



Review Article

Transdermal Patches: Formulation, Development and Evaluation: A Comprehensive Review

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ABSTRACT:

Transdermal drug delivery systems (TDDS) offer a non-invasive and controlled method of drug administration, enhancing patient compliance while bypassing hepatic first-pass metabolism. Among these, transdermal patches have gained significant attention due to their ability to provide sustained drug release, reduce dosing frequency, and minimize systemic side effects. This review explores the formulation, development, and evaluation of transdermal patches, highlighting key advancements and challenges. The formulation of transdermal patches involves selecting appropriate drugs, polymers, permeation enhancers, and plasticizers to ensure effective drug delivery. Various fabrication techniques, including solvent casting and hot-melt extrusion, are employed to optimize drug release and adhesive properties. The physicochemical characteristics of the drug, such as molecular weight, solubility, and partition coefficient, play a crucial role in determining its suitability for transdermal delivery. Evaluation of transdermal patches includes physicochemical characterization, in-vitro drug release studies, ex-vivo permeation testing, and in-vivo pharmacokinetic assessments. Additionally, regulatory guidelines emphasize the importance of adhesion performance, stability, and skin irritation studies. Despite their advantages, transdermal patches face challenges such as limited drug permeability, variability in absorption, and potential skin irritation. Recent advancements, including microneedle-assisted delivery, nanocarriers, and iontophoresis, aim to overcome these limitations and enhance drug permeation. This review provides insights into the latest trends and future prospects in transdermal patch technology, paving the way for more effective and patient-friendly drug delivery systems.

INTRODUCTION:

Transdermal drug delivery systems (TDDS) have revolutionized drug administration by

providing a non-invasive, controlled, and sustained release of therapeutic agents (1). Unlike conventional oral and parenteral routes,

transdermal patches offer several advantages, including improved patient compliance, avoidance of hepatic first-pass metabolism, reduced gastrointestinal side effects, and the ability to maintain steady plasma drug concentrations over an extended period. These benefits make transdermal patches an attractive alternative for the delivery of a wide range of pharmaceutical compounds, including analgesics, hormones, antihypertensives, and neurological drugs (2).

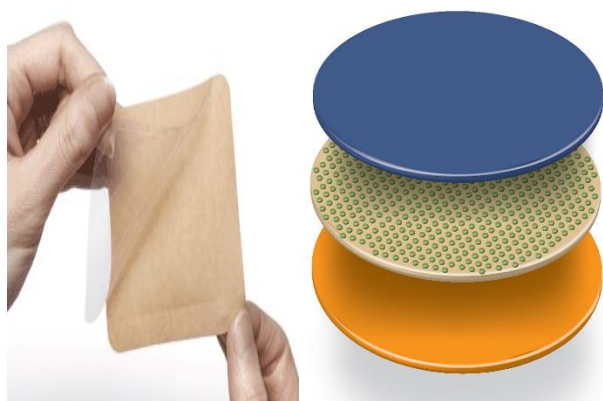


Figure 1: Transdermal Patches

Transdermal patches have emerged as a promising drug delivery system, offering controlled and sustained drug release through the skin into systemic circulation. Unlike conventional drug administration routes, transdermal patches provide several advantages, such as improved patient compliance, reduced dosing frequency, avoidance of hepatic first-pass metabolism, and minimized gastrointestinal side effects (3,4). These benefits have led to the widespread application of transdermal patches in delivering drugs for pain management, hormone replacement therapy, cardiovascular diseases, and neurological disorders.

A transdermal patch typically consists of multiple components, including a drug reservoir or matrix, a polymeric backing layer, an adhesive layer, a release liner, and permeation enhancers. The formulation of these patches involves selecting suitable drug candidates with optimal physicochemical properties, such as molecular weight, solubility, and skin permeability, to ensure effective transdermal

absorption. Additionally, the choice of polymers and excipients plays a crucial role in determining the patch's adhesion, flexibility, and drug release characteristics (5).

Despite their advantages, transdermal patches face challenges such as the barrier properties of the stratum corneum, limited drug permeability, and the need for enhanced adhesion properties. To overcome these limitations, advanced formulation approaches, including microneedles, nanocarriers, and iontophoresis-assisted drug delivery, have been explored. The concept of transdermal drug delivery is based on the ability of drugs to penetrate the skin barrier and enter systemic circulation at a controlled rate (6). However, the skin's outermost layer, the stratum corneum, poses a significant challenge due to its selective permeability. Therefore, the formulation of transdermal patches requires careful consideration of drug properties, polymer matrices, permeation enhancers, and adhesive components to ensure efficient drug transport across the skin. Various technologies, such as chemical enhancers, iontophoresis, microneedles, and nanocarriers, have been explored to enhance transdermal drug penetration (7,8).

The development of transdermal patches involves multiple stages, including formulation optimization, process development, and evaluation of physicochemical properties, drug release kinetics, and in-vivo pharmacokinetics. Regulatory guidelines further necessitate rigorous testing to assess adhesion, stability, and safety parameters (9). This review aims to provide a comprehensive overview of the formulation, development, and evaluation of transdermal patches, discussing key advancements, challenges, and future perspectives in transdermal drug delivery technology.

Types of Transdermal Patches:

Transdermal patches are classified based on their drug delivery mechanisms and structural designs. Each type is formulated to ensure

optimal drug permeation through the skin while maintaining adhesion, flexibility, and stability.

The major types of transdermal patches include:

1. Reservoir-Type Patches:

Reservoir patches contain a drug reservoir enclosed between an impermeable backing layer and a rate-controlling membrane. The drug is typically in a liquid or gel form, allowing for controlled diffusion through the membrane at a predetermined rate. Examples include nitroglycerine and fentanyl patches. While these patches provide precise drug release, they require careful formulation to prevent leakage or dose dumping (10).

2. Matrix-Type Patches:

In matrix patches, the drug is uniformly dispersed within a polymer matrix, eliminating the need for a separate reservoir. The drug is released through diffusion as the polymer gradually dissolves or degrades. These patches offer a simpler design, improved stability, and reduced risk of dose dumping. Matrix patches are commonly used in hormone replacement therapy and nicotine replacement therapy (9,10).

3. Drug-in-Adhesive (DIA) Patches:

In DIA patches, the drug is directly incorporated into the adhesive layer, ensuring intimate contact with the skin for enhanced absorption. These patches are easy to manufacture and offer flexible dosing options. Examples include Estradiol and fentanyl patches. However, achieving consistent drug release while maintaining strong adhesion can be challenging (11).

4. Micro reservoir-Type Patches:

Micro reservoir patches combine aspects of both reservoir and matrix systems. The drug is suspended in a semisolid form and dispersed within a polymeric matrix containing microparticles. This design enhances controlled drug release while maintaining patch flexibility. Scopolamine patches for motion sickness use this technology.

5. Vapour Patches:

Unlike traditional patches, vapor patches release volatile therapeutic agents, such as menthol or essential oils, for inhalation rather than transdermal absorption. These patches are commonly used for nasal decongestion and aromatherapy (12).

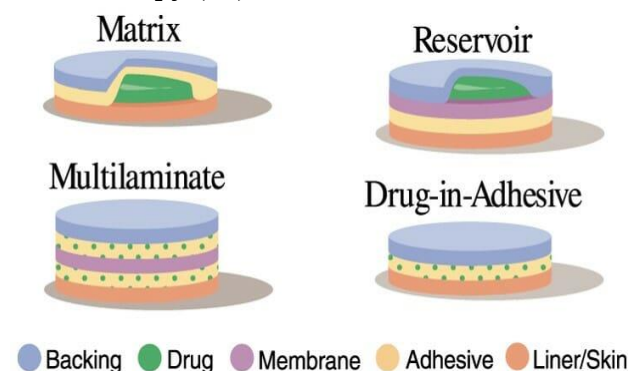


Figure 2: Types of Transdermal Patches

Formulation of Transdermal Patches:

The formulation of transdermal patches is a critical aspect that determines their efficacy, stability and patient acceptability (13). A well-designed patch ensures controlled drug release, good adhesion, and efficient drug permeation through the skin. The formulation of transdermal patches involves the selection of key components, including the drug, polymers, permeation enhancers, plasticizers, adhesives, and backing materials.

1. Drug Selection:

Not all drugs are suitable for transdermal delivery. The ideal drug candidate should have:

- Low molecular weight (< 500 Da)
- Moderate lipophilicity (log P between 1–3)
- Low dose requirement (< 10 mg/day)
- Good skin permeability
- Stability in formulation and skin environment.

2. Polymers:

Polymers play a crucial role in controlling drug release and providing structural integrity to the patch. They are classified into:

- Rate-controlling polymers: Regulate drug diffusion (e.g., ethyl cellulose, hydroxypropyl methylcellulose).

- Adhesive polymers: Ensure patch adhesion to the skin (e.g., polyisobutylene, acrylates, silicones).
- Biodegradable polymers: Used in advanced patches for sustained release (e.g., chitosan, poly (lactic-co-glycolic acid) (PLGA)).

3. Permeation Enhancers:

These compounds enhance drug penetration by modifying the stratum corneum barrier. Common types include:

- Chemical enhancers: Oleic acid, isopropyl myristate, ethanol, propylene glycol.
- Physical enhancers: Microneedles, iontophoresis, ultrasound.
- Biochemical enhancers: Enzymatic action to disrupt skin lipids.

4. Plasticizers:

Plasticizers improve the flexibility and durability of the patch. Common plasticizers include:

- Dibutyl phthalate
- Propylene glycol
- Polyethylene glycol.

5. Adhesives:

Adhesives ensure that the patch remains in contact with the skin throughout the intended duration. The adhesive should be non-irritating, skin-compatible, and capable of holding the patch securely. Common adhesives include:

- Acrylic adhesives.
- Silicone adhesives.
- Polyisobutylene adhesives.

6. Backing Layer:

The backing layer provides structural support and prevents drug loss from the patch. It should be impermeable to the drug and protect the patch from external environmental factors. Examples include polyethylene, polyester, and polyurethane films.

7. Release Liner:

The release liner protects the adhesive and drug-containing layer before application. It must be easily removable without leaving residue. Common materials used are siliconized polyester or fluoropolymer-coated films (14,15).

Methods for Formulating Transdermal Patches:

The formulation of transdermal patches involves different manufacturing techniques that ensure precise drug loading, uniform distribution, adhesion, and controlled drug release. The choice of method depends on the type of patch, drug properties, and desired release characteristics.

Below are the major methods used in transdermal patch formulation:

1. Solvent Casting Method:

The solvent casting method is one of the most widely used techniques for formulating transdermal patches. In this method, the drug and polymer are dissolved in a suitable solvent along with permeation enhancers, plasticizers, and other excipients. The resulting solution is then poured onto a flat surface or backing membrane, spread evenly, and allowed to dry, forming a thin film. Once dried, the film is cut into desired patch sizes and laminated with a release liner. This method ensures uniform drug distribution and is relatively easy to scale up. However, residual solvents in the final product may pose safety concerns, and polymer-solvent interactions can affect drug stability (16).

2. Hot Melt Extrusion Method:

Hot melt extrusion is a solvent-free technique that involves melting the polymer and drug at an elevated temperature and extruding the molten mixture into a thin film. The extruded film is then cooled and solidified before being cut into patches. This method eliminates solvent-related toxicity issues and improves batch uniformity, making it suitable for drugs with low thermal sensitivity. However, it is not ideal for heat-sensitive drugs and requires specialized equipment.

3. Direct Milling Method:

The direct milling method is a dry processing technique where the drug and polymer are blended and then compressed into a thin film. This method does not require solvents or heat, making it suitable for thermosensitive drugs.

The prepared mixture is passed through rollers or compressed under controlled pressure to form a uniform patch. Direct milling is fast and environmentally friendly but may result in non-uniform drug distribution if mixing is not done properly (17, 18).

4. Electro spraying Method:

Electro spraying is an advanced method that uses a high-voltage electric field to generate fine droplets of a polymer-drug solution, which solidify upon deposition to form ultrathin films. The process involves dissolving the drug and polymer in a suitable solvent, spraying the solution through a nozzle under an electric field, and allowing the droplets to land on a substrate, where they dry and solidify. This technique produces nanostructured films with enhanced drug loading and permeability. However, electro spraying requires specialized equipment and has limited scalability for large-scale production (18).

5. Vapour Deposition Method:

The vapor deposition method involves the evaporation of the drug-polymer mixture in a controlled chamber, followed by condensation onto a backing layer to form a thin, uniform drug film. The condensed material is then cooled and solidified to create a stable patch. This method allows precise control over drug layer thickness and uniformity, making it suitable for specialized applications. However, it is expensive and not commonly used in commercial transdermal patch production (19).

6. Printing-Based Techniques (3D Printing & Inkjet Printing):

Printing-based techniques, such as 3D printing and inkjet printing, offer advanced formulation approaches for transdermal patches. In these methods, the drug and polymer are formulated into an ink-like solution, which is then printed onto a backing layer in a controlled manner. The printed film is dried, cut, and laminated for final use. These techniques allow precise drug dosing, customizable release profiles, and personalization for individual patients.

However, the high cost of technology and limited scalability remain challenges for large-scale production (18, 20).

Evaluation of Transdermal Patches:

Physicochemical Evaluation:

Thickness of the Patch:

The thickness of the drug loaded patch is measured in different points by using a digital micrometre and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch (21).

Uniformity of weight:

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination:

An accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution (22-26).

Moisture content:

The prepared films are weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula (27).

$$\% \text{ Moisture Content} = \frac{(\text{Initial Wt.} - \text{Final Wt.})}{(\text{Final Wt.})} \times 100$$

Uptake Moisture:

Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % Moisture uptake is calculated as given below (28).

% Moisture Uptake= (Final Wt.- Initial Wt.)/ (Initial Wt.) X 100

Flatness:

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness (29).

% Constriction=(L1-L2)/(L2) X 100

L1 = Initial length of each strip

L2 = Final length of each strip.

Folding Endurance:

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it breaks. The number of times the films could be folded at the same place without breaking is folding endurance value (30).

Tensile Strength:

To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation (31).

Tensile Stress (s)= (Applied force)/ (Cross sectional area) = (m X g)/ (b X t)

Where, S = tensile stress in 980 dynes/cm², m = mass in grams, g = acceleration due to gravity (980 dynes/cm²) b = breadth of strip in centimetres, t = thickness of strip in centimeters.

Water vapor transmission studies (WVT):

For the determination of WVT, weighed one gram of calcium chloride and placed it in previously dried empty vials having equal diameter. The polymer films were pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials were accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials were again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch (32-34).

In other reported method, desiccators were used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccator was measured by using hygrometer. The weighed vials were then placed in desiccator and procedure was repeated.

Water vapor transmission rate= (Final Wt.- Initial Wt.)/ (Time X Area) X 100

Adhesive studies:

The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure. The adhesive properties of a TDDS can be characterized by considering the following factors:

- Peel Adhesion properties
- Tack properties
- Thumb tack test
- Rolling ball test
- Quick stick (Peel tack) test
- Probe tack test
- Shear strength properties or creep resistance (35).

Swellability:

The patches of 3.14 cm² was weighed and put in a petridish containing 10 ml of double distilled

water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed. The degree of swelling (S) was calculated using the formula:

$$\% \text{ Swelling} = (W_t - W_0) / (W_0) \times 100$$

Where S is percent swelling, W_t is the weight of patch at time t and W_0 is the weight of patch at time zero (36).

In Vitro Release Studies:

There are various methods available for determination of drug release rate of TDDS.

- The Paddle over Disc
- The Cylinder modified USP Basket
- The reciprocating discs
- Diffusion Cells e.g., Franz Diffusion Cell and its modification Keshary- Chien Cell (37).

In Vitro Permeation Studies:

Usually, permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as Franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophilic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually $32 \pm 5^\circ\text{C}$ for skin) and is continuously stirred at a constant rate. Sample analyzed by spectrophotometric method (38,39).

Applications of Transdermal Patches:

Transdermal patches have gained widespread acceptance in various therapeutic areas due to their ability to provide controlled and sustained drug release while minimizing systemic side effects. Their non-invasive nature and improved patient compliance make them suitable for the treatment of a wide range of conditions. The major applications of transdermal patches include:

1. Pain Management:

Transdermal patches are widely used for delivering analgesic drugs in chronic pain conditions, post-operative pain, and cancer pain management. Fentanyl patches provide continuous opioid analgesia, reducing the need for frequent dosing. Lidocaine patches are also used for localized pain relief in conditions such as post-herpetic neuralgia.

2. Hormone Replacement Therapy (HRT):

Transdermal patches are an effective alternative to oral hormone therapy, offering steady hormone levels while avoiding hepatic metabolism. Estradiol patches are used for managing menopausal symptoms, osteoporosis, and hormonal imbalances. Testosterone patches are also available for treating testosterone deficiency in men.

3. Cardiovascular Disorders:

Several transdermal patches are available for cardiovascular disease management. Nitroglycerine patches help prevent angina by providing a sustained release of the vasodilator. Clonidine patches are used for managing hypertension, offering prolonged blood pressure control with reduced systemic side effects.

4. Smoking Cessation:

Nicotine transdermal patches are a popular option for smoking cessation therapy. They deliver controlled amounts of nicotine to reduce withdrawal symptoms and cravings, allowing smokers to gradually wean off nicotine dependence.

5. Neurological and Psychiatric Disorders:

Transdermal patches are used for treating neurological and psychiatric conditions such as Parkinson's disease, Alzheimer's disease, and depression. Rotigotine patches provide continuous dopaminergic stimulation in Parkinson's patients, while rivastigmine patches improve cognitive function in Alzheimer's disease. Selegiline patches are used as an antidepressant, ensuring steady drug levels without significant gastrointestinal side effects.

6. Motion Sickness and Nausea:

Scopolamine transdermal patches are used for the prevention and treatment of motion sickness. They work by delivering a steady dose of scopolamine to the bloodstream, reducing nausea and dizziness associated with motion sickness and postoperative nausea.

7. Dermatological and Cosmetic Applications:

Transdermal patches are also used in dermatology for localized drug delivery. Anti-acne, anti-aging, and skin-lightening patches containing ingredients like retinol, hyaluronic acid, and vitamin C are increasingly popular in the cosmetic industry.

8. Contraception:

Hormonal contraceptive patches, such as the ethinyl estradiol/norelgestromin patch, provide a convenient and effective alternative to oral contraceptives. These patches release hormones transdermally to prevent ovulation, offering a once-weekly dosing regimen compared to daily pills.

9. Diabetes Management:

Research is ongoing to develop transdermal patches for insulin delivery. While commercial insulin patches are not yet widely available, microneedle-based patches are being explored as a painless and effective alternative to insulin injections (40-46).

CONCLUSION:

Transdermal patches have emerged as a promising drug delivery system, offering controlled drug release, improved patient compliance, and reduced systemic side effects. Their formulation involves selecting suitable drugs, polymers, permeation enhancers, adhesives, and backing materials to ensure effective skin permeation and prolonged therapeutic action. Various types of transdermal patches, including reservoir, matrix, drug-in-adhesive, and microreservoir systems, have been developed for different applications such as pain management, hormone therapy, cardiovascular disorders, and neurological conditions. The formulation of transdermal

patches requires careful consideration of drug properties and excipients, with several fabrication methods available, including solvent casting, hot-melt extrusion, direct milling, electrospraying, vapor deposition, and advanced printing techniques. Each method has its own advantages and limitations, influencing the drug release profile, adhesion properties, and scalability of production. Despite their advantages, transdermal patches face challenges such as skin barrier resistance, limited drug permeability, and adhesion issues. Advances in permeation enhancement strategies, nanotechnology, and microneedle-assisted delivery systems continue to improve the efficacy of transdermal patches. With ongoing research and technological advancements, transdermal patches are expected to play a crucial role in future drug delivery, providing more efficient and patient-friendly therapeutic solutions.

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