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TRANSDERMAL PATCHES: AN UPDATED REVIEW AS A NOVEL DRUG DELIVERY SYSTEM

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REVIEW ON TRANSDERMAL PATCHES

ABSTRACT: Transdermal patches represent a sophisticated approach to medication delivery, leveraging the skin as a medium for administering drugs directly into the bloodstream. These patches are typically small adhesive strips designed to adhere firmly to the skin, where they provide a controlled and sustained release of medication. The primary advantage of transdermal patches is their ability to deliver a consistent dose of medication over an extended period, which can improve therapeutic outcomes and patient adherence to treatment regimens. By bypassing the digestive system and liver metabolism, transdermal patches minimize potential gastrointestinal side effects and avoid the first-pass effect, where the drug's efficacy is reduced as it is metabolized in the liver before reaching systemic circulation. This method ensures that medication levels remain steady, which is crucial for managing conditions that require precise and continuous dosing. Transdermal patches are versatile and used for a range of therapeutic purposes. For instance, in pain management, patches like those containing fentanyl provide long-lasting relief without the need for oral opioids. Hormone replacement therapies often use patches to deliver hormones like estrogen or testosterone, facilitating easier absorption and stable hormone levels. Additionally, patches designed for smoking cessation, such as those containing nicotine, help to gradually reduce dependence on cigarettes by delivering a controlled amount of nicotine over time, thereby supporting the process of quitting smoking. Overall, transdermal patches offer a user-friendly alternative to oral and injectable medications, with the benefits of ease of use, reduced side effects, and improved patient compliance.

KEYWORDS: Transdermal Patches, mechanism of action, components, characterization.

INTRODUCTION

Transdermal patches, approved by the FDA in 1981, have revolutionized drug delivery by administering medication directly through the skin into the bloodstream. These patches are used for various conditions, including motion sickness (with scopolamine), cardiovascular issues (with clonidine and nitroglycerin), chronic pain (with fentanyl), and smoking cessation (with nicotine). They offer several key advantages: a controlled and constant drug administration ensures a steady release of medication, minimizing fluctuations in drug levels; they eliminate the peaks and troughs associated with oral or injectable methods; they reduce strain on the digestive tract and liver by bypassing the digestive system; they improve patient compliance with simplified dosing schedules, including patches that require application only once a week; and they minimize side effects by preventing temporary overdoses and related risks. Overall, transdermal patches provide a convenient and effective alternative to traditional oral and injectable treatments, enhancing both patient experience and therapeutic outcomes.[1]

Condition in which transdermal patches are used

1. The patient experiences intolerable side effects, such as constipation, or has difficulty swallowing (dysphagia) and needs an alternative to oral medication.
2. Reliable drug administration is needed for improved pain control, particularly in patients with cognitive impairment or those unable to self-medicate with analgesics.[3]

Condition in which transdermal patches are used not used

Transdermal patches are not used when
- Acute pain relief is necessary.
- Rapid dose adjustments are required.
- The required dose is 30 mg/24 hours or less.[3]

Definition

Transdermal patches are sticky, skin-applied devices that release medication straight into the blood through the skin.[4]

BASIC COMPONETS OF TRANSDERMAL PATCHES

Polymer matrix

For a polymer to be suitable for transdermal patches, it should
- Have the appropriate molecular weight, glass transition temperature, and chemical functionality for effective drug diffusion and release.
- Allow for the incorporation of a large amount of drug.
- Remain non-reactive with the drug, both physically and chemically.
- Ensure that both the polymer and its degradation products are non-toxic.[5,6]

Table 1: Summarizing the classifications of polymers used in transdermal drug delivery systems (TDDS).[7]

Category	Examples
Natural Polymers	Cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber, chitosan
Synthetic Elastomers	Polybutadiene, hydrin rubber, polyisobutylene, silicone rubber, nitrile, acrylonitrile, neoprene, butyl rubber
Synthetic Polymers	Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate

Drug: The drug solution should be in direct contact with the release liner.[2,8]

- **Physicochemical properties**

For effective transdermal delivery (TDD), a drug should:
a) Be moderately soluble in both oil and water (ideally >1 mg/ml).
b) Have a molecular weight under 1000 units.
c) Maintain a pH of 5 to 9 in a saturated aqueous solution.
d) Contain no more than 2 hydrogen bonding groups.

- **Biological properties**

a) The drug should be highly potent, requiring only a few milligrams per day for effective dosing.
b) The drug should have a short half-life (t½) to ensure rapid clearance from the body.
c) The drug must be non-allergenic, avoiding any allergic reactions.
d) The drug should not lead to tolerance, even with a near zero-order release profile from transdermal patches.

Penetration Enhancers

Penetration enhancers are compounds that improve skin permeability by modifying the skin's barrier properties, thereby facilitating the flux of a drug through the skin. They are essential components in most transdermal formulations.[9]

The flux of a drug across the skin can be defined by the equation

$$J=D(dc/dx)$$

where
- J: - is the drug flux,
- D: - is the diffusion coefficient,
- dc/dx:- represents the concentration gradient of the drug,
- x: - denotes the spatial coordinate.

Table 2: Certainly! Here's the classification of penetration enhancers presented in a table format.[10]

Category	Examples
Terpenes (Essential Oils)	Nerolidol, menthol, cineol, limonene, carvone
Pyrrolidone's	N-methyl-2-pyrrolidone (NMP)
Fatty Acids and Esters	Oleic acid, linoleic acid, lauric acid, capric acid
Sulfoxides and Similar Compounds	Dimethyl sulfoxide (DMSO), N, N-dimethyl formamide
Alcohols, Glycols, and Glycerides	Ethanol, propylene glycol, octyl alcohol
Miscellaneous Enhancers	Phospholipids, cyclodextrins, amino acid derivatives, enzymes

Pressure-sensitive adhesives (PSAs)[11]: Pressure-sensitive adhesives are essential for maintaining effective contact between a transdermal patch and the skin. They should adhere with minimal finger pressure, be persistently tacky, and provide a strong hold. Common types of PSAs include polyacrylates, polyisobutylene, and silicon-based adhesives.

The selection of a PSA depends on the patch design and drug formulation. It must be compatible with both the skin and the drug, and should not affect drug release. PSAs can be applied either on the face of the patch, as in reservoir systems, or around the edges, as in matrix systems.

Backing laminate[12]: Backing laminates are supportive materials that are impermeable to both drugs and penetration enhancers. They must be chemically compatible with the drug, enhancer, adhesive, and other excipients. Common types of backing laminates include vinyl, polyethylene, and polyester films.

Release liner[13]: The release liner is the primary packaging material that protects the patch until it is applied to the skin. It consists of a base layer, which can be non-occlusive (e.g., paper or fabric) or occlusive (e.g., polyethylene or polyvinyl chloride), and a release coating layer made of silicon or Teflon. The release liner must be chemically inert and permeable to drugs, penetration enhancers, and water.

Other excipients used in the manufacture of transdermal patches include solvents and plasticizers[14]

(a) Solvents: Chloroform, methanol, acetone, isopropanol, and dichloromethane are utilized to produce drug reservoirs.

(b) Plasticizers: Dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol are added to impart plasticity to the transdermal patch.

Table 3: Drug product and clinical use of transdermal patches on the present market.[23]

Drug	Product name	Clinical use
Scopolamine	Transderm-Scop	Motion sickness
Nitroglycerin	Transderm-Nitro	Angina pectoris
Clonidine	Catapres-TTS	High blood pressure
Estradiol	Estraderm	Menopause
Fentanyl	Duragesic	Chronic pain
Nicotine	NicoDerm	Smoking cessation
Testosterone	Testoderm	Testosterone low level
Lidocaine/epinephrine	Iontocaine	Pain relief
Estradiol/norethidrone	Combi patch	Menopause
Lidocaine	Lidoderm	Pain relief
Norelgestromin	Ortho Evra	Contraception

TYPES OF TRANSDERMAL PATCHES

- **Single layer drug in adhesive:** The adhesive layer, which contains the drug, adheres the various layers together and is responsible for drug release to the skin. It is surrounded by a temporary liner and a backing layer.[15]

- **Multi-layer drug in adhesive:** This patch is similar to a single-layer patch in that the adhesive layer is responsible for drug release. However, it features an additional layer for drug adherence, typically separated by a membrane, though this is not always the case. It also includes both a temporary and a permanent liner layer.[15]

- **Reservoir:** Unlike Single-layer and Multi-layer Drug-in-adhesive systems, the reservoir transdermal system features a separate drug layer, which is a liquid compartment containing a drug solution or suspension. This drug layer is isolated from the adhesive layer and is supported by a backing layer. The release rate in this system is zero-order.[16]

- **Matrix:** In the Matrix system, the drug layer consists of a semisolid matrix containing a drug solution or suspension. The adhesive layer partially surrounds and overlays this drug layer.[2]

- **Vapor:** The adhesive layer in these patches not only holds the layers together but also facilitates vapor release. These relatively new patches are commonly used to release essential oils for congestion relief and are also employed to enhance sleep quality.[17]

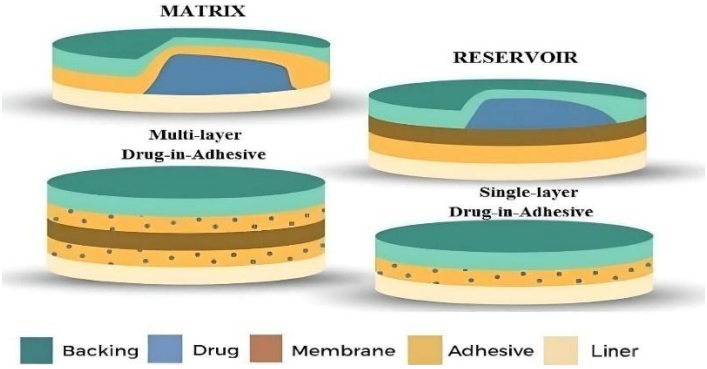

Figure 1: Types of transdermal Patches.

Advantages of transdermal patches[7,18,19,20]

- Avoidance of first-pass metabolism of drugs.
- Reduction in peak plasma levels, leading to fewer side effects.
- Minimization of fluctuations in plasma drug levels.
- Discontinuation of drug release is straightforward by simply removing the patch from the skin.
- Provides a longer and predetermined duration of action.
- Maintains stable plasma drug concentrations.
- Reduces the quantity of doses required, thereby improving patient compliance.

Disadvantages of transdermal patches[1,21,22]

- Local irritation, such as erythema, itching, and edema, can occur at the application site due to the drug, adhesive, or other patch components, with possible allergic reactions.
- Effective transdermal delivery requires a drug with a molecular weight less than 500 Da and sufficient aqueous and lipid solubility, ideally with a log P between 1 and 3.
- Hydrophilic drugs have low skin permeability, which reduces their efficacy, while only small, lipophilic drugs are currently suitable for skin application.
- Patches are limited in the amount of drug they can deliver, so the drug must be potent, and higher dosages are not feasible.
- The patch's adhesion can be affected by its type and environmental conditions, and skin sensitivity or allergic reactions may occur.
- Drugs with high blood levels are unsuitable for transdermal delivery.

MECHANSIM OF ACTION OF TRANSDERMAL PATCHES

The mechanisms of action for transdermal patches utilizing various technologies[21]

1. Iontophoresis: This method uses a low-level electric current to enhance drug delivery through the skin. Electrodes in contact with the drug formulation help to drive ions into the skin, improving the delivery of medications such as pilocarpine for cystic fibrosis diagnosis and lidocaine for rapid anesthesia.

2. Electroporation: By applying high-voltage pulses, electroporation creates transient pores in the skin, temporarily increasing its permeability. This technique is effective for delivering a wide range of molecules, including large biopharmaceuticals.

3. Ultrasound (Sonophoresis): Low-frequency ultrasound waves disrupt the lipid structure of the stratum corneum, enhancing the transdermal transport of drugs, including macromolecules. This method helps to increase drug delivery by creating temporary openings in the skin barrier.

4. Electro-osmosis: This technique involves applying a voltage across a porous membrane to induce fluid flow, which helps to enhance the delivery of both positively charged and neutral drugs through the skin by increasing their flux.

5. Magnetophoresis: Magnetic fields are used to facilitate the diffusion of diamagnetic substances through the skin. Exposure to a magnetic field can alter skin structure and enhance drug permeability, making it a promising method for improving transdermal drug delivery.

These advanced techniques are designed to overcome the skin barrier and improve the efficacy of transdermal drug delivery systems

EVALUATION OF TRANSDERMAL PATCHES

1. Physicochemical Evaluation[24]

a) Thickness: Measured at various points of the transdermal film using tools like a travelling microscope, dial gauge, screw gauge, or micrometer.

b) Uniformity of Weight: Weigh 10 random patches, calculate the average, and ensure individual weights are close to this average.

c) Drug Content Determination: Dissolve a weighed film portion in a solvent, shake, sonicate, filter, and estimate drug content using spectrophotometry.

d) Content Uniformity Test: Measure drug content in 10 patches. If 9 patches are within 85%-115% of the specified value and 1 is between 75%-125%, the test passes. If not, test 20 additional patches for a passing result.

e) Moisture Content: Weigh films before and after desiccation to determine moisture content using a specific formula.

% Moisture content= [Initial Weight–Final Weight/Final Weight] x100.

f) Flatness: Ensure the film has a smooth surface and no constriction over time, determined by measuring and calculating percent constriction.

g) Folding Endurance: Fold the film repeatedly at the same spot until it breaks; the number of folds before breaking indicates endurance.

h) Tensile Strength: Measure the force needed to break the film, and calculate tensile strength based on film dimensions and elongation.

i) Tack Properties: Evaluate the polymer's ability to adhere to a substrate with minimal contact pressure, influenced by the polymer's molecular weight and composition.

2. In Vitro Evaluation Method[25]

a) In Vitro Drug Release Studies

- **Method:** Use the paddle over disc method (USP Apparatus V).
- **Procedure**

➢ Cut dry films into shapes, weigh them, and fix them on a glass plate.
➢ Place the plate in 500 mL of phosphate buffer (pH 7.4) at 32 ± 0.5°C.
➢ Operate the paddle at 50 rpm, positioned 2.5 cm from the glass plate.
➢ Withdraw 5 mL samples at intervals up to 24 hours and analyze using UV spectrophotometry or HPLC.
➢ Perform the experiment in triplicate and calculate the mean.

b) In Vitro Skin Permeation Studies

- **Method:** Use a diffusion cell with rat abdominal skin.
- **Procedure**

➢ Prepare the skin by removing hair, cleaning, and equilibrating in phosphate buffer (pH 7.4).
➢ Mount the skin in the diffusion cell with the epidermis facing upward.
➢ Maintain the temperature at 32 ± 0.5°C and use a magnetic stirrer for uniform diffusant distribution.
➢ Remove samples from the receptor compartment at regular intervals, replace with fresh medium, filter, and analyze by spectrophotometry or HPLC.
➢ Determine flux from the steady-state slope of the drug permeated versus time, and calculate permeability coefficients by dividing flux by the initial drug load.

3. In-Vivo Studies[26]

- **Purpose:** Reflects the true performance of the drug, addressing variables not covered in in-vitro studies.
- **Methods**

➢ **Animal Models:** Commonly used species include mice, hairless rats, hairless dogs, hairless rhesus monkeys, rabbits, and guinea pigs.

➢ **Human Models:** In the final development stage, human volunteers are used to gather pharmacokinetic and pharmacodynamic data, assessing efficacy, risks, side effects, and patient compliance.

4. Stability Studies[26]

- **Procedure:** Store TDDS samples at 40±0.5°C and 75±5% relative humidity for 6 months.
- **Analysis:** Withdraw samples at 0, 30, 60, 90, and 180 days to analyze drug content, following ICH guidelines.

Various methods for preparing transdermal drug delivery systems (TDDS)[27]

1. Asymmetric TPX Membrane Method: A polyester film with a concave area is used as a backing for drug placement, which is then covered with a TPX asymmetric membrane and sealed with adhesive.

2. Circular Teflon Mould Method: Drug and polymer solutions, mixed with plasticizers and enhancers, are poured into Teflon moulds. The solvent evaporates in a controlled environment, and the dried films are stored for further evaluation.

3. Mercury Substrate Method: A homogeneous dispersion of drug, polymer, and plasticizer is poured onto a mercury surface, where it is covered to manage solvent evaporation.

4. IPM Membranes Method: Drug is dispersed in a water-propylene glycol mixture with carbomer, neutralized with triethanolamine, and used to prepare a gel incorporated into an IPM membrane.

5. EVAC Membranes Method: A Carbopol gel containing the drug is prepared in propylene glycol, applied to a backing layer, and covered with an EVAC membrane, sealed by heat.

6. Aluminum Backed Adhesive Film Method: Drug and adhesive are dissolved in chloroform, applied to an aluminum-lined former, and prepared to form stable TDDS matrices.

7. Proliposomes Method: Drug and lecithin are mixed in an organic solvent and loaded onto mannitol powders. The resulting proliposomes are dried, sieved, and stored for further use.

8. Free Film Method: A cellulose acetate solution is cast on a mercury surface to form a free film. The solvent evaporation is controlled, and the resulting film is stored between wax paper sheets until use.

These methods each offer different approaches to creating TDDS with specific characteristics and applications.

METHOD FOR PREPARING TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS) PATCHES INVOLVES THE FOLLOWING STEPS

1. **Preparation:** Dissolve the polymer (e.g., PVP/HPMC) in a beaker with a small amount of solvent.

2. **Mixing:** Add 2/3 of the solvent mixed with other polymers (e.g., PVA) to the beaker. Stir initially at low rpm, then increase speed.

3. **Additives:** Incorporate the plasticizer and mix thoroughly.

4. **Drug Addition:** Add the drug while stirring continuously and adjust the volume.

5. **Casting:** Pour the mixture onto a glass mold to cast the film.

6. **Drying:** Dry the films in an oven at 40°C.

7. **Removal:** Carefully remove the dried films using a sharp blade.

8. **Storage:** Wrap the films in butter paper and store them in a closed container, away from light, in a cool place.[17]

APPLICATIONS OF TRANSDERMAL PATCHES

- Transdermal patches have various applications across different medical fields
- Nicotine patches provide a controlled release of nicotine to aid in smoking cessation.
- Clonidine, an antihypertensive drug, and non-steroidal anti-inflammatory drugs (NSAIDs) are available as transdermal patches.
- Nitroglycerin patches are used to manage angina pectoris.
- Patches are also used to deliver medication for attention deficit hyperactivity disorder (ADHD).
- The selegiline patch, a MAO inhibitor, was the first transdermal delivery system approved for major depressive disorder.[28]

CONCLUSION

Transdermal patches have revolutionized drug delivery since their FDA approval in 1981, providing an effective and convenient alternative to oral and injectable treatments for various conditions, including motion sickness, cardiovascular issues, chronic pain, and smoking cessation. They offer significant benefits such as controlled drug release and improved patient compliance while avoiding first-pass metabolism. Despite these advantages, challenges like drug limitations and skin irritation persist.

Advancements in technologies such as iontophoresis, electroporation, and ultrasound are expanding the capabilities of transdermal patches, allowing for the delivery of a broader range of therapeutic agents. Continued research into novel polymers, penetration enhancers, and improved patch designs is expected to further enhance their effectiveness and applications. The field of transdermal drug delivery is rapidly advancing, promising improved patient outcomes and new therapeutic possibilities.

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