Sustainable Materials and Eco-Friendly Approaches in Transdermal Patch Development: A Comprehensive Review

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***Abstract*—A novel drug delivery system in the form of a transdermal patch is designed to deliver therapeutic agents through the skin for a systemic effect. Transdermal patches, unlike traditional oral or injectable drugs, allow a non-invasive, controlled, and sustained release of drug. Transdermal patches have a number of advantages including improved patient compliance, reduced side effects, and bypassing the first-pass metabolism of the liver. Many medications, including hormones, analgesics, nicotine, and antihypertensive, are administered through these patches. A substrate layer, drug storage of matrix-type, a rate-controlling the membrane itself, an adhesive layer, and a protective liner constitute the basic elements of transdermal patches. Emerging technologies in transdermal delivery, such as smart patches, nanoparticles, and microneedles, have widened the scope of applications for this drug delivery method and opened the way to administer insulin, biologics, and even vaccines. Moreover, the integration of detectors and surveillance systems in transdermal pads provides new possibilities for real-time health monitoring and customized drugs. Despite these advances, challenges like medication stability, skin permeability, and the need for patient-specific formulations remain. While the future is headed in the direction of more efficacious, targeted, and adaptive therapies, transdermal patches are still a viable candidate for controlling chronic diseases and administering non-invasive therapeutics.**

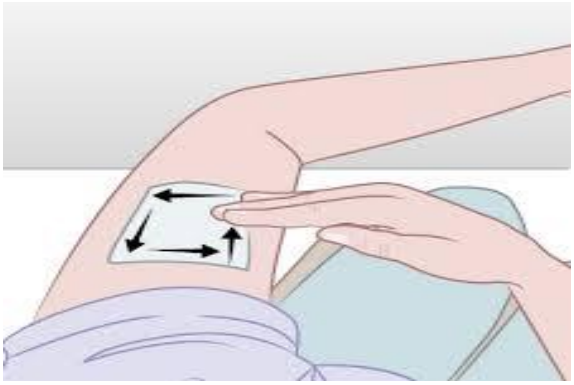
***Index Terms*—Analgesics, Controlled release, Sustained release, Transdermal patch**

1. INTRODUCTION

The aspiration of all biopharmaceutical researchers and companies is to create a safe and efficient method of medication delivery. Drug administration through the transdermal route can produce both local and systemic therapeutic consequences. Because transdermal drug delivery circumvents gastrointestinal side effects and first pass metabolism, it is a preferred option to oral drug administration. It can also overcome the poor patient compliance associated with other routes of drug delivery. Self-applied transdermal drug delivery allows the drug to enter healthy skin over a set period of time to achieve an individual as well as general effect(1). First-pass liver metabolism, enzymatic digestion, breakdown of drugs in acidic environments, alimentary irritation, drug oscillations, unwanted effects and therapeutic failure, risk of disease transmission, are just a few issues that transdermal delivery systems try to evade(1). Other advantages are controlled drug delivery, low cost, and patient compliance. Disadvantages of transdermal drug delivery are that skin irritation is possible, ionic drugs, macromolecular drugs cannot be administered, and that it is not compatible with patients under stress or with low peripheral blood volume. Depending upon the drug molecule size and the lack of absorption enhancement material, transdermal drug delivery systems have been divided into three generations(2).
Many permeation promoter materials are available for modifying transdermal systems for the delivery of medication to modify the absorption of the drug profile in a controlled manner. Various transdermal systems of drug delivery such as vapour patches, membrane-moderated transdermal systems, matrix devices with drug-in-adhesive or matrix-dispersion structure, and single or multilayer drugs in adhesive

systems possess different mechanisms for controlling the rate of drug release(3). Consequently, the present review encompasses a brief summary of various types of FDA-approved transdermal patches now available on the market, including details about their designs, physicochemical properties, structural components, preparation methods, polymeric matrix materials, and analysis methods required for the evaluations (3, 1).

The following represent the FDA-approved transdermal patches now available on the market. Transdermal patches are medicated adhesive strips that slowly release medication into the blood through the skin (4). The controlled, extended release of medications provided by these patches provides therapeutic effects without a need for frequent dosing. Percutaneous absorption is a fundamental part of the mechanism of a transdermal patch (4). The active drug chemical (API), which typically addresses the epidermis and dermis, is released gradually into the layers of epidermis upon topical administration. A systemic effect is caused by the API's penetration into the walls of blood vessels and further distribution into the systemic circulation (4,2).



(Fig 1 Transdermal patches)

1.1 TYPES OF TRANSDERAL PATCHES

Transdermal patches are categorized according to their design, drug release mechanism, and mode of administration (6). The primary varieties of transdermal patches are listed below:

Single-layer-drug-in-adhesive-patches¶	Matrix-system:-drug-in-adhesive¶	Microreservoir-transdermal-patches¶	Multilayer-drug-in-adhesive-patches¶	Iontophoretic-Transdermal-Patches¶

(Fig 2 Table of Transdermal Patches)

a) Single layer drug-in-adhesive patches

A drug reservoir for dispersion is simply one layer of copolymer with adhesive properties. The single layer has a covering impermeable backing laminate. The drug is released from the substrate laminate layer upon which the drug reservoir is located following deposition in and attachment to the single polymers layer. Another example of one-layered drug-in-adhesive patches containing methylphenidate is transdermal medication Daytrana® (6.1)

b) Multilayer drug-in-adhesive patches

Both a drug storage layer and an adhesive layer constitute layered transdermal patches, which provide controlled release of medication over time. Multilayer systems contain a permanent base layer and a temporary protective layer. Multilayer patches extend drug administration for a period of seven days and are applied to give hormone treatment, painkillers, and drugs that encourage smoking cessation(6, 2).

c) Micro reservoir transdermal patches

Matrix dispersion and drug reservoir are blended together in microreservoir transdermal patches. The reservoir is formed by uniformly spreading the drug suspension on a lipophilic polymer after suspending it in a solution composed of hydrophilic polymer. When a high shear mechanical force is used in dispersion, millions of very small, impermeable

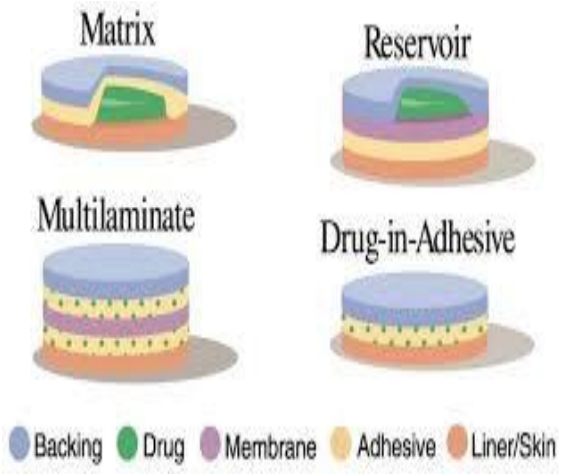
spheres are created. The blood drug concentration is maintained constant by the drug release profile, which follows a 0-order amount of kinetic drug release. Crosslinking polymeric agents are usually required since the dispersion of the medication needs to be thermally inert(6.3).

d) Matrix system: drug-in-adhesive

Drug reservoir is prepared to deliver the drug over an adhesive polymer by a single layer or multi-layered transdermal patches. By solvent casting or melting the sticky polymeric material, the drug-polymer mesh is coated on a waterproof backing layer(6.4).

e) Iontophoretic Transdermal Patches

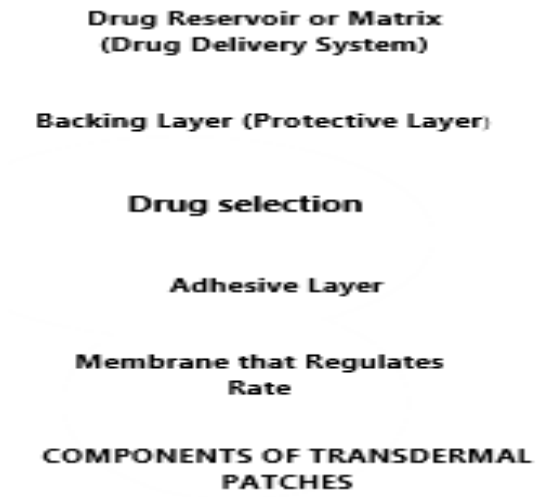
To enhance the passage of charged molecules (ions) through the skin, such patches utilize iontophoresis, a small electrical current. The drug is propelled into the skin by the electrical current, enhancing the efficacy of drug delivery, particularly for hydrophilic (water-soluble) drugs that otherwise would have difficulty penetrating the skin (6, 5.)



(Fig 3 Types of Transdermal Patches)

2. STRUCTURAL COMPONENTS OF TRANSDERMAL PATCHES

Transdermal patches have structural elements designed to help active pharmaceutical ingredients (APIs) be delivered effectively through the skin. A transdermal patch usually consists of several layers, each serving a specific purpose(9). These layers control how the medication is released, provide adhesive qualities, and ensure the patch's durability(9). The main structural elements of transdermal patches are listed below:



(Fig 4 Table of the Components of Transdermal Patches)

- Drug selection:

When designing patches for transdermal distribution, it is essential to consider the physicochemical properties of medications. Medication solubility and how it diffuses across the outer skin layer depend on hydrophobicity and ionization state, which are key factors in drug selection (9.1).

- Backing Layer (Protective Layer):

The backing layer is the outermost part of the patch, made from synthetic fibers like polyethylene, polyester, or polypropylene, or from laminated films. This layer protects the patch and its medication from moisture, light, and air. It also helps keep the patch intact during use. These materials are chosen for their strength, flexibility, and ability to form a barrier (9, 2).

- Drug Reservoir or Matrix (Drug Delivery System):

a) Reservoir System: A membrane that controls the rate surrounds a liquid or gel chamber that contains the medication. The medication diffuses through this membrane at a steady pace (9,2).

b) Matrix System: The medication is spread throughout a polyamide matrix and gradually moves through the matrix to reach the skin. In this system, the matrix itself controls the drug release (9).

- Membrane that Regulates Rate:

The medicine is delivered at a steady rate over time because of the rate-controlling membrane. This membrane manages the release of the drug from the

reservoir or matrix. It is usually made of silicone, polyethylene, ethylene-vinyl acetate (EVA), or polyvinyl chloride (PVC). The choice of these materials is based on their permeability to the specific drug (9,3).

- Adhesive Layer:

The adhesive layer ensures the patch sticks well to the skin. It also controls the medication absorption by regulating how much of the drug is released from the patch to the skin over time. Transdermal patches use pressure-sensitive adhesives (PSAs), which can include hydrocolloid, silicone, and acrylate-based adhesives. These adhesives are designed to minimize discomfort, be comfortable, and form a strong bond with the skin (9, 4).

- Liner (Protective Release Liner):

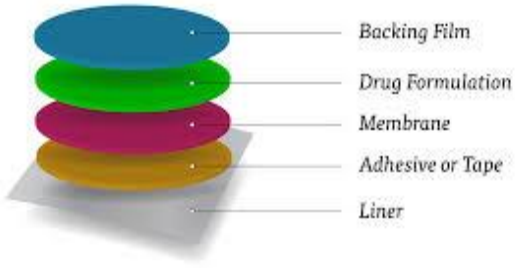
Before applying the patch, the liner covers the adhesive layer. This protective layer safeguards the medication and the adhesive, preventing the patch from sticking too quickly. The liner is often made of silicone-coated paper, polyethylene, or polypropylene. Users remove the liner just before putting the patch on their skin (9, 5).

- Permeation Enhancers:

While optional, penetration enhancers are commonly used to improve the skin absorption of a drug, especially for those with low skin permeability. These substances temporarily alter the skin's barrier properties to aid penetration. Common permeation enhancers include urea, propylene glycol, ethanol, and surfactants. They are typically included in the patch's formulation, often within the matrix or adhesive layer (9, 6).

- Other excipients

Plasticizers like dibutyl phthalate and triethyl citrate make up 5 to 20% of transdermal patches, providing them with flexibility. Solvents used in the drug reservoir include methanol, ethanol, dichloromethane, and acetone(9.7).



(Fig 5 Components of Transdermal Patches)

3. CHARACTERIZATION AND ASSESSMENT TOOLS FOR TRANSDERMAL PATCH PREPARATION

Transdermal patches should be described and characterized using various evaluation and development techniques. These include dissolving, in vitro drug release, in vitro skin penetration, adhesive qualities, and excipient control (16). The tests listed below follow the European Medicines Agency Recommendations from the Commission for Medicinal Products for Humanitarian Use regarding the manufacturing standards of transdermal patches. Additional physical, chemical, and biological tests, evaluations, and assessments should also be conducted. These include checking material interaction, patch thickness, weight uniformity, folding power, moisture level, moisture uptake or weight gain, vaporization, water permeability, pharmaceutical content, flatness, stability, swellability, and skin irritation (16). These are detailed below.

(Fig 6 Table of the Evaluation of Transdermal Patches)

a) Patch thickness

Using a digital microscope screw gauge, we take measurements at three to five places on the patch to determine its thickness. We calculate the mean depth and the average variance of these measurements to ensure the patch thickness is appropriate

b) Uniformity of weight

We weigh ten different, randomly selected patches and compute the average weight and standard

deviation. This helps us assess how consistent the weight is across the patches. Each patch's weight should not vary much from the average

c) Folding stamina

Folding stamina is the total number of times the paper can be folded without breaking. We cut a specific area of the patch and fold it repeatedly in the same spot until it breaks

d) Content of moisture

We find a transdermal patch's moisture content by weighing it, placing it in a dryer with chlorine dioxide for 24 hours, and then weighing it again. We use the following equation to determine the patch's percentage of moisture:

Moisture content (%) = (Initial mass - Final mass) / Initial mass × 100

e) Assessment of the permeability of water vapor

The moisture-vapor permeability (WVP) in a patch is measured using an organic air circulation oven, where: WVP = W/A (3), where W is the quantity of water vapor (g per 24 hours) that infiltrated the patch, A is the surface area (m2) exposed on the patch sample, and WVP is the water vapor permeability, given in g m–2 per 24 hours

f) Content of drugs

We determine the drug content in a transdermal patch by dissolving a specific patch area in a set amount of solvent. After shaking the mixture for up to 24 hours, we sonicate it for a designated time and filter it. We then use an appropriate analytical method to measure the drug content in the filtrate

g) Assessing the adhesive qualities

We can describe adhesive properties using various tests, such as peel force, adhesive strength, and tack tests. Both in vitro and in vivo testing can evaluate the adhesive qualities of the drug in a transdermal formulation

h) Peel-tack test or quick stick test

In this test, we pull an adhesive tape over the transdermal application at a 90° angle and at a speed of 12 inches per minute. The force needed to break the adhesive-substrate bond is known as the tack value .

i) Strength in tensile

A tensiometer measures tensile strength. A patch attaches to the tensiometer assembly. We calculate the weight needed to break it and measure the patch's elongation using the instrument's pointer. To find the patch's tensile strength, we average three readings. Let a be the patch width, b be the patch thickness, L be the patch length, ΔL be the patch elongation at the breakage point, and break force be the weight (kg) required to break the patch. The formula for the patch's tensile strength is as follows: Tensile strength = break force / a * b (1 + ΔL/L)

j) Swell Ability

To assess a transdermal patch's swell ability, we apply the sample to a preweighed slip of plastic in a Petri dish containing 50 mL of pH 7.4 phosphate buffer. The sample absorbs over a time t, which is usually about 30 minutes (17).

4. CLINICAL USE OF TRANSDERMAL PATCHES IN THE CURRENT MARKET

Table1. Clinical use of Transdermal Patches in the current market

S.no	DRUG	PRODUCT NAME	CLINICAL USE
01	Scopolamine	Transderm-Scop	Motion sickness
02	Nitroglycerin	Transderm-Nitro	Angina pectoris
03	Clonidine	Catapres-TTS	High blood pressure
04	Estradiol	Estraderm	Menopause
05	Fentanyl	Duragesic	Chronic pain
06	Nicotine	Nicoderm	Smoking cessation
07	Testosterone	Testoderm	Testosterone low level
08	Lidocaine/epinephrine	Iontocaine	Pain relief
09	Estradiol/norethidrone	Combipatch	Menopause
10	Lidocaine	Lidoderm	Pain relief
11	Norelgestromin	Ortho Evra	Contraception

12	Estradiol/levonorgestrel	Climara Pro	Menopause
13	Oxybutynin	Oxytrol	Overactive bladder
14	Rotigotine	Neupro	Parkinson's disease
15	Rivastigmine	Exelon	Dementia

5. FUTURE PROSPECTIVE

In the future, medicine delivery through transdermal patches will be a wonderful step forward as it will be more effective, personalized, and flexible. Due to the nanotechnology advancements, micro-needles, programmable patches, and biologics, transdermal skin patches have the ability to surpass several existing limitations and extend the range of therapeutic applications. This could potentially result in better patient outcomes, increased compliance with treatment plans, and more readily available and convenient therapy for a wider range of diseases. As these technologies evolve, they will become increasingly integral in the treatment of chronic conditions and the provision of tailored therapies

6. CONCLUSION

Transdermal patches represent a significant leap in drug delivery technologies, being a non-invasive and handy alternative to traditional oral or injectable drugs. The ability of these patches to provide regular, stable, and extended drug release over several hours or days, encourages the patient to follow the treatment and decreases the probability of side effects that are caused by high drug concentrations. Moreover, transdermal patches are equipped with great features such as being able to completely bypass the gastrointestinal tract and hepatic first-pass metabolism, which is of huge importance for patients with long-term therapies e.g. pain, quitting smoking, hormone replacement therapy or hormonal imbalances. Furthermore, they also provide a new route to deliver such types of drugs as biologics, insulin and vaccines which, are difficult to administer orally.

Transdermal patches, with the benefits of simplicity, accuracy, and patient-centered care, are an increasingly important unit of modern medicine. As technological advancements continue to play a large role in the treatment of various diseases, the drug delivery system is expected to become safer, more efficient, and more patient-friendly.

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