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Medical Patches for Transdermal Drug Delivery System

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Abstract:
Transdermal drug delivery systems (TDDS) provide a non-invasive and controlled method of administering therapeutic agents through the skin for systemic absorption. These adhesive patches bypass first-pass metabolism and gastrointestinal degradation, thereby improving drug bioavailability and patient compliance. Structurally, TDDS consist of a backing layer, drug reservoir or matrix, adhesives, penetration enhancers, and release liners, all designed to regulate drug release and skin permeation. The stratum corneum serves as the primary barrier, with appendageal, transcellular, and intercellular pathways facilitating absorption. Various patch designs, including reservoir, matrix, and micro-reservoir systems, have been developed to optimize release kinetics. Clinically, transdermal patches are widely applied in pain management, smoking cessation, cardiovascular therapy, and hormone replacement, while recent advances explore their potential for biologics. Despite challenges such as skin irritation, limited drug suitability, and patient variability, ongoing innovations in materials and formulation technologies continue to expand their therapeutic applications.

Keywords: Transdermal Drug delivery system,TDDS, Patches, Skin Permeation, Layers

INTRODUCTION:
Transdermal drug delivery systems (TDDS) have emerged as a transformative innovation in pharmaceutical sciences, offering a non-invasive, patient-friendly, and controlled method of drug administration. Unlike conventional oral or injectable routes, TDDS deliver therapeutic agents directly through the skin into systemic circulation. This approach bypasses hepatic first-pass metabolism and avoids degradation in the gastrointestinal tract, thereby improving bioavailability and ensuring more consistent plasma drug concentrations. By maintaining steady drug levels, TDDS reduce fluctuations that often lead to adverse effects or therapeutic failure, making them particularly valuable for chronic conditions requiring long-term therapy.The development of TDDS can be traced back to the late 20th century. The first FDA-approved transdermal system was introduced in 1979 for motion sickness using scopolamine patches. This was followed by nitroglycerin patches in 1985, which marked a milestone in controlled drug release technology. Since then, transdermal patches have been widely adopted for diverse therapeutic categories, including pain management (fentanyl), smoking cessation (nicotine), hormone replacement (estradiol), and cardiovascular therapy (nitroglycerin, clonidine). These clinical successes established TDDS as a reliable platform for sustained drug delivery and encouraged further exploration into new drug classes, including biologics. Structurally, a transdermal patch is composed of several critical components that work synergistically to regulate drug release and absorption. The backing layer protects the formulation from environmental exposure, while the drug reservoir or matrix holds the active ingredient. Adhesives ensure attachment to the skin, penetration enhancers facilitate diffusion across the stratum corneum, and release liners are removed prior to application. Depending on design, patches may follow reservoir, matrix, or micro-reservoir systems, each offering distinct release kinetics. The stratum corneum, the outermost layer of the skin, serves as the primary barrier to drug penetration. Molecules can cross this barrier through appendageal, transcellular, or intercellular pathways, with physicochemical properties such as lipophilicity, molecular weight, and solubility playing decisive roles in absorption efficiency.

Figure 1. Introduction To Transdermal Patches

The advantages of TDDS extend beyond pharmacokinetics. They provide painless administration, improve patient adherence, and allow convenient discontinuation simply by removing the patch. Drug release can be sustained for hours to several days, depending on formulation, making TDDS particularly suitable for drugs with short biological half-lives that otherwise require frequent dosing. Furthermore, therapeutic failure or side effects associated with intermittent dosing can be minimized, as TDDS maintain a stable infusion of the drug over extended periods.

Despite these benefits, TDDS face several challenges. The stratum corneum restricts penetration of large or hydrophilic molecules, limiting the range of drugs suitable for this route. Skin irritation, variability in absorption due to age, hydration, or environmental factors, and restricted drug loading capacity remain significant hurdles. To overcome these limitations, researchers have explored advanced strategies such as chemical penetration enhancers, iontophoresis, sonophoresis, and microneedle-assisted patches. These approaches aim to temporarily disrupt or bypass the skin barrier, thereby expanding the scope of TDDS to include peptides, proteins, and other biologics.Recent innovations in polymer science and adhesive technologies have further improved patch performance. Smart materials capable of responding to physiological signals are being integrated into TDDS, enabling personalized dosing and real-time monitoring. Wearable devices that combine drug delivery with biosensors represent the next frontier, offering the potential for closed-loop therapeutic systems. Such advances highlight the growing importance of TDDS not only as a controlled release platform but also as a versatile system adaptable to the evolving demands of modern medicine

The Transdermal Patch:

A transdermal patch is a specialized drug delivery system designed to transport medication directly into the bloodstream through the skin. By controlling the rate of drug release, the patch ensures that a precise dose is administered over time. This controlled release not only enhances therapeutic effectiveness but also reduces systemic side effects compared to conventional routes such as oral, intravenous, or intramuscular administration. The central objective of transdermal drug delivery is to achieve consistent systemic circulation of the medication at a predetermined rate, while minimizing variability among patients.

Advantages And Disadvantages of Transdermal Patches:

A. Advantages:

1. Avoids first-pass metabolism ; drug bypasses the liver, improving bioavailability.
2. Extended and predictable duration ; provides sustained release over hours or days.
3. Bypasses gastrointestinal issues ; useful when oral absorption is poor or patients have vomiting/diarrhea.
4. Maintains stable plasma concentration ; reduces fluctuations in drug levels.
5. Non-invasive ; avoids injections and their discomfort.
6. Improves patient compliance ; less frequent dosing, easier schedules.

7. Suitable for short half-life drugs ; ensures continuous therapeutic effect.
8. Quick discontinuation possible ; therapy can be stopped immediately if toxicity occurs.
9. Useful alternative when oral route unsuitable ; e.g., unconscious patients or those with GI irritation. 10. Enhances drug effectiveness ;circumvents poor absorption and irritation in stomach/intestines

B. Disadvantages:

1. Limited to potent drugs ; only small doses (generally ≤ 5–25 mg/day) can be delivered.
2. Skin impermeability barrier ; hydrophilic or large molecules (>1000 Da) poorly absorbed.
3. Dose restriction ; patch size limits drug quantity.
4. Local skin reactions ; itching, rash, edema, or inflammation possible.
5. Variable absorption ; depends on skin condition, hydration, thickness, and individual differences.
6. Not suitable for high plasma levels ;difficult to achieve with patches.
7. Comfort issues ; patches may feel bulky or inconvenient to wear.
8. Cost considerations ; may be more expensive than oral formulations.
9. Risk of patch failure ; detachment or inconsistent drug release.
10. Clinical justification required ; not every drug or patient benefits from TDDS.

Design Of. Transdermal Patches:

The transport of drugs across the skin is influenced by several factors, including the permeability of the skin, the surface area and duration of application, and the metabolic activity of the skin, which can contribute to first-pass metabolism. Since each drug has distinct physicochemical properties, these characteristics play a critical role in determining its suitability for transdermal delivery. For effective absorption, the drug should ideally be non-ionic and relatively lipophilic to cross the stratum corneum barrier. Molecular size is another limiting factor, as compounds larger than 500 Daltons face difficulty penetrating the skin. Additionally, transdermal systems are most practical when the therapeutic dose required is less than 10 mg per day, ensuring efficient delivery without overloading the skin's absorption capacity.

Basic Component of Transdermal Patch:

Transdermal patches are designed with multiple layers that work together to deliver medication through the skin and into the bloodstream. The outermost backing layer protects the patch from environmental exposure and is typically made of flexible, waterproof materials such as polyethylene or polypropylene. Beneath this lies the adhesive layer, which secures the patch to the skin using a strong, hypoallergenic adhesive that is gentle on contact. The drug layer contains the active pharmaceutical ingredient, formulated to release at a controlled rate over time. To regulate this process, a rate-controlling membrane made of semi-permeable material ensures steady drug diffusion. Additionally, a protective liner shields the patch and adhesive until use, and must be removed before application. Structurally, transdermal patches can be classified into four main types—drug-in adhesive, reservoir, matrix, and micro-reservoir systems—with reservoir and matrix designs being the most commonly used in commercial products.

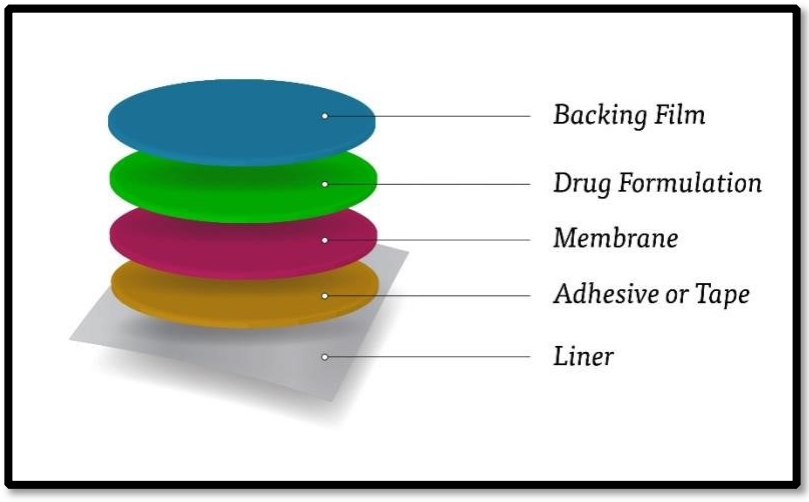

Figure 2. Components of Transdermal patches

Common materials used for making patches:

1. **Polymer matrix/drug reservoir**

In transdermal drug delivery systems (TDDS), polymers play a crucial role in regulating the release of medication from the patch. To be effective, these polymers must exhibit strong biocompatibility and chemical compatibility not only with the drug itself but also with other components of the system, such as penetration enhancers and pressure-sensitive adhesives (PSA). Their function is to ensure consistent and reliable drug delivery over the intended period of application. Depending on their origin, polymers used in TDDS are broadly classified into two categories: natural polymers and synthetic polymers, each offering distinct advantages in formulation and performance. Examples: Sodium alginate, Chitosan, Gelatin, Polyethylene etc.

2. **Membrane:**

In multilayer transdermal patches, the membrane plays a critical role in regulating drug release from the reservoir. Its diffusion properties determine how much of the drug or excipients become available to the skin over time, ensuring controlled and sustained delivery. Commonly used materials for these membranes include ethylene vinyl acetate, silicone rubber, and polyurethane, all of which provide semi-permeable characteristics that allow precise modulation of drug diffusion rates. By tailoring the membrane composition, manufacturers can achieve predictable and effective therapeutic outcomes.

3. **Drugs:**

The effectiveness of transdermal drug delivery systems (TDDS) largely depends on the properties of the drug selected for formulation. Transdermal patches are particularly advantageous for drugs that undergo extensive firstpass metabolism, as this route bypasses the liver and enhances bioavailability. They are also suitable for drugs with a narrow therapeutic window, where controlled release helps maintain stable plasma concentrations, and for drugs with short half-lives, since continuous delivery reduces the need for frequent dosing and improves patient adherence.

4. **Permeation enhancer:**

In transdermal drug delivery systems, enhancers are used to increase skin permeability so that drugs can reach the desired therapeutic level. For safe and effective use, an ideal enhancer should be non-toxic, non-allergic, and nonirritating, while providing a controlled and reversible effect on skin permeability. It must also be pharmacologically inert, acting specifically for a predictable duration without interfering with the drug's activity. Additionally, enhancers should demonstrate chemical and physical compatibility with both the drug and other excipients in the formulation. To ensure patient acceptability, they are preferably odorless and colorless, maintaining the patch's safety and comfort during application.

5. **Pressure-sensitive adhesives (PSA)**

In transdermal drug delivery systems (TDDS), pressure-sensitive adhesives (PSAs) are essential for attaching the patch securely to the skin with minimal force, while ensuring that no residue is left behind upon removal. These adhesives must provide strong yet gentle adhesion to maintain patient comfort and compliance. Commonly used PSA polymers in TDDS include polyacrylates, polyisobutylene, and silicone-based adhesives, all of which offer reliable bonding properties and compatibility with other patch components.

6. **Backing Film:**

In transdermal drug delivery systems, the backing film is chosen for its appearance, flexibility, and ability to provide occlusion. When designing this layer, it is essential to ensure strong chemical resistance and compatibility with excipients, since prolonged contact may lead to additive detachment or unwanted diffusion of drugs and enhancers through the film. Common materials used for backing films include vinyl, polyethylene, polyester, aluminium, and polyolefin films. In addition to the backing layer, other excipients are incorporated to optimize patch performance. Solvents such as chloroform, methanol, acetone, isopropanol, and dichloromethane are used during the preparation of drug reservoirs, while plasticizers like dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol are added to impart flexibility and maintain the mechanical integrity of the patch.

7. **Other excipients such as plasticizers or solvents:**

In addition to the primary components of a transdermal patch, other excipients such as solvents and plasticizers are incorporated to optimize performance. Solvents like chloroform, methanol, acetone, isopropanol, and

dichloromethane are commonly used during the preparation of drug reservoirs, as they help dissolve active ingredients and facilitate uniform distribution within the patch. Meanwhile, plasticizers such as dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol are added to improve flexibility and mechanical strength, ensuring that the patch remains durable and comfortable during use. Together, these excipients enhance the stability, usability, and effectiveness of TDDS formulations.

Routes of Drugs penetrations Through Skin:

Drug molecules can enter the body through the skin by two primary routes: the transepidermal pathway and the transappendageal pathway. Each pathway has distinct mechanisms and is influenced by the physicochemical properties of the drug.

1. **Transepidermal Pathway**

This is the most common route and involves penetration directly through the layers of the epidermis, particularly the stratum corneum, which is the outermost barrier of the skin. The stratum corneum is highly structured, consisting of corneocytes (dead keratinized cells) embedded in a lipid matrix, often described as a "brick-andmortar" arrangement.

1. **Intracellular Route:**

Drugs pass through the corneocytes themselves.This pathway is more favorable for hydrophilic or polar molecules, which can dissolve in the aqueous environment inside the cells. However, because corneocytes are densely packed with keratin, diffusion is relatively slow.

1. **Intercellular Route:**

Drugs move between the corneocytes, navigating through the lipid-rich spaces.

This pathway is more suitable for lipophilic or non-polar molecules, which can dissolve in the continuous lipid layers. It is considered the dominant route for most drugs, since the lipid matrix provides a relatively continuous pathway for diffusion.

Together, these two sub-routes make the transepidermal pathway the primary mechanism for drug absorption in transdermal drug delivery systems.

2. **Transappendageal Pathway**

This pathway bypasses the stratum corneum by allowing drugs to penetrate through skin appendages such as hair follicles and sweat glands.

a. Hair Follicles:

Act as small reservoirs that can store drugs temporarily, releasing them gradually into deeper skin layers.

Particularly useful for drugs that are poorly absorbed through the stratum corneum. **b.**

Sweat Glands:

Provide narrow channels through which certain molecules can diffuse. Although their surface area is relatively small compared to the stratum corneum, they can contribute to localized drug penetration. While the transappendageal pathway accounts for a smaller fraction of overall drug absorption, it can be significant for certain formulations, especially those targeting follicular delivery (e.g., treatments for acne or localized skin conditions).

Types and Preparation Methods Of Transdermal Patches:

Transdermal medical patches are generally classified into four main types based on their design and drug delivery mechanism: drug-in-adhesive, reservoir, matrix, and micro-reservoir systems. In the drug-in-adhesive type, the active substance is directly incorporated into the adhesive layer, which both secures the patch to the skin and controls drug release. Reservoir systems, on the other hand, contain a liquid or gel formulation enclosed within a compartment, with a rate-controlling membrane regulating the diffusion of the drug. Matrix systems disperse the drug within a polymer matrix, allowing the material itself to govern the release rate. Micro-reservoir systems combine features of reservoir and matrix designs by suspending the drug in microscopic reservoirs embedded within a polymer structure. Among these, reservoir and matrix systems are the most widely used in commercially available patches because they provide reliable drug release profiles and are easier to manufacture at scale.

Single-layer Drug in Adhesive:

In the single-layer drug-in-adhesive system, the adhesive itself plays a dual role by both securing the patch to the skin and serving as the medium for drug delivery. The active ingredient is incorporated directly into the adhesive layer, which ensures continuous contact with the skin and controlled release of the drug. To protect the formulation before use, the adhesive layer is enclosed between a backing material and a removable protective liner. This design is simple, flexible, and widely used because it minimizes the number of components while maintaining effective drug release.

Multi-layer Drug in Adhesive:

The multi-layer drug-in-adhesive patch is designed much like the single-layer system, but with added complexity. In this type, two adhesive layers are incorporated, and both are responsible for releasing the drug to the skin. Between these adhesive layers, an additional layer is often included to hold the drug formulation, which may or may not be separated by a membrane depending on the design. To ensure stability and usability, the patch is protected by a temporary liner that is removed before application and a permanent backing layer that provides structural support. This configuration allows for more controlled drug delivery compared to the simpler single-layer system.

Reservoir:

In the reservoir type of transdermal patch, the drug formulation is stored within a distinct compartment located between the backing support layer and a rate-controlling membrane. The membrane, often designed with micropores, regulates the diffusion of the drug to the skin surface, ensuring a controlled release profile. The reservoir can contain the active ingredient in various forms, such as a solution, suspension, gel, or dispersed within a solid polymer matrix. This design allows for precise control over drug delivery, but it also requires careful manufacturing to prevent leakage and maintain stability.

Matrix:

In the matrix type of transdermal patch, the drug is evenly distributed within a polymer base, which may be either hydrophilic or lipophilic depending on the formulation requirements. This drug-loaded polymer is then fabricated into discs of defined thickness and surface area to ensure consistent dosing and release. The polymer matrix itself acts as the rate-controlling element, gradually releasing the active ingredient as it comes into contact with the skin. This design is relatively simple, stable, and widely used in commercial patches because it minimizes the risk of leakage while maintaining predictable drug delivery.

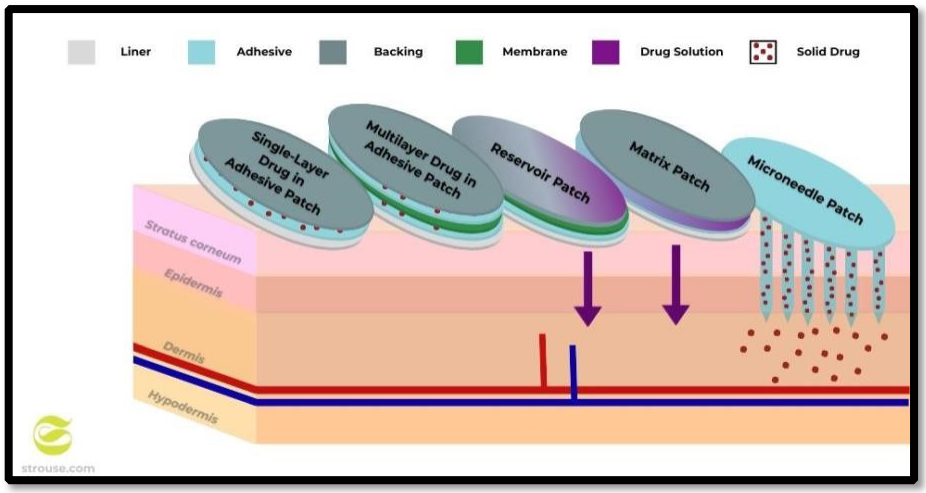

Figure3 Type of Transdermal Patches

Ideal Medicinal Properties for Transdermal Patches:

Transdermal patches possess the important property of controlled drug release, allowing medications to be delivered steadily over an extended period, which helps maintain consistent plasma concentrations and reduces fluctuations that could cause side effects. Another valuable property is their ability to bypass first-pass metabolism, ensuring higher bioavailability of drugs compared to oral administration and often requiring lower doses for the same therapeutic effect. Additionally, they provide a non-invasive and reversible route of administration, offering convenience to patients while allowing immediate discontinuation of therapy simply by removing the patch.

TABLE 1 medicinal properties of Transdermal Patches:

Parameters	Properties
Dose	Drug dosage should be low <20 mg/day
Half life	<10 hours
Molecular weight	<500 Dalton
Partition coefficient	Log P (octanol-water) between 1.0 and 3.0
Skin permeability partition coefficien	>0.5 × 10-3 cm/h
Lipophilicity	10 <Ko/w <1000
Solubility in water	>1 mg/mL
Oral bioavailability	Must be low
Therapeutic index	Must be low
Melting point	<200◦C
PH	5.0-9.0
Skin reaction	Non-irritating and non-sensitizing

Table 2. Marketed Available Transdermal Patches

Market-Available Transdermal Patches

Drug/Active Ingredient	Brand Examples	Therapeutic Use
Nicotine	Nicoderm CQ. Habitrol, Nicorette	Smoking cessation aid
Fentanyl	Duragesic	Chronic pain management (opioid analgesic)
Buprenorphine	Butrans	Pain relief (opioid partial agonist)
Clonidine	Catapres-TTS	Hypertension
Nitroglycerin	Nitro-Dur, Minitran	Angina pectoris (anti-anginal)
Estradiol	Climara, Vivelle-Dot	Hormone replacement therapy (HRT
Testosterone	Androderm	Male hypogonadism (testosterone deficiency)
Rivastigmine	Exelon Patch	Alzheimer's disease and dementia
Selegiline	Emsam	Depression (MAO inhibitor)
Scopolamine	Neupro	Motion sickness prevention
Lidocaine	Transderm Scop	Local pain relief (post-herpetic neuralgia)
Diclofenac	Lidoderm	Overactive bladder
Methyiphenidate	DaytranPatch	ADHD (Attention Deficit Hiteractivity Disorder)

Recent advancements in Medical Transdermal Patches:

Recent advancements in transdermal patches have significantly expanded their role as innovative drug delivery systems. Traditionally used for small, lipophilic drugs, modern patches now incorporate microneedle arrays, nanocarriers, and smart sensor technologies to overcome the skin's natural barrier and deliver a wider range of therapeutics, including biologics and vaccines. Microneedle-based patches create microscopic channels that allow painless and efficient transport of macromolecules, while nanocarrier systems such as liposomes and solid lipid nanoparticles enhance solubility and controlled release of poorly permeable drugs. Smart patches represent another breakthrough, integrating biosensors that monitor physiological parameters like glucose levels and adjust drug release in real time, paving the way for personalized medicine. In addition, advances in polymer science and adhesive technology have improved patch flexibility, breathability, and patient comfort, reducing skin irritation and enhancing compliance. These innovations not only broaden the therapeutic scope of transdermal patches but also align with the growing demand for non-invasive, patient-friendly, and precise drug delivery solutions in modern healthcare.

Smart Patches:

Smart patches represent a new generation of transdermal systems that integrate sensors and advanced materials to monitor patient conditions and automatically regulate drug delivery. In 2014, researchers introduced a microneedle-based smart patch capable of painless, continuous intradermal glucose monitoring for diabetics. This design employed the conducting polymer poly(3,4-ethylenedioxythiophene) (PEDOT) both as an electrical mediator for glucose detection and as a stabilizing matrix for the enzyme glucose oxidase. Building on this concept, subsequent developments led to an insulin-releasing smart patch composed of 121 microneedles embedded with nanoparticles. These nanoparticles encapsulate insulin along with glucose oxidase, which converts glucose into gluconate. Surrounded by hypoxia-responsive polymers, the system detects oxygen depletion caused by elevated glucose oxidase activity and responds by degrading the nanoparticles, thereby releasing insulin in a controlled, painless manner. This innovation highlights the potential of smart patches to provide real-time monitoring and responsive therapy, particularly for chronic conditions such as diabetes.

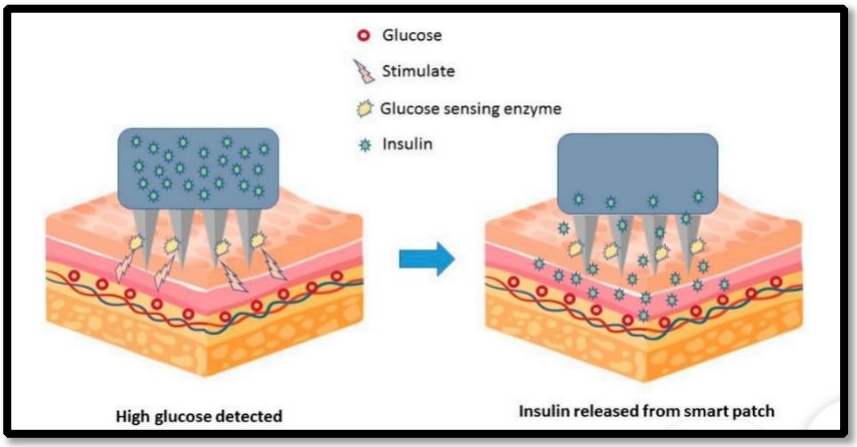

Figure 4 The microneedle-based smart patch is designed to penetrate the skin layer painlessly, delivering therapy directly into the interstitial fluid. Each microneedle contains nanoparticles loaded with insulin and the glucosesensing enzyme glucose oxidase. When glucose levels rise, glucose oxidase activity increases, converting glucose into gluconate. This biochemical reaction creates an oxygen-depleted environment within the nanoparticles. The surrounding hypoxia-responsive polymers detect this change and respond by degrading, which in turn triggers the controlled release of insulin. This mechanism allows the patch to act as a self-regulating system, providing insulin only when needed and offering a promising approach for diabetes management.

Wound healing is a highly dynamic regenerative process influenced by changing physical and chemical conditions, making its monitoring especially valuable for bedridden patients. Recent innovations include flexible, fully printed smart patches capable of measuring wound pH and fluid volume using electrodes printed on a polydimethylsiloxane (PDMS) substrate. These sensors demonstrated high sensitivity to pH changes and could quantify hydration levels through resistivity measurements. Beyond general wound healing, smart patches have been developed for diabetic foot ulcers (DFU), using conductive hydrogel networks with ultra-high transparency. Such patches not only allow visual monitoring of healing but also promote haemostasis, enhance cell communication, prevent infection, stimulate collagen deposition, and improve vascularity through angiogenesis. They can even indirectly monitor blood glucose levels from wound fluid while simultaneously treating chronic wounds. Another advancement involves smart patches for controlled delivery of natural compounds like curcumin. These systems employ paraffin wax and polypropylene glycol as phase change materials (PCM), combined with graphene-based heating elements. By electronically controlling the solid-to-liquid transition of PCM, drug release can be repeatedly initiated or stopped, offering precise dosing beyond passive diffusion. Together, these technologies highlight the versatility of smart patches in wound care, combining monitoring, therapy, and controlled drug delivery in a single platform.

Dissolving/Degradable Patches:

Dissolving transdermal patches represent a novel approach to drug delivery, designed to break down on the skin and eliminate the need for removal or disposal. These systems are typically fabricated from biodegradable materials that are naturally absorbed by the body after use. A notable proof-of-concept study in 2019 demonstrated the effectiveness of a gentamicin-loaded dissolving microarray patch in a mouse model of bacterial infection. When applied to the ears of mice, the patch successfully controlled Klebsiella pneumoniae infection. Furthermore, animals treated with these lysing patches showed a marked reduction in bacterial burden within nose-associated lymphoid tissue and lungs compared to untreated controls. This innovation highlights the potential of dissolving patches as a painless, eco-friendly, and efficient method for delivering antibiotics and managing infectious diseases.

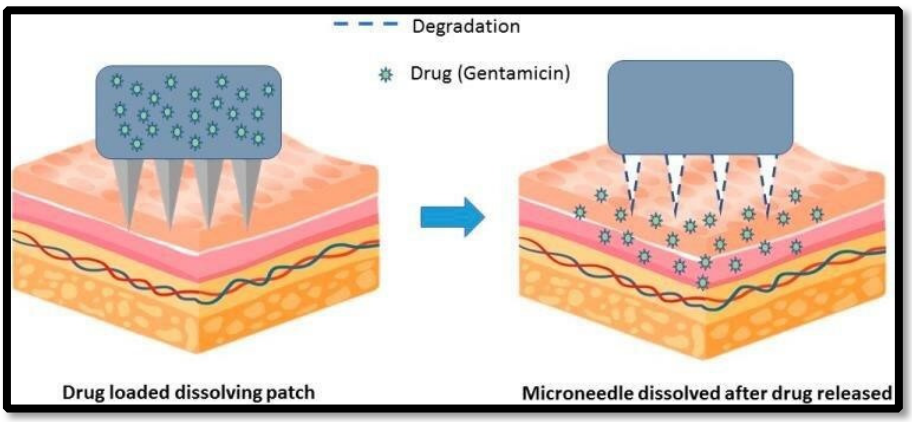

Figure 5. Dissolving/Degradable Patches

microneedles were engineered to deliver antigen-peptide conjugates such as SIINFEKL directly to the skin's immune system. Although this strategy successfully enhanced antigen-specific cytotoxic T-cell responses, it paradoxically accelerated tumor progression in melanoma models, underscoring the complexity of immune modulation and the need for further refinement. In cardiovascular applications, dissolvable microneedles fabricated by centrifugal casting were loaded with sodium nitroprusside (SNP) and sodium thiosulfate (ST) to provide rapid blood pressure reduction in hypertensive emergencies. The inclusion of ST was particularly important, as it mitigated the toxic side effects associated with continuous SNP administration, thereby offering a safer and more effective therapeutic option. Meanwhile, in the cosmetic industry, concerns about environmental pollution from non-degradable polymers have prompted the development of biodegradable alternatives. A promising candidate is polylactic acid (PLA), which, when combined with a phycocyanin-alginate composite at an optimized 40/60 ratio, demonstrated superior film flexibility and controlled release properties under mild processing conditions. Collectively, these studies illustrate the versatility of microneedle patches across diverse therapeutic and cosmetic domains, while also emphasizing the importance of continued in vivo and clinical investigations to ensure safety, efficacy, and sustainability.

Three-Dimensional (3D)-Printed Patches:

Recent advances in 3D printing have opened new possibilities for the design of personalized transdermal patches, enabling drug delivery systems that can be tailored to the unique therapeutic needs of individual patients. One notable example is the use of gelatin methacrylate (GelMA) hydrogels for wound healing applications. Owing to their shear-thinning properties, GelMA hydrogel inks can be successfully printed into porous, water-absorbing structures that incorporate vascular endothelial growth factor (VEGF)-mimicking peptides. These patches gradually release VEGF, thereby promoting cell viability, proliferation, and tubular structure formation, which are essential for tissue regeneration and wound closure. Beyond wound care, continuous liquid interface production (CLIP) has been employed to fabricate microneedle arrays with multifaceted geometries that provide greater surface area compared to conventional pyramid designs. This innovation allows for improved coating of vaccine components such as ovalbumin and CpG, leading to enhanced skin charge retention, stronger activation of immune cells in draining lymph nodes, and robust humoral and cellular immune responses. Such CLIP-printed microneedles represent a promising platform for non-invasive, self-administered vaccination. In another application, stereolithography (SLA) technology has been used to print microneedle patches for the delivery of rifampicin, a high molecular weight antibiotic that

suffers from poor oral bioavailability and hepatotoxicity. By incorporating sub-apical holes into the needle tips, researchers improved mechanical strength and penetration efficiency, achieving effective drug transport through porcine skin and desirable bioavailability in vivo. Powder extrusion (DPE) has also emerged as a versatile method, allowing direct incorporation of excipients and drugs such as ibuprofen and diclofenac sodium into ethylene-vinyl acetate (EVA) copolymer matrices. This process modifies polymer crystallinity, enabling controlled drug release and thermal stability across different formulations, which is particularly advantageous for personalized medicine. Finally, digital light processing (DLP) has been applied to create patient-specific patches for cosmetic applications, such as the delivery of Acetyl-hexapeptide 3 (AHP-3) for wrinkle management. By optimizing photocurable resins with polyethylene glycol diacrylate (PEGDA) and vinylpyrrolidone (VP), researchers achieved patches with improved mechanical strength, swelling behavior, and biocompatibility. These personalized patches, designed using 3D facial scans and CAD software, demonstrated effective skin penetration and minimal cytotoxicity, marking the first successful use of photopolymers in drug-loaded transdermal systems. Collectively, these studies highlight the versatility of 3D printing technologies—from wound healing and vaccination to antibiotic therapy and cosmetic care—while emphasizing their potential to revolutionize personalized transdermal drug delivery.

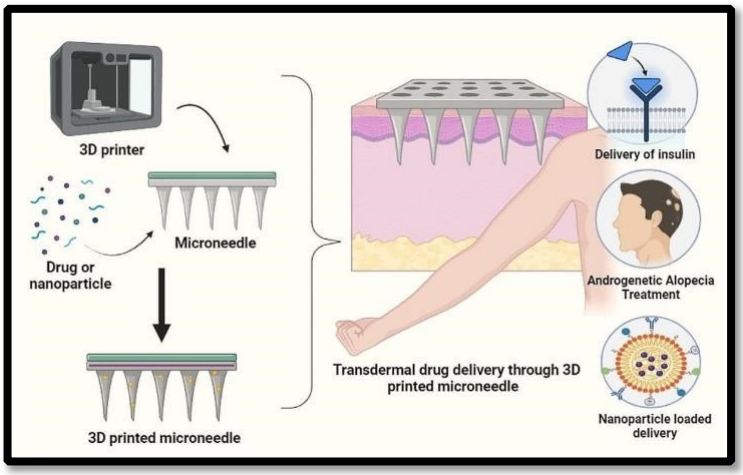

Figure 6. Three-Dimensional (3D)-Printed Patches:

High Loading/Release Patches:

Long-acting transdermal drug delivery systems require both high drug loading and precise control over release kinetics, and recent innovations in polymer chemistry have made significant progress toward this goal. One promising approach involves the development of hydroxyphenyl (HP)-modified pressure-sensitive adhesives (PSAs), which improve drug–polymer miscibility through the formation of dual-ionic hydrogen bonds. These bonds, established between R(3)N and R(2)NH-type drugs and HP-PSA, are relatively strong yet reversible, unlike conventional ionic or neutral hydrogen bonds. As a result, drug loading capacity was increased by 1.5- to 7-fold, while release rates could be finely tuned between one-fifth and one-half of the original rate without altering the overall release profile. Pharmacokinetic studies confirmed that HP-PSA patches maintained sustained plasma drug concentrations, avoided sudden bursts of release, and extended both the area under the concentration–time curve (AUC) and average dwell time by more than six-fold. Mechanistic investigations revealed that ionic drug repulsion within HP-PSA enhanced drug loading, while incomplete hydrogen bond transfer ensured reversibility, ultimately making the release percentage comparable to non-functional PSAs. This unique balance of high loading efficiency and controlled release positions HP-PSA as a strong candidate for long-acting transdermal systems, and the concept of dual-ionic hydrogen bonding may inspire new drug delivery strategies in non-polar environments.

Complementary research has explored alternative methods to overcome the limitations of conventional pharmaceutical polymers, which often inhibit drug recrystallization through strong intermolecular bonding but compromise release rates. A novel ionic liquid (drug IL) strategy was introduced using carboxyl-based PSAs, achieving a five-fold increase in drug loading through synergistic interactions between carbonyl groups of the drug and PSA. This mechanism provided a new pathway for designing high-capacity, high-release patches. Building on this, researchers developed a COOH polyacrylate polymer (PA-1) patch for non-steroidal

anti-inflammatory drugs (NSAIDs) such as ibuprofen. The PA-1 system improved drug loading and skin absorption by 2.4-fold and 2.5-fold, respectively. Interestingly, the hydrogen bonds between COOH groups of the drug and polymer were weakened by repulsive interactions, which simultaneously enhanced conductivity of PA-1, as confirmed by dielectric spectroscopy, electron paramagnetic resonance (EPR), four-point probe analysis, and molecular modeling. The appearance of COO^- groups indicated ion–ion repulsion as a key driver of performance. Together, these findings demonstrate that reducing hydrogen bonding through ionic repulsion can be a viable strategy for constructing large-capacity, high-emission transdermal patches, paving the way for more effective and personalized long-acting drug delivery platforms.

Applications Of Transdermal Patches:

Transdermal Patches for Patches for Vaccination:

Scientists are working on transdermal patches that can deliver vaccines directly through the skin, offering a simpler and less painful alternative to traditional injections. One example is a microneedle patch developed for smallpox vaccination. When tested in mice, this patch triggered the production of neutralizing antibodies within three weeks, and the immune response was sustained for up to twelve weeks. In addition, there was a marked rise in interferon-gamma (IFN-γ) secreting cells, suggesting that such patches could serve as effective tools for vaccine delivery and long-term immune protection. Another team designed a dissolvable microneedle patch for influenza vaccination, specifically targeting antigen-presenting cells in the skin. The microneedles, made from a biocompatible polymer, encapsulated an inactivated influenza virus and dissolved within minutes after application. This approach generated strong antibody responses along with robust cell-mediated immunity in mice, providing complete protection against lethal influenza infection. The findings highlight how microneedle patches can improve vaccine effectiveness, simplify administration, and potentially expand coverage by enabling self-application without the need for injections.

Transdermal Patches for Gene Therapy:

In recent years, transdermal patches have been explored as innovative platforms for gene therapy, offering a non-invasive route to deliver genetic material directly to defective cells. One pioneering study combined gene therapy with photothermal treatment by designing patches co-loaded with p53 DNA and IR820, a near-infrared dye. The patches were fabricated using a two-step casting method, in which hyaluronic acid served as the structural matrix before incorporation of the therapeutic agents. Once applied, the patches were able to penetrate the stratum corneum and dissolve rapidly, releasing both p53 DNA and IR820 at tumor sites beneath the skin. This dual-delivery approach produced a strong anti-tumor effect in vivo, attributed to the synergistic action of restoring tumor suppressor gene function while simultaneously applying localized photothermal therapy. These findings highlight the potential of transdermal patches as a promising strategy for subcutaneous cancer treatment, combining convenience, precision, and therapeutic efficacy.

Transdermal Patches for Insulin Delivery:

In recent years, transdermal patches have been explored as innovative platforms for gene therapy, offering a non-invasive route to deliver genetic material directly to defective cells. One pioneering study combined gene therapy with photothermal treatment by designing patches co-loaded with p53 DNA and IR820, a near-infrared dye. The patches were fabricated using a two-step casting method, in which hyaluronic acid served as the structural matrix before incorporation of the therapeutic agents. Once applied, the patches were able to penetrate the stratum corneum and dissolve rapidly, releasing both p53 DNA and IR820 at tumor sites beneath the skin. This dual-delivery approach produced a strong anti-tumor effect in vivo, attributed to the synergistic action of restoring tumor suppressor gene function while simultaneously applying localized photothermal therapy. These findings highlight the potential of transdermal patches as a promising strategy for subcutaneous cancer treatment, combining convenience, precision, and therapeutic efficacy.

Transdermal Patches for Infectious Diseases:

Recent progress in transdermal drug delivery has broadened the scope of this technology beyond conventional applications, unlocking new possibilities for the administration of antibiotics and vaccines. One innovative

example is the incorporation of cephalexin, a zwitterionic antibiotic, into solid lipid nanoparticles (SLNs) to create a transdermal patch. This formulation demonstrated a stable antibacterial effect while requiring only minimal amounts of the drug, highlighting its efficiency. Another promising approach involves bacterial cellulose/polycaprolactone (BC/PCL) composite patches, which have been successfully loaded with antibiotics such as amoxicillin, ampicillin, and kanamycin. These patches exhibited strong bactericidal activity against common pathogens including Staphylococcus aureus and Escherichia coli, suggesting their potential for broad clinical use. Hydrogel-forming microarray patches have also been explored for the delivery of tetracyclines. In vivo studies in rats revealed that this system achieved a maximum plasma concentration (Cmax) of 7.40 µg/mL at 24 hours, compared to the oral route which produced a Cmax of 5.86 µg/mL at just 1 hour. This indicates that transdermal delivery not only improves drug exposure but also prolongs release. A similar strategy was applied to vancomycin, where hydrogel-forming microarray patches achieved a Cmax of 3.29 µg/mL at 48 hours, while dissolving microarray patches reached 1.58 µg/mL at 24 hours. For comparison, oral administration produced a Cmax of 3.37 µg/mL, and intravenous injection reached a much higher Cmax of 50.34 µg/mL. These findings demonstrate that although transdermal delivery may not match the peak concentrations of intravenous therapy, it offers sustained release, reduced dosing frequency, and improved patient comfort.

Transdermal Patches for Hormonal Deficiencies and Contraception:

The concept of delivering hormones through the skin dates back to 1938, when researchers first attempted to apply a testosterone-containing ointment to castrated male guinea pigs. Since then, transdermal hormone therapy has evolved considerably, with early investigations focusing on the cutaneous application of estrone and follicle-stimulating hormone to treat amenorrhea. A major milestone came in 1984 with the introduction of the first estradiol reservoir patch. This system, delivering 0.05 mg/day twice weekly for three weeks, achieved a mean steady-state plasma estradiol concentration (Css) of 38 ng/L (0.038 ng/mL). Subsequent innovations led to the development of Menorest®, which utilized a matrix delivery system rather than a reservoir. The matrix design provided a more stable pharmacokinetic profile, reduced fluctuations in plasma estradiol levels, and improved local tolerability. Menorest® 50 achieved a steady-state Cmax of 51 pg/mL (0.051 ng/mL). Later, Climara®, another matrix-type estradiol patch, was introduced at a nominal dose of 50 µg per 24 hours. Climara demonstrated a higher Cmax of 98 pg/mL (0.098 ng/mL) compared to Menorest's 87 pg/mL (0.087 ng/mL), although Menorest showed faster absorption and a shorter Tmax.Beyond estradiol, ethinylestradiol has been widely used for contraception. In 2001, the FDA approved Ortho Evra™, the first transdermal contraceptive patch combining norelgestromin and ethinyl estradiol. Pharmacokinetic studies revealed that transdermal ethinyl estradiol reached Cmax values between 58.7 and 71.2 pg/mL, with a minimum half-life of 16.1 hours depending on the site of application. Importantly, clinical trials demonstrated that patient compliance with transdermal contraceptive patches was statistically superior to oral contraceptive pills, highlighting their convenience and reliability.For male hypogonadism, testosterone replacement therapy has also been adapted to transdermal systems. Intravenous testosterone enanthate achieves high plasma concentrations (Cmax > 1200 ng/L or 1.2 ng/mL) within 24 hours and maintains a long half-life of 7–9 days. In contrast, reservoir-type testosterone patches such as Androderm® provide a Cmax of 765 ng/L (0.765 ng/mL) with a mean Tmax of 8 hours after 16 weeks of treatment. More recently, matrix-type testosterone patches have demonstrated improved delivery, achieving mean Cmax values between 4.33 and 6.18 ng/mL at 15–19.5 hours post-application. Once the patch is removed, testosterone levels decline rapidly, with a mean half-life of approximately 1.3 hours.

Transdermal Patches for Central Nervus System (CNS) Disorder:

Transdermal patches have become an important option for managing central nervous system (CNS) disorders because they provide steady drug release, reduce side effects, and improve patient compliance compared to oral or injectable therapies. In Parkinson's disease, rotigotine patches deliver continuous dopaminergic stimulation, helping to control motor symptoms and reducing fluctuations. For Alzheimer's disease and dementia, rivastigmine patches offer cholinesterase inhibition with fewer gastrointestinal side effects than oral formulations. In depression, selegiline patches act as monoamine oxidase inhibitors (MAOIs) and avoid the dietary restrictions often associated with oral MAOIs by bypassing gut metabolism. Additionally, patches containing lidocaine or capsaicin are used for neuropathic pain, providing localized relief with minimal systemic

exposure. Collectively, these examples highlight how transdermal patches can enhance treatment outcomes in CNS disorders by combining convenience, tolerability, and effective drug delivery.

Conclusion:

Transdermal patches have emerged as a versatile drug delivery system that bypasses the gastrointestinal tract and first-pass metabolism, offering controlled release and improved patient compliance. Over the years, different types of patches have been developed, including reservoir patches, matrix patches, microneedle patches, hydrogel patches, and nanoparticle-based systems, each designed to optimize drug absorption and therapeutic outcomes.

The advantages of transdermal patches include non-invasive administration, sustained plasma drug levels, reduced dosing frequency, and enhanced convenience compared to oral or injectable routes. They also improve adherence, particularly in chronic conditions. However, disadvantages remain, such as limited suitability for large biomolecules, potential for skin irritation, variability in absorption due to skin physiology, and higher costs compared to conventional formulations

Applications span a wide range of therapeutic areas: hormonal therapy (estradiol, testosterone), pain management (lidocaine, fentanyl), CNS disorders (rotigotine, rivastigmine, selegiline), metabolic diseases (insulin), antibiotics, vaccines, and even gene therapy. These examples highlight the adaptability of patches in both systemic and localized drug delivery.

Recent advancements—including 3D printing, microneedle arrays, hydrogel-forming systems, nanoparticle incorporation, and smart patches with sensors—have further expanded the potential of transdermal technology. These innovations enable higher drug loading, controlled release, personalized designs, and novel applications such as cancer therapy and self-administered vaccination.

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