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Review Article

Transdermal Drug Delivery Systems: An Updated Review on Design, Evaluation, and Recent Advances

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Transdermal drug delivery systems (TDDS) have emerged as an effective alternative to conventional oral and parenteral dosage forms by delivering therapeutic agents through the skin into the systemic circulation. This route offers several advantages, including avoidance of first-pass hepatic metabolism, improved patient compliance, sustained drug release, reduced dosing frequency, and minimization of gastrointestinal side effects. The present review provides a comprehensive overview of transdermal patches, covering the structure and physiology of the skin, mechanisms of drug permeation, essential components, formulation strategies, different types of transdermal patches, methods of preparation, and evaluation parameters. The review also discusses the factors influencing transdermal drug absorption, along with the advantages, limitations, and therapeutic applications of TDDS. Furthermore, recent advances in transdermal drug delivery, including microneedle-based systems, iontophoresis, sonophoresis, electroporation, nanocarrier-based formulations, and smart transdermal patches, are highlighted for their potential to enhance drug permeation and therapeutic efficacy. Future perspectives emphasize the integration of advanced biomaterials and wearable technologies for personalized drug delivery. Overall, transdermal drug delivery systems represent a rapidly evolving field with significant potential to improve clinical outcomes and expand the range of drugs suitable for non-invasive administration.

Keywords: Transdermal drug delivery system; Transdermal patches; Skin permeation; Permeation enhancers; Microneedles; Controlled drug delivery; Novel drug delivery system; Nanocarriers.

INTRODUCTION

Drug delivery systems have undergone significant development over the past few decades with the aim of improving therapeutic efficacy and patient compliance. Among the various novel drug delivery approaches, the transdermal drug delivery system (TDDS) has gained considerable attention because it delivers drugs through the skin directly into the systemic circulation. This route provides an effective alternative to conventional oral and injectable dosage forms for suitable drug candidates. The oral route remains the most commonly used method of drug administration due to its convenience and patient acceptance. However, it has several limitations, including first-pass metabolism, degradation of drugs in the gastrointestinal tract, variable absorption, and the need for frequent dosing. These factors may reduce the bioavailability of many drugs and affect therapeutic outcomes. Transdermal drug delivery helps overcome many of these limitations by providing controlled and sustained drug release while avoiding the gastrointestinal tract and hepatic first-pass metabolism. A transdermal patch is a medicated adhesive dosage form that is applied to intact skin to deliver a predetermined amount of drug over a prolonged period. The drug diffuses across the skin layers and reaches the systemic circulation, maintaining relatively constant plasma drug concentrations. The success of transdermal therapy depends on factors such as the physicochemical properties of the drug, the condition of the skin, and the design of the patch, including the use of suitable polymers, adhesives, backing membranes, and

permeation enhancers. Recent advances, including microneedles, iontophoresis, sonophoresis, and nanotechnology-based delivery systems, have further expanded the scope of transdermal drug delivery and improved its clinical applications. The present review discusses the basic principles of transdermal drug delivery systems, their components, types, methods of preparation, evaluation parameters, advantages, limitations, recent developments, and future prospects. It aims to provide a concise and updated overview of TDDS and its growing importance in modern pharmaceutical research.

- **Main components of Transdermal Patches**

1. Polymer matrix
2. Permeation enhancers
3. Adhesive layer
4. Backing laminates
5. Release laminates
6. Drug

1. Polymer Matrix

The polymer matrix forms the main body of the transdermal patch and holds the drug uniformly. It controls the rate of drug release and provides mechanical strength and flexibility to the patch. Commonly used polymers include hydroxypropyl methylcellulose (HPMC), ethyl cellulose, polyvinyl alcohol (PVA), and Eudragit.

2. Permeation Enhancers

Permeation enhancers are substances that temporarily increase the permeability of the skin, allowing the drug to pass more easily through the stratum corneum. They improve drug absorption without causing permanent damage to the skin. Examples include ethanol, dimethyl sulfoxide (DMSO), oleic acid, and propylene glycol.

3. Adhesive Layer

The adhesive layer secures the patch firmly to the skin throughout the application period. In some formulations, it also serves as a drug-containing layer. Pressure-sensitive adhesives such as acrylic, silicone, and polyisobutylene adhesives are commonly used.

4. Backing Laminate

The backing laminate is the outermost layer of the patch. It protects the formulation from moisture, oxygen, and environmental contaminants while providing support and flexibility. It should be impermeable, non-irritating, and compatible with the other components.

5. Release Liner (Release Laminate)

The release liner is a protective layer that covers the adhesive surface before application. It is removed immediately before the patch is applied to the skin. This layer prevents contamination and preserves the adhesive properties of the patch during storage.

6. Drug

The drug is the active pharmaceutical ingredient incorporated into the patch. It should possess suitable physicochemical properties, such as low molecular weight, adequate lipid and water solubility, and sufficient potency, to enable effective absorption through the skin and achieve the desired therapeutic effect.

- **Routes of Drug Permeation Through the Skin**

Drugs incorporated into transdermal patches penetrate the skin through three main pathways:

1. **Intercellular Route**

The drug diffuses through the lipid matrix present between the cells of the stratum corneum. This is the most common route for the permeation of lipophilic drugs.

2. **Transcellular Route**

In this pathway, drug molecules pass directly through the corneocytes and the surrounding lipid layers. This route is generally preferred by small molecules possessing both hydrophilic and lipophilic properties.

3. **Appendageal (Shunt) Route**

The drug enters the skin through its appendages, including:

Hair follicles: Act as reservoirs for drug absorption and provide an alternative pathway through the skin.

Sweat glands: Provide small channels that allow limited drug permeation.

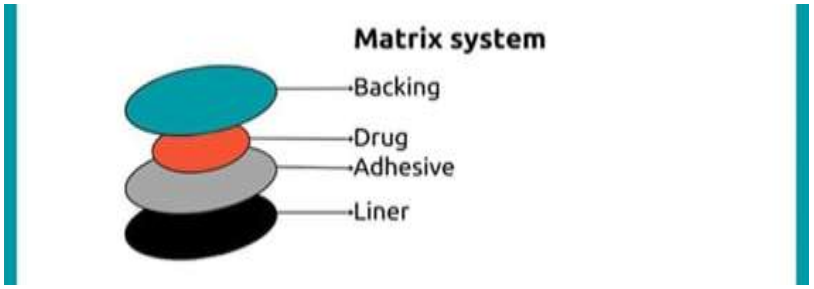
Sebaceous glands: Contribute minimally to drug transport but may facilitate the penetration of lipophilic drugs

➢ **Types of Transdermal Patches**

1. Matrix type
2. Reservoir type
3. Micro reservoir type
4. Drug in adhesive
5. Miscellaneous

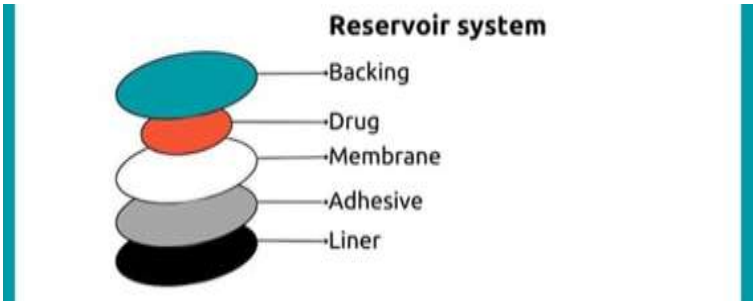
1. Matrix type.

In the matrix-type patch, the drug is uniformly dispersed within a polymer matrix that controls the rate of drug release. The adhesive layer keeps the patch attached to the skin, while the drug diffuses gradually from the polymer into the skin. This type is simple to manufacture, flexible, and widely used in commercial products.



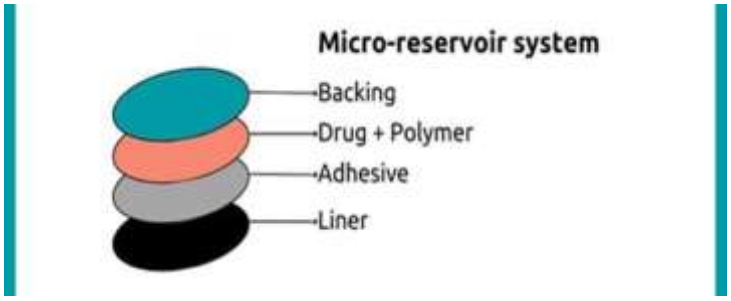
2. Reservoir type.

The reservoir-type patch contains the drug in a separate liquid or gel reservoir enclosed between a backing layer and a rate-controlling membrane. The membrane regulates the release of the drug, providing a nearly constant release rate over an extended period. However, damage to the membrane may result in dose dumping.



3. Micro reservoir type

The microreservoir-type patch combines the features of both matrix and reservoir systems. In this design, microscopic drug reservoirs are uniformly dispersed within a polymer matrix. This system offers better control over drug release while maintaining the stability of the formulation.



4. Drug in adhesive

In the drug-in-adhesive system, the drug is incorporated directly into the pressure-sensitive adhesive layer, which also attaches the patch to the skin. This design is thin, flexible, easy to manufacture, and is one of the most commonly used transdermal patch systems. It is available as single-layer and multi-layer drug-in-adhesive patches.

There are two types of drug in adhesive

a) Single-layer drug-in-adhesive

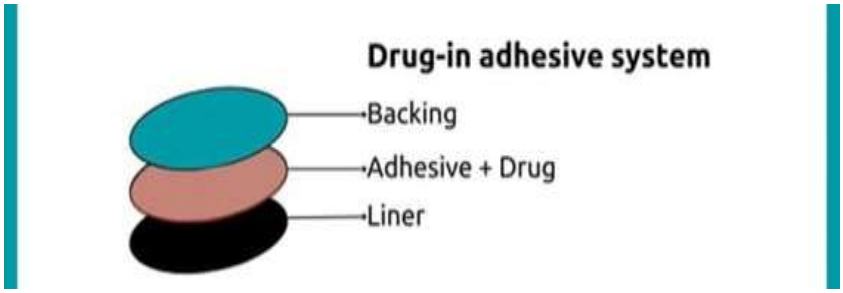
b) Multilayer drug-in-adhesive

Single-layer drug-in-adhesive

The drug-filled sticky layer. In this kind of patch, the adhesive layer is in charge of the medication release from the patch in addition to keeping the different layers of patch attached to one another and the skin.

Multilayer drug-in-adhesive

It resembles single-layer drug-in-adhesive technology. In this case, the medication is released by both sticky layers. The multilayer patch, on the other hand, differs slightly in that it incorporates an additional layer of drug-in-adhesive and, in certain situations, is divided by a membrane. This patch has both a permanent backing and a transient liner layer.

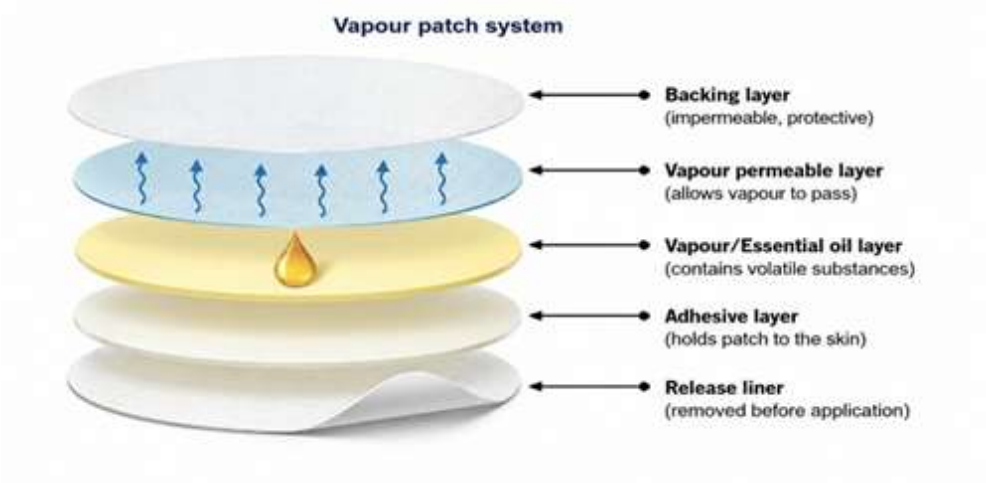


5. Miscellaneous

This category includes advanced transdermal systems such as vapour patches, hybrid matrix patches, and other modified designs developed for specific therapeutic applications. These systems are intended to improve drug delivery, enhance patient comfort, and increase therapeutic effectiveness.

In addition to holding the different surfaces together, the adhesive layer-containing patch also lets go of the vapour. Recently introduced to the market, vapor patches are frequently utilized to release essential oils for decongestion. There are numerous other kinds of vapor patches on the market that are intended to lessen the effects of cigarette smoking and enhance sleep quality.

i) Vapour patch



➢ **Methods of Preparation of TDDS**

1. Assymetric TPX membrane method.
2. Circular Teflon mould method.
3. By using "IPM Membrane" method.
4. Mercury substrate method.
5. Preparation of TDDS by using proliposomes.
6. By using "EVAC Membrane" method.
7. By using free film method.

- **Assymetric TPX Membrane Method:** In 1994, Berner and John made this method's discovery. With a concave backing membrane of 1 cm in diameter, heat sealable polyester film (type 1009, 3m) can be used to create a prototype patch using this method. A concave membrane containing the drug was coated with an asymmetric TPX [poly (4-methyl-1-pentene)] membrane and sealed with an adhesive.

- **Circular Teflon Mould Method:** In 1989, Baker and Heller made the discovery. As an organic solvent, polymeric solutions in different ratios are employed. The answer is then split into two sections. A certain amount of the medicine is dissolved in one part, and enhancers in varying concentrations are dissolved in another part. The two portions are then combined. Subsequently, the drug polymer solution is mixed with plasticizer (such as Di-N-Butylphthalate). Before pouring the entire mixture into a circular Teflon mold, it must be swirled for 12 hours. To regulate the vaporization of solvents in a laminar flow hood model, the molds must be positioned on a level surface and covered with an inverted funnel at a speed of 0.5 meters per second. It takes twenty-four hours for the solvent to dissipate. It then formed a dry film, which, in order to prevent the effects of aging, must be stored for a further 24 hours at 25±0.5°C in a desiccator filled with silica gel.

- **By Using "IPM Membranes" Method:** The medication is dissolved in the water and polymer mixture (propylene glycol with Carbomer 940 polymer) and is agitated with a magnetic stirrer for a duration of 12 hours. Triethanolamine is to be added to the dispersion in order to neutralize it and make it viscous. Buffer with a pH of 7.4 is used to create solution gel in cases where the drug's solubility in aqueous solution is extremely low. The IPM membrane will incorporate the gel that has produced.

➢ **Mercury Substrate Method:** This process involves dissolving the medication and plasticizer in the polymeric solution. After stirring for ten to fifteen minutes to achieve a uniform dispersion, the mixture is poured onto a leveled mercury surface and covered with an inverted funnel to regulate the evaporation of the solvent.

➢ **Preparation of TDDS by Using Proliposomes:** Proliposomes are made via the film deposition process with a carrier approach. The ideal drug to lecithin ratio, as determined by earlier sources, is 0.1:2.0. 5 mg of mannitol powder is used to manufacture proliosomes in a 100 ml round-bottom flask. The flask is then held at a temperature between 60 and 70 °C, spun at 80 to 90 rpm, and vacuum-dried for 30 minutes. The water bath's temperature is changed to between 20 and 30°C after drying. Following the dissolution of the drug and lecithin in an appropriate organic solvent mixture, a 0.5 ml aliquot of the organic solution is added to the round-bottomed flask at 37°C. After the solution has completely dried, another 0.5 ml aliquot of the solution is to be added. Following the final loading, the proliposome-containing flask is attached to a lyophilizer. The drug-loaded mannitol powders (proliposomes) are then left in a desiccator for the entire night before being sieved through 100 mesh. Until it is characterized, the gathered powder is kept at the freezing temperature in a glass bottle.

➢ **By Using "EVAC Membranes" Method:** Polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membrane, and 1% carbopol reservoir gel are required as rate control membranes for the manufacture of TDS. For the manufacture of gels, utilize propylene glycol if

the medication is insoluble in water. Propylene glycol is used to dissolve the drug. Carbopol resin is then added to the mixture and neutralized using a 5% w/w sodium hydroxide solution. The medication (in gel form) is applied to a backing layer sheet that covers the designated area. To create a leak-proof device, a rate-regulating membrane will be placed over the gel and the edges will be heated to seal.

- **By using Free Film Method:** First, cellulose acetate free film is made in this procedure by casting it onto a mercury surface. And chloroform is used to prepare a 2% w/w polymer solution. Plasticizers must be applied at a 40% weight-to-weight concentration of the polymer. Subsequently, a glass ring containing 5 milliliters of polymer solution is positioned over the mercury surface within a glass petridish. Over the petridish, an inverted funnel can be used to regulate the solvent's rate of evaporation. When the solvent has completely evaporated, the mercury surface is examined to detect the film formation. Before being used, the dried film will be removed and kept in a desiccator in between the wax paper sheets.

- **Factors Affecting on Transdermal Patches**

There are a variety of factors that are affecting on the Action Of Transdermal patches

A. Biological Factors

B. Formulation Factors

C. Physicochemical Factors

A. Biological Factors: -

1. pH of the skin
2. Hydration condition of the skin
3. Site of application
4. Sex and race
5. Age of candidate
6. Pathological condition of the skin
7. Lipid films over the skin

B. Formulation Factors: -

1. Permeation enhancers
2. Release Characteristics of Patch or Drug
3. pH of vehicles

C. Physicochemical Factors: -

1. Molecular Size and shape of drug molecules
2. Stability and Half-life of Patch or Drug inside of patch
3. Partition coefficient
4. Drug Concentration

- **Evaluation Parameters for Transdermal Patches.**

A. Physicochemical evaluation

B. In vitro evaluation

C. In vivo evaluation

A. Physicochemical evaluation: -

Physicochemical evaluation is done by considering the following parameters -

1. Thickness

At various locations along the film, the screw gauge, dial gauge, and microscope were used to measure the thickness of the transdermal patches.

2. Uniformity of weight

Another name for it is weight fluctuation. Ten randomly chosen patches can be weighed in order to study it separately. Next, the patches' average weight was determined. The weight of each individual should not differ from the weight of the average.

3. Drug content determination

Weigh the film precisely, then dissolve it in 100 mL of a suitable solvent that the medication will dissolve in. After that, the shaker incubator is used to continually shake this solution for a full day. This solution can then be requested. Following mixing and filtering, the drug's concentration in the solution is calculated using spectroscopy and the proper dilutions.

4. Drug content uniformity test

Ten patches were chosen at random, and each patch's content is different. The results should look like this: of these 10 patches, 9 should fall between 85% and 115% of the given value, and the remaining patch should fall between 75 and 125%. At that point, the patches are deemed to have passed the test. To pass the test, further 20 patches must be taken with content in the range of 85–125% if the first three have content in the 75–125% range.

5. Moisture content

The prepared films were removed, weighed separately, and then stored in a desiccator that holds calcium chloride. Following a 24-hour period at room temperature, each film needs to be weighed once again. The moisture content percentage is calculated using the formula provided.

6. Flatness

The transdermal patch should be smooth and should not be constricted with the time. Hence, this study was performed. For the determination of the flatness, one patch is cut down from the center and the two from each side of the patch.

7. Folding endurance

The process of evaluating folding endurance for films is figuring out how well they fold after putting them under rigorous folding circumstances. Folding endurance can be assessed by folding the film repeatedly without breaking at the same spot. That is the patch's folding endurance value.

B. In vitro evaluation

The drug's release from the polymeric transdermal film determines how much of it is available for blood absorption. The medication that reaches the skin's surface is next subjected to standard penetration tests, which were carried out by affixing the transdermal patch to the skin of rats or to the artificial membrane found in vertical diffusion cells between the donor and receptor. The hydrophilic side of the membrane receives application from the transdermal system, while the lipophilic side comes into touch with the receptor fluid. The receiver compartment is constantly stirred and kept at a set temperature, often 32°C. At regular intervals, the samples were removed, and each time, the same volume of buffer was added. A UV spectrophotometer is used to measure the absorbance after the samples were diluted. Calculations are made to determine how much medication has permeated each square centimeter at each interval. The system's architecture, the patch's size, the skin's surface area, thickness, temperature, and other factors all affect how much drug is released.

C. In Vivo evaluation

The medication performance can be accurately represented in these study evaluations. The TDDS in this study can be completed using –

• Animal models.

• Human volunteers or human models.

- **Advantages Of Transdermal Drug Delivery System: -**

1) It does not cause variations in the drug level.
2) The gastrointestinal incompatibility is avoided.
3) It is feasible to take medication on your own.
4) An improvement in the patients' compliance.
5) Action's duration may be anticipated.
6) Reduces the amount of negative side effects.
7) Easy and painless self-medication.
8) Prevents unintentional overdosing.
9) It is possible to prevent first pass metabolism.
10) It is possible to enhance physiological and pharmacological reaction.

- **Disadvantages of Transdermal Drug Delivery System: -**

1) Possibility of localized rashes and edema.
2) Unable to provide medications that need high blood pressure.

3) Unsuitable for a medication without a favorable O/W partition coefficient.

4) When it comes to administering significant quantities of medication via the skin, neither practical nor economical.

5) Selectivity and cost for particular physicochemical medicinal qualities.

6) This method works well for delivering very few medications at a variable rate.

7) The skin's limited permeability allows a certain number of medications to go through it.

8) Potential sensitivity and inflammation of the skin.

9) The skin's barrier function varies depending on the individual and the location.

- **Future of Transdermal Drug Delivery System:**

In the future, drug delivery systems may incorporate microemulsion, niosomes, and liposomes. The purpose of this discovery is to enhance medication delivery, as the majority of classical formulation excipients have limited intrinsic solubility. Numerous medications, including steroids, methotrexate, interferon, antifungals, and antibiotics, are being developed for possible administration. Transdermal patch sales are expected to rise in the future and have grown at a rate of 25% annually in previous years. As new devices are developed and the number of transdermal drugs that are marketed rises, this number will rise in the future. As long as design advancements are made, transdermal analgesic administration is expected to gain more and more traction. Studies are being conducted to improve efficacy and safety. To enhance practical aspects such as the patch wearer's experience and to offer more accurate medication delivery linked to longer duration of action. Other possible advancements include enhanced transdermal technology, which raises the energy of the drug molecules or modifies the skin barrier to increase drug flux through the skin by using mechanical energy. Many "active" transdermal technologies are being researched for a variety of medications following the successful construction of patches utilizing iontophoresis. These include sonophoresis, which uses low frequency ultrasonic energy to disrupt the stratum corneum, thermal energy, which uses heat to increase the energy of drug molecules and make the skin more permeable, and electroporation, which uses short electrical pulses of high voltage to create transient aqueous pores in the skin. Drug flux over the skin has been studied in relation to magnetic energy, or magnetophoresis. It's possible that the transdermal patch is a neglected method for treating both acute and chronic pain.

- **Marketed Transdermal Patches**

Several transdermal patches have been successfully commercialized for the treatment of various acute and chronic conditions. These products provide controlled drug release, improve patient compliance, and reduce dosing frequency. Some commonly marketed transdermal patches are listed in Table 1.

Table 1. Commonly Marketed Transdermal Patches

Drug	Brand Name	Therapeutic use	Duration
Nicotine	Nicoderm CQ	Smoking cessation	24 hours
Nitroglycerin	Nitro-Dur	Angina pectoris	12-24hours
Rivastigmine	Exelon Patch	Alzheimer's Disease	24 hours
Fentanyl	Duragesic	Chronic pain	72 hours
Clonidine	Catapres-TTS	Hypertension	7 days

CONCLUSION

Transdermal drug delivery systems have emerged as an effective alternative to conventional drug administration by providing controlled drug release, improved bioavailability, and enhanced patient compliance. Continuous advances in polymer science, nanotechnology, microneedles, and wearable drug delivery devices have significantly expanded the therapeutic potential of transdermal systems. Although challenges such as limited skin permeability

and drug selection remain, ongoing research is expected to overcome these limitations. Consequently, transdermal drug delivery systems are likely to play an increasingly important role in modern pharmaceutical therapy and personalized medicine.

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