilitate their transport across the skin. These structures may interact directly with skin lipids or partially infiltrate the stratum corneum, improving drug absorption. Similarly, solid lipid nanoparticles (SLNs) function as carriers that enhance skin hydration and form an occlusive layer, further increasing drug uptake. SLNs have been explored for delivering sunscreens, vitamins, and anti-inflammatory drugs. Iontophoresis employs a low-level electrical current to drive charged and uncharged drugs into the skin through mechanisms such as electro-repulsion and electro-osmosis. Its efficiency depends on parameters like electrode design, current strength, and formulation pH.

In contrast, electroporation utilizes short bursts of high-voltage pulses to create temporary pores in the skin, allowing larger molecules such as peptides and proteins to pass through. Ultrasound-based techniques, including sonophoresis, use sound waves to disrupt the lipid layers of the skin, facilitating deeper penetration of therapeutic agents. Laser radiation has also been employed, where controlled laser energy selectively removes parts of the stratum corneum to create channels for enhanced drug delivery without damaging underlying tissues.

Another advanced method is radiofrequency (RF) treatment, which applies high-frequency electrical currents to create heat-induced microchannels in the skin. The depth and number of these channels directly influence the rate of drug absorption. Magnetophoresis uses a magnetic field to improve the diffusion of diamagnetic molecules and can also alter skin structure to ease penetration. Microneedle technology has gained widespread use; these tiny needles painlessly pierce the stratum corneum, enabling drugs to reach the dermis without the discomfort associated with traditional injections.

In addition, skin abrasion techniques, inspired by dermatological resurfacing methods, involve mechanically disrupting the outer skin layers to reduce resistance to drug passage. Needle-free injection systems deliver drugs at supersonic speeds using compressed gases like helium, allowing penetration through the skin without needles, reducing pain and improving safety. Lastly, the application of external pressure, such as 25 kPa, can temporarily enhance the permeability of certain small molecules like caffeine through the skin, providing a non-invasive means to boost drug delivery efficiency.

These **advanced transdermal drug delivery techniques** offer

**alternative pathways** for drug administration, improving **bioavailability, patient compliance, and therapeutic efficacy** while overcoming traditional barriers to skin permeability.

**APPROACHES USED IN THE DEVELOPMENT OF TRANSDERMAL PATCHES**

A. Membrane-Moderated Systems

In this design, the drug reservoir is enclosed within a shallow compartment constructed from a drug-impermeable laminate made of metallic and plastic layers. This reservoir holds the drug either dispersed in a solid polymer matrix or suspended in a non-leachable, thick liquid medium such as silicone fluid. A polymeric membrane, which may be microporous or nonporous (e.g., ethylene vinyl acetate copolymer), regulates the drug release rate from the reservoir. To ensure consistent contact with the skin, a hypoallergenic and skin-friendly adhesive layer is applied on the outer surface of the membrane, facilitating effective adhesion of the transdermal drug delivery system (TDDS) to the skin.

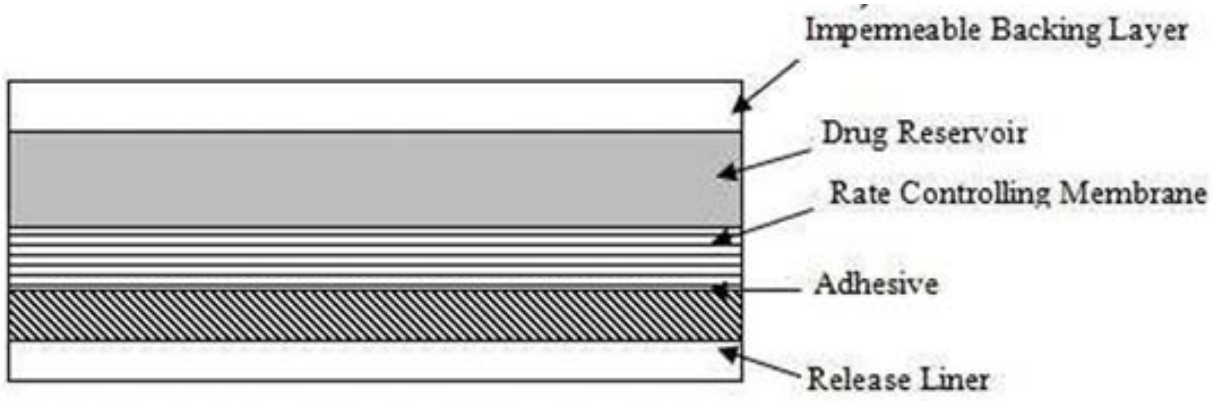


**Fig. 1: Design of Membrane moderated transdermal patch**

**Commercially Available Transdermal Systems**

Some well-known transdermal drug delivery products include Transderm-Nitro, which is designed for once-daily use to manage conditions like angina. Transderm-Scop offers medication delivery over several days and is commonly used for motion sickness prevention. Catapres-TTS provides a sustained release of medication over a one-week period and is typically prescribed for managing high blood pressure.

**B. Adhesive Diffusion-Controlled System**

This type of drug delivery system represents the most basic form of membrane-controlled transdermal patches. In this approach, the drug is mixed directly with an adhesive polymer to form the reservoir. This mixture is then applied as a thin film onto a backing layer made of a metallic-plastic laminate that does not allow drug passage. This setup creates the primary drug-containing layer.

To control the rate of drug release, one or more additional layers of adhesive polymer without any drug content are placed over the drug layer. These layers are of consistent thickness and help regulate the diffusion of the drug to the skin. These systems are known as drug-in-adhesive patches and can be either single-layer or multi-layer. The single-layer version contains one uniform layer with the drug incorporated directly into the adhesive. In contrast, the multi-layer design includes a second adhesive layer that also contains the drug, usually separated from the first by a membrane to further control release rates.

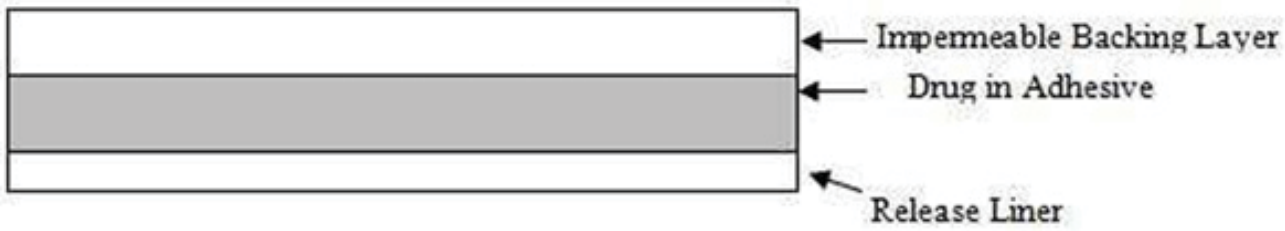


**Fig. 2: Design of adhesive diffusion controlled transdermal patch**

**Key Features of Drug-in-Adhesive Patches:**

Drug-in-adhesive transdermal systems offer several advantages. They often require less frequent application sometimes just once a week which can significantly boost patient adherence to treatment. These patches also tend to have a more discreet appearance, making them more cosmetically acceptable. Additionally, they provide strong adhesion to the skin, ensuring consistent drug delivery throughout the application period.

**Examples of Marketed Products:**

Some well-known drug-in-adhesive patches available in the market include Climara®, used for hormone replacement therapy, and Nitro-Dur®, commonly prescribed for angina relief.

**C. Matrix Dispersion Systems**

Matrix Dispersion Systems are a type of transdermal drug delivery system in which the active drug is evenly distributed throughout a polymer matrix. This matrix can be either hydrophilic (water-attracting) or lipophilic (fat-attracting), depending on the drug's compatibility. Once the drug is uniformly mixed with the polymer, the mixture is shaped into a disc with specific dimensions both area and thickness are carefully controlled to ensure consistent drug release.

This medicated disc is then placed on an occlusive backing layer, which prevents the drug from escaping in directions other than toward the skin. To ensure the patch stays in place during use, an adhesive material is applied around the edge of the disc, forming a ring that helps the system stick securely to the skin without interfering with drug release.

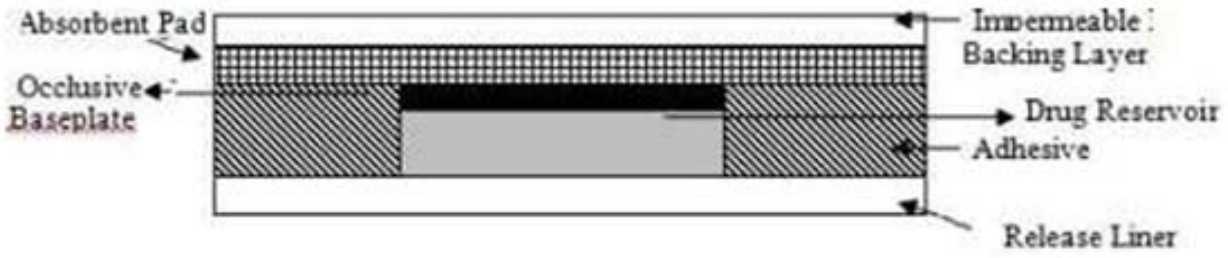


**Fig. 3: Design of matrix dispersion transdermal patch**

**Benefits of Matrix-Type Transdermal Patches:**

Matrix patches offer several notable advantages. First, they minimize the risk of dose dumping, meaning the drug is released at a controlled rate rather than all at once. Since the polymer matrix that contains the drug is in direct contact with the skin, it allows for efficient and consistent drug absorption. Additionally, because the adhesive is applied only around the edge, it does not interfere with the drug release process, enhancing the system's reliability.

**Examples of Marketed Matrix Patch Products:**

Several transdermal systems using matrix technology are commercially available, including Nitrodisc® (for angina), Nicotrol® (used in smoking cessation), and Deponit® (another nitroglycerin patch for heart conditions).

**D. Microreservoir System**

Microreservoir transdermal systems are a hybrid of the reservoir and matrix dispersion approaches. In this method, the drug is initially suspended in a water-based solution that contains a water-soluble polymer. This drug-polymer mixture is then blended into a lipophilic (fat-loving) polymer using high-shear mechanical mixing. This process creates tiny, uniform drug-containing reservoirs that are evenly distributed throughout the polymer matrix. These microscopic reservoirs are designed to prevent drug leakage (they are unleachable), ensuring controlled and sustained release.

To maintain the stability of this system, the polymer matrix is cross-linked, meaning chemical bonds are formed between polymer chains to lock the structure in place. The final product is shaped into a medicated disc with a fixed surface area and thickness, ensuring consistent drug delivery over time.

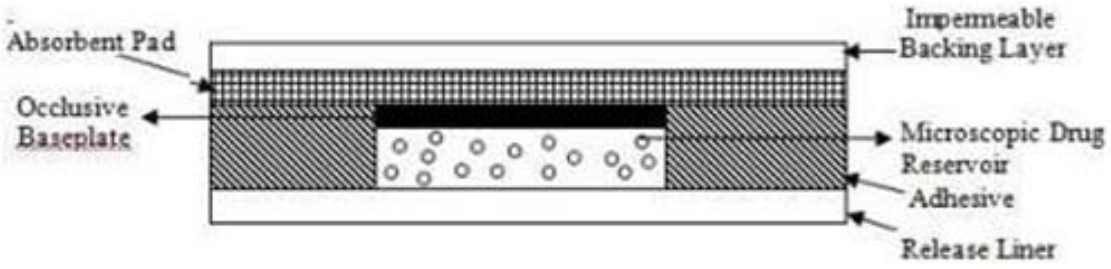


**Fig. 4: Design of micro reservoir transversal patch**

Commercially Available Matrix-Based Transdermal Patches:

Several transdermal drug delivery products that utilize matrix technology are available on the market. Nitrodisc® is used for managing angina by delivering nitroglycerin through the skin. Nicotrol® is designed to aid in smoking cessation by gradually providing nicotine. Deponit® is another nitroglycerin-based patch used to treat heart-related chest pain.

**RECENT ADVANCEMENTS IN THE FIELD OF TRANSDERMAL PATCHES**

Research in transdermal drug delivery has made remarkable progress recently, resulting in several innovative advancements. Some of the cutting-edge developments in this area include:

**Patch Technology for Protein Delivery**

Delivering large protein molecules through the skin is an emerging and promising area in transdermal drug delivery, although no commercial products currently incorporate proteins in patch form. TransPharma has developed an innovative printed patch technology designed to enable the delivery of proteins via the skin, which works alongside their existing ViaDerm delivery system. These patches contain accurately measured doses of proteins in a dry form. The underlying idea is that when the patch is applied, water-soluble proteins dissolve in the fluid naturally secreted by the skin through tiny openings created by radiofrequency (RF) microchannels. This process creates a concentrated protein solution directly on the skin's surface. The proteins then move by diffusion through these microchannels into the deeper, living layers of the skin, driven by a steep concentration gradient, allowing effective protein delivery.

**Painless Diabetic Monitoring Using Transdermal Patches**

A prototype transdermal patch, roughly 1 cm in size, is designed using polymers combined with thin metallic films. This patch includes a 3-by-3 grid of sampling points connected by metallic pathways. If the protective seal of the patch is broken, fluids and biomolecules from the skin's interstitial space can reach the patch surface. The patch contains built-in micro-heaters that generate brief, high-temperature pulses to safely disrupt the outermost skin layer, known as the stratum corneum. This process is painless and avoids damaging nerve endings or living cells beneath the skin. The tiny openings created, measuring about 20 to 50 micrometers wide, allow interstitial fluid to come into contact with the patch's electrodes, enabling effective sampling or drug delivery.

**Testosterone Transdermal Patch System for Young Women with Spontaneous Premature Ovarian Failure**

In women who have not yet reached menopause, the body typically produces about 300 micrograms of testosterone daily, with roughly half coming from the ovaries and the other half from the adrenal glands. However, women experiencing spontaneous premature ovarian failure (sPOF) often have reduced levels of androgens, including testosterone. To address this deficiency, a Testosterone Transdermal Patch (TTP) was designed to deliver testosterone at a rate similar to what the ovaries normally produce. When used alongside a hormone therapy regimen of cyclic estrogen and medroxyprogesterone acetate (E/MPA) in women with sPOF, the patch helped raise their free testosterone levels to near the higher end of the typical range seen in healthy premenopausal women.

**Transdermal Patch of Oxybutynin for Overactive Bladder**

A transdermal patch designed to deliver oxybutynin is available under the brand names Oxytrol in the United States and Kentera in Europe. This patch is thin, flexible, and transparent, and it is typically applied to areas like the abdomen, hip, or buttocks twice a week. It provides a steady

and continuous release of the medication over a period of three to four days. Compared to oral oxybutynin, this patch helps patients manage bladder control more effectively while reducing common side effects such as dry mouth and constipation.

**Nanotechnology in Transdermal Patches**

Microneedle technology is an innovative method for delivering drugs through the skin that combines the advantages of traditional needles and transdermal patches. These small devices, roughly the size of a dime, are made from polymers and contain hundreds of tiny hollow needles measuring between 200 and 1,000 micrometers in length. These microneedles penetrate the outermost layers of the skin, creating channels that allow drugs to pass through more easily. Additionally, this technology can be paired with an electronically controlled micropump, enabling precise timing and dosage of drug delivery, either automatically or on demand. Once approved by regulatory bodies like the FDA, such systems could give doctors and patients enhanced control over medication administration.

One example of this technology is Alza's patented Macroflux system, which uses microscopic projections to temporarily bypass the skin's protective barrier. Drugs are placed at the tips of these projections and delivered rapidly as a single, controlled dose when applied.

**Pain Relief Using Transdermal Patch Technology**

Transdermal patches are becoming more popular for managing pain effectively. One of the most recognized patches is Duragesic, which delivers fentanyl, a powerful opioid pain reliever. Another commonly used option is Lidoderm, a patch containing 5% lidocaine, which is specifically designed to relieve pain from post-herpetic neuralgia (nerve pain following shingles). A recent advancement in this field is the E-Trans fentanyl patch, which is about the size of a credit card and uses a built-in battery to actively control the release of fentanyl. This technology functions similarly to intravenous patient-controlled analgesia (PCA) systems but offers greater convenience and reduces the workload for healthcare providers.

**Molecular Absorption Enhancement Technology**

Molecular absorption enhancement technology focuses on improving how drugs penetrate the outermost layer of the skin, the stratum corneum. Researchers have explored various absorption enhancers, such as terpene derivatives and specific phenolic compounds, which help increase drug delivery through the skin. For example, compounds like linalool, alpha-terpineol, and carvacrol have been found to boost the absorption of haloperidol, with linalool raising it to therapeutic levels. Similarly, limonene, menthone, and eugenol have been shown to enhance the skin penetration of tamoxifen, while phloretin—a type of polyphenol—improves the absorption of lignocaine. Most of these findings come from studies conducted on excised skin samples, either from animals like pigs and rabbits or from human sources such as cadaver skin or skin removed during plastic surgery.

**FUTURE TECHNOLOGIES AND APPROACHES**

1. **Thermal Poration:** This technique uses short bursts of heat to create tiny water-filled channels through the stratum corneum, enabling drug delivery and the extraction of interstitial fluid glucose in humans.
2. **Jet Injectors:** These needle-free devices are being improved to deliver drugs in a controlled manner by propelling medication through the skin and into deeper tissues without the use of traditional needles.
3. **Micro-Infusion Pumps:** Utilizing a small needle inserted just below the skin surface, these pumps administer drug solutions at precise rates, with the delivery controlled by a large patch adhered to the skin. This method has been effectively used to deliver morphine.
4. **Combination Approaches:** Researchers are investigating the synergy of multiple technologies to enhance drug absorption, such as combining chemical enhancers with iontophoresis, electroporation, or ultrasound, as well as pairing iontophoresis with ultrasound or electroporation with either iontophoresis or ultrasound.
5. **TransPharma Innovations:** This company is developing transdermal therapies that prioritize patient safety, ease of use, and sustained drug release, aiming to maximize the benefits of patch-based delivery systems.
6. **ViaDerm System:** Designed for targeted delivery, this system may be utilized in dermatology and cosmetic treatments, as well as for administering painless, non-invasive vaccines.
7. **Altea Therapeutics:** The company focused on Parkinson's disease. Altea is working on a transdermal patch designed to reduce “off” periods in patients,

offering a more consistent and effective treatment option.

## CONCLUSION

The field of transdermal drug delivery has witnessed significant advancements, offering innovative solutions for controlled and sustained drug release. Various approaches, such as membrane-moderated systems, adhesive diffusion-controlled systems, matrix dispersion, and microreservoir systems, have been developed to enhance drug permeability and therapeutic efficacy. Recent breakthroughs, including protein-based patches, microneedle technology, and molecular absorption enhancers, have expanded the scope of transdermal patches beyond conventional drug delivery.

Emerging technologies, such as thermal poration, jet injectors, and micro-infusion pumps, continue to improve the efficiency, safety, and patient compliance of transdermal systems. The integration of electroporation, iontophoresis, and ultrasound further enhances drug absorption and bioavailability. As research progresses, transdermal patches are expected to revolutionize drug administration, providing non-invasive, effective, and convenient alternatives for treating various medical conditions.

With ongoing advancements and clinical trials, transdermal drug delivery holds great promise for the future, offering targeted therapies, enhanced patient comfort, and improved treatment outcomes.

## REFERENCES


1. Prausnitz, M. R., & Langer, R. (2008). Transdermal drug delivery. Nature Biotechnology, 26(11), 1261-1268.
2. Guy, R. H. (1996). Current status and future prospects of transdermal drug delivery. Pharmaceutical Research, 13(12), 1765-1769.
3. Kim, Y. C., Park, J. H., & Prausnitz, M. R. (2012). Microneedles for drug and vaccine delivery. Advanced Drug Delivery Reviews, 64(14), 1547-1568.
4. El Maghraby, G. M., Barry, B. W., & Williams, A. C. (2006). Liposomes and skin: From drug delivery to model membranes. European Journal of Pharmaceutical Sciences, 18(1), 1-26.
5. Gao, W., Emaminejad, S., Nyein, H. Y. Y., Challa, S., Chen, K., & Pebley, J. (2016). Fully integrated wearable sensor arrays for multiplexed in situ perspiration analysis. Nature, 529(7587), 509-514.
6. Gaur PK, Mishra S, Purohit S, Dave K. Transdermal drug delivery system- A review. Asian Journal of Pharmaceutical and Clinical Research. 2009; 2:14-20.
7. Aggarwal G, Dhawan S. Development, Fabrication and Evaluation of Transdermal Drug Delivery System - A Review. Pharmainfo.net. 2009; 7(5).
8. Heather AE. Transdermal Drug Delivery: Penetration Enhancement Techniques. Current Drug Delivery. 2005; 2:23-33.
9. Dhiman et al. Int J Pharm Pharm Sci, Vol 3, Suppl 5, 26-34 Touitou E, Junginger H, Weiner ND, Nagai T, Mezei M. Liposomes as carriers for topical & transdermal delivery. Journal of Pharmaceutical Science. 1994; 83:1189-1203.
10. Wissing SA, Muller RH. The influence of solid lipid nanoparticles on skin hydration & viscoelasticity-In vivo study. European Journal of Pharmaceutics and Biopharmaceutics. 2003; 56:67-72.
11. Guy RH, KaliaYN, Delgado-Charro MB, Merino V, Lopez A, Marro D. Iontophoresis: electro repulsion and electroosmosis. J control release. 2000; 64:129-132.
12. Mitragotri S, Blankschtein D, Langer R. Ultrasound mediated transdermal protein delivery. Science. 1995; 269:850-853.
13. Lee WR, Shen SC, Lai HH, Hu CH, Fang JY. Transdermal drug delivery enhanced and controlled by erbium:YAG laser. J controlled release. 2001; 75:155-166.
14. Treffel P, Panisset FF, Humbert P, Remoussenard O, Bechtel Y, Agache P. Effect of pressure on in vitro percutaneous absorption of caffeiene. Acta.Derm. Venereo.1993; 73:200 202.
15. Brown MB, Traynor MJ, Martin GP, Akomeah FK. Drug Delivery Systems: Skin Perturbation Devices. Methods in Molecular Biology. 2008; 437:119-139.
16. Keleb E, Sharma RK, Mosa EB, Aljahwi A-AZ. Transdermal Drug Delivery System – Design and Evaluation. International Journal of Advances in Pharmaceutical Sciences. 2010; 1:201-211.
17. Willams AC, Barry B W. Penetration Enhancers. Adv Drug Del Rev. 2004; 56:603-618.
18. Rhaghuram RK, Muttalik S, Reddy S. Once – daily sustained-release matrix tablets of nicorandil: formulation and invitro evaluation. AAPS Pharm.SciTech. 2003; 4(4):480–488.
19. Shaila L, Pandey S, Udupa N. Design and evaluation of matrix type membrane controlled
20. Transdermal drug delivery system of nicotin suitable for use in smoking cessation. Indian Journal of pharmaceutical sciences. 2006; 68:179-184.
21. Aarti N, Louk ARMP, Russsel OP. Richard HG. Mechanism of oleic acid induced skin Permeation enhancement in vivo in humans. Jour. Control. Release. 1995; 37:299-306.
22. Baichwal MR. Polymer films as drug delivery systems,

Advances in drug delivery systems. Bombay, MSR Foundation; 1985; 136-147.

23. Vyas SP, Khar RK. Targetted and controlled Drug Delivery Novel carrier system. 1st ed. CBS Publishers and distributors New Delhi; 2002; 411- 447.
24. Singh J, Tripathi KT, Sakia TR. Effect of penetration enhancers on the invitro transport of Ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. Drug Dev Ind Pharm. 1993; 19:1623-1628.
25. Ghosh B, Preethi GB, Mishra R, Parcha V. Transdermal Delivery of Ibuprofen and Its Prodrugs by Passive Diffusion and Iontophoresis. Int J Pharm Pharm Sci. 2010; 2(1):79-85.
26. Rajesh N, Siddaramaiah, Gowda DV, Somashekar CN. Formulation and Evaluation of Biopolymer Based Transdermal Drug Delivery. Int J Pharm Pharm Sci. 2010; 2(2):142-147.
27. Levin G, Kornfeld J, Patel Y R, Damon S. Transdermal Delivery : Success Through A Deep Understanding Of The Skin. Corium. [Serial Online]. [cited oct ]. Available online: URL: http:// www.ondrugdelivery.com.
28. Joseph S D. Transdermal Patches: An )nnovative Drug Delivery System That (as Raised Serious Safety Concerns. NewsInferno. [ serial online ]. [cited feb ]. Availaible online: URL: http://www.newsinferno.com.
29. Scheindlin S.Transdermal Drug Delivery: Past, Present, Future. Molecular interventions.
30. Chandrashekhra N S. Current Status and Future Prospects in Transdermal Drug Delivery. Pharmainfo.net.