International Journal of Medical and Pharmaceutical Sciences
Open access peer-reviewed Journal
Volume 2, Issue 3, Page 400-406.
https://doi.org/10.5281/zenodo.19228353

Review Article

A Systematic: Review Article on Transdermal Drug Delivery System

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Transdermal Drug Delivery Systems (TDDS) are advanced therapeutic technologies designed to deliver drugs through the skin into systemic circulation at a controlled and sustained rate. They offer a promising alternative to conventional oral and parenteral drug delivery routes by overcoming drawbacks such as first-pass metabolism, gastrointestinal degradation, and poor patient compliance. A typical TDDS consists of several essential components, including a polymer matrix or drug reservoir, permeation enhancers, pressure-sensitive adhesives, backing laminate, release liner, and other excipients. Each component plays a crucial role in ensuring controlled drug release, stability, and effective skin adhesion. The success of TDDS depends on various factors such as the physicochemical properties of the drug, formulation design, and biological characteristics of the skin. Drugs suitable for TDDS generally possess low molecular weight, adequate lipophilicity, and high potency. Despite limitations like skin irritation, dose restrictions, and variability in skin permeability, TDDS provides numerous advantages, including sustained drug release, reduced dosing frequency, improved bioavailability, and enhanced patient comfort. In conclusion, TDDS represents a non-invasive, efficient, and patient-friendly method for systemic drug delivery. With continuous research and advancements in polymer and formulation technologies, TDDS is expected to play an increasingly significant role in modern pharmaceutical development.

Keywords: Transdermal drug delivery System, Patches, controlled release.

INTRODUCTION

Transdermal Drug Delivery Systems (TDDS) are advanced dosage forms designed to deliver a specific amount of drug across the skin into the systemic circulation in a controlled manner. They provide an alternative route of drug administration to oral and parenteral methods, overcoming limitations such as first-pass metabolism, gastrointestinal degradation, and poor patient compliance.[1,2] The skin, being the largest organ of the body, acts as a natural barrier; however, TDDS utilizes this surface for the controlled release of medication through the stratum corneum and deeper skin layers into the bloodstream. Transdermal patches are the most common form of TDDS, consisting of multiple layers that regulate the rate of drug release and ensure adhesion to the skin.[4]

These systems offer several advantages, including sustained drug release, reduced dosing frequency, improved bioavailability, and minimal side effects.[5] However, they are limited to drugs with low molecular weight, adequate lipophilicity, and potent pharmacological action.[1] Thus, TDDS represents a non-invasive, convenient, and effective approach for systemic drug delivery, significantly improving therapeutic outcomes and patient compliance.[2,5]

Basic Components of a Transdermal Drug Delivery System

- Polymer Matrix or Drug Reservoir
- The Drug
- Permeation Enhancers
- Pressure Sensitive Adhesive (PSA)
- Backing Laminate
- Release Liner

- Other Excipients

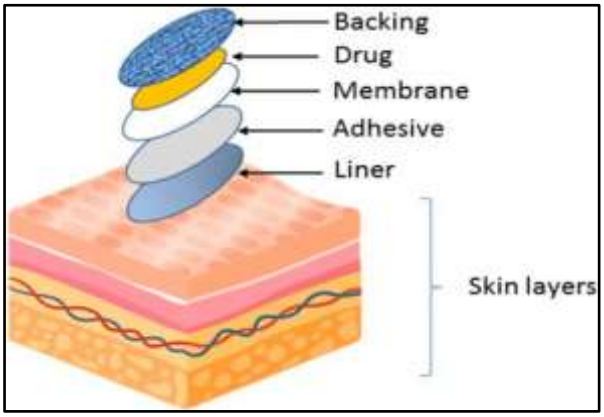

Fig.1. Basic component of a transdermal medical patch

Polymer Matrix or Drug Reservoir:

To make the polymer matrix, the drug is mixed into a man-made polymer that can be either liquid or solid. This polymer then controls how fast the drug comes out of the patch or device, and it is the most important part of how transdermal drug delivery systems work.[9] The polymer must exhibit biocompatibility and chemical compatibility with the drug and other components of the formulation, including penetration enhancers. The mechanism of drug release is affected by the physicochemical characteristics of both the drug and the polymer utilized in the formulation.[9] Furthermore, the polymer must guarantee reliable and efficient drug delivery for the entire intended shelf life of the product and must be safe for application.[10]

Examples: Ethyl cellulose, polyvinyl alcohol, polyurethane, and hydroxypropyl methylcellulose (HPMC).[9]

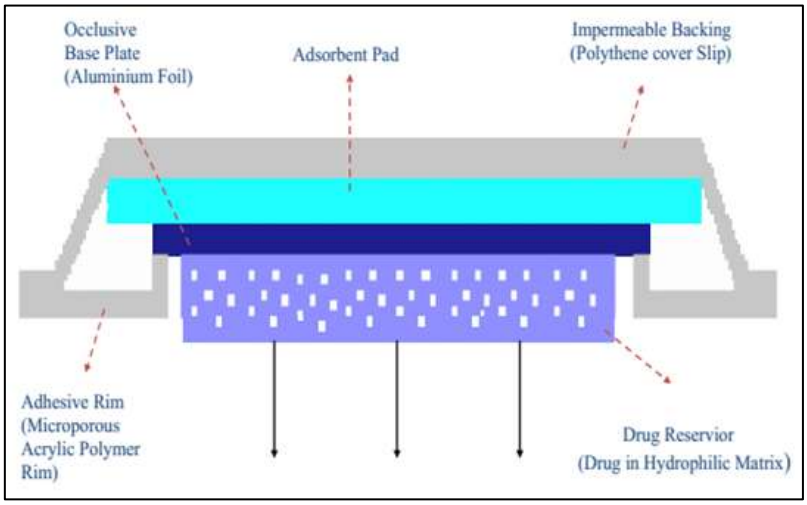

Fig.2. Polymer matrix

Ideal properties of polymers

- The polymer should be non-toxic, non-irritating, and compatible with both the drug and the skin.[9]
- It should be chemically stable and should not react with the drug, excipients, or environmental factors such as light and temperature.[9]
- The polymer should allow predictable and consistent drug release through diffusion or degradation mechanism.[9,10]
- It must provide adequate adhesion to the skin during application while being easily removable without causing irritation.[10]
- The polymer should permit drug permeation while maintaining the integrity of the system.[9]

- It should be flexible enough to confirm to skin movements and have adequate mechanical strength to prevent tearing or deformation.[9]
- The polymer should not chemically interact with or alter the stability or efficacy of the drug and other formulation components.[10]
- It should easily form a smooth, uniform, and thin film suitable for patch fabrication.[9]
- The polymer should be affordable, easily available, and suitable for large-scale manufacturing.[10]
- It should have a good aesthetic feel, odourless, and not lead to any discomfort or skin irritation during use.[10]

Classification of Polymers Used in TDDS:

Natural polymer	Synthetic Elastomer	Synthetic Polymer
Cellulose derivative	Polybutadiene	Polyvinyl alcohol
Zein	Hydrin rubber	PVC
Gelatin	Polyisobutylene	Polyethylene
Gums	Silicon rubber	Polypropylene
Chitosan	Acrylonitrile	Polyacrylate
Shellac waxes, etc.	Neoprene, etc.	Polyvinyl pyrrolidone, etc.

The Drug:

One of the most important steps in creating a transdermal drug delivery system is choosing the medication. The drug is the most important factor in determining the formulation's effectiveness, so it must be carefully chosen.[1,9] The ideal characteristics of a medication and crucial elements to consider when creating transdermal patches are as follows:

Ideal properties of a drug:

Sr. No.	Parameters	Properties
1	Oral Bioavailability	Low
2	Molecular weight	Less than 600
3	Skin permeability coefficient	>0.5*10-3 cm/hr
4	Dose	Must be less in weight (less than 20 mg/day)
5	Skin reaction	Non-sensitizing, non-irritating
6	Half-life	Less than 10 hours

Factors Affecting: -

Pharmacokinetic	Biological	Physicochemical
Therapeutic plasma concentration	Skin metabolism	Polarity
Bioavailable factor	Skin toxicity	Melting point
Half-life	Allergic reaction	Crystallinity
Total body clearance	Site of application	Molecular weight
Volume of distribution	—	Solubility

Penetration Enhancers:

In order to help the medication reach therapeutic levels, penetration enhancers are substances that make the skin more permeable, especially the stratum corneum. They work by temporarily changing the epidermal barrier, which facilitates the passage of the targeted drug.[12]

Examples: Oleic acid, propylene glycol, DMSO, and ethanol.[8]

Ideal Properties of Penetration Enhancers:

The following traits are essential for a successful penetration enhancer:[12]

- It should be non-irritating, non-toxic, and non-allergenic.
- It must have a pleasing skin feel when applied and be aesthetically acceptable.
- It should not bind to receptor sites or show any pharmacological activity, which is known as pharmacological inertness.
- It should serve as a suitable solvent for the medication.
- To promote speedy drug absorption, it should have a quick onset of action.
- The transdermal delivery system must be able to incorporate it with ease.
- It should not result in fluid loss or harm to the integrity of the skin.
- It needs to work both chemically and physically with the medication and other excipients in the formulation.
- For both practical and decorative purposes, it should be inexpensive, colorless, and odorless.

Pressure Sensitive Adhesive (PSA):

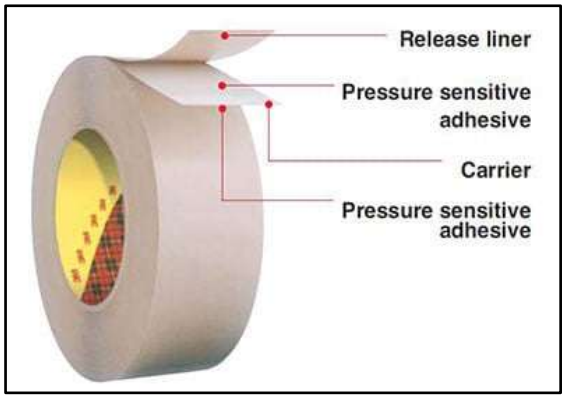

Fig. Pressure Sensitive Adhesive

One essential part of the Transdermal Drug Delivery System (TDDS) is Pressure Sensitive Adhesive (PSA). It enhances the transdermal patch's adherence to the skin's surface.[13] It serves as a matrix that contains the medication and additional excipients, which is more significant. Additionally, it is easily and residue-free removed from smooth surfaces.[9]

- Polyacrylates
- Adhesives made of silicone
- Polyisobutylene

Backing Laminate:

Fig. Backing laminate

The backing laminate, sometimes referred to as the backing membrane, is a flexible substance that offers the drug reservoir good support and a strong bond. Usually impermeable to the medication, it serves as a barrier that keeps it from leaking through the patch's top.[14] Along with improving drug penetration, it protects the formulation when applied topically. It is important that the backing material has chemical

compatibility with the drug, adhesive, penetration enhancer, and other excipients.[9]

Examples: Vinyl, polyethylene, and polyester films.

Release Liner:

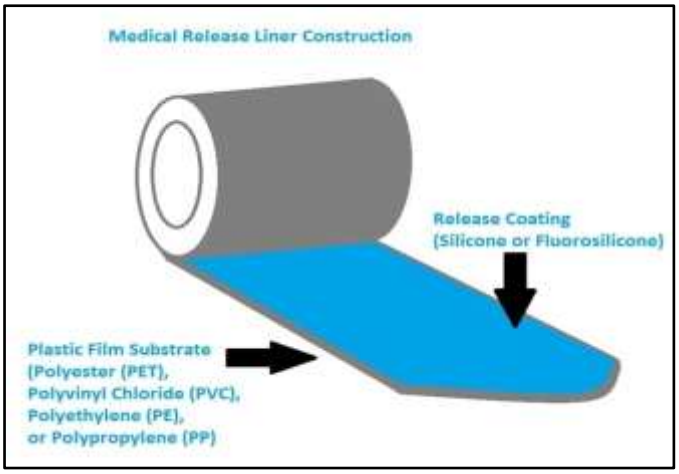

Fig. Release liner

The patch is protected during storage by a liner, which is taken off and discarded right before the patch is applied to the skin.[13] Instead of being a component of the dosage form that delivers the active principle, it is considered to be a part of the primary packaging material.[9] It will take an excessive amount of force to remove the release liner if cross-linking is created between the adhesive and the liner.[13]

Other Excipients:

Other excipients, such as plasticizers and solvents, are also used in the formulation.[10]

Plasticizers: Triethyl citrate, propylene glycol, dibutyl phthalate, and polyethylene glycol.

Solvents: Isopropanol, Dichloromethane, Acetone, Chloroform, Methanol.

Method of Preparation Of Transdermal Drug Delivery System

- Asymmetric TPX Membrane Technique
- Formulation of Transdermal Drug Delivery Systems Utilizing Proliposomes
- IPM Membrane Approach
- Circular Teflon Mold Technique
- Free Film Fabrication Method
- Mercury Substrate Technique
- EVAC Membrane Methodology

Advantages of Transdermal Drug Delivery System

- First-pass metabolism should be avoided.[15]
- Fit for drug candidates with a low therapeutic index and short half-life.[15]
- A decrease in the frequency of doses.[15]
- Preventing gastrointestinal incompatibility.[15]
- Reducing daily drug consumption.[15]
- Less variation in the drug's plasma concentration.[15]
- Enhances adherence by patients.[15]
- Reduction of adverse effects.[15]
- Easy and unobtrusive.[15]
- An alternative oral administration method.[15]
- Vomiting or diarrhea has no effect on dose delivery.[15]
- By removing the patch, drug administration can be hated.[15]
- Adequate for self-management[15]
- Increases the efficacy of treatment [15]

Disadvantages of Transdermal Drug Delivery System

- The drug should have proper physical and chemical properties so it can pass through the outer layer of the skin (stratum corneum).[15]
- Drugs that need less than 5 mg per day work best. If the dose is more than 10–25 mg per day, it becomes difficult to deliver through the skin.[15]

- Sometimes, the drug, adhesive, or other ingredients in the patch can cause skin irritation.[15]
- There should be a clear medical reason or need to use the transdermal route.[15]
- The skin barrier is different in different body parts and between people and also changes with age.[15]
- Only a few drugs can be used in TDDS because most drugs do not pass easily through the skin.[15]
- Ionic (charged) drugs cannot be delivered through the skin using TDDS.[15]
- TDDS cannot produce very high drug levels in the blood or plasma.[15]
- Drugs with large molecular sizes cannot be used in TDDS.[15]
- TDDS cannot give drugs in a sudden or pulsating way; it releases the drug slowly and steadily.[15]

Factors Affecting Transdermal Patches:

The effectiveness and performance of transdermal patches depend on various factors, which can be grouped into the following categories:

1. Biological Factors
2. Formulation Factors
3. Physicochemical Factors

1. Biological Factors:

- The pH level of the skin
- The hydration level of the skin
- The location where the patch is applied
- The sex and race of the individual
- The age of the patient
- Any existing skin conditions
- The presence of a lipid layer on the skin surface

2. Formulation Factors:

- The type and concentration of permeation enhancers used
- How the patch or drug is released from the formulation
- The pH level of the formulation or vehicle used

3. Physicochemical Factors:

- The size and shape of the drug molecules
- The stability and half-life of the drug or patch formulation
- The partition coefficient of the drug
- The concentration of the drug within the formulation

Evaluation Test for Transdermal Drug Delivery System

Physical Appearance of the Transdermal Patch:

All transdermal patches undergo visual inspection to assess their flexibility, color, and surface smoothness, thereby ensuring consistency in their appearance.[11]

Weight Uniformity:

This assessment verifies the uniformity of the prepared patches. From the complete batch, three small samples, each approximately 2 × 2 cm (4 cm^2) in size, are randomly selected and individually weighed. Subsequently, the standard deviation of the mean weight is computed and documented to confirm consistency.[11]

Moisture Content:

The fabricated films were individually weighed and subsequently stored in a desiccator containing silica gel and calcium chloride at ambient temperature for a duration of 24 hours. Following this interval, the films were reweighed, and the moisture content percentage was calculated using the formula below:[11]

Percentage Moisture Content = [(Initial Weight - Final Weight) / Initial Weight] × 100

Folding Endurance/Tolerance:

Folding endurance, also referred to as folding tolerance, is assessed by preparing a sample of consistent dimensions (2 × 2 cm) and subjecting it to repeated folding at a single location until failure occurs. The total number of folds the sample withstands at the identical point before rupture serves as a measure of its folding endurance or tolerance.[11]

Flatness:

A transdermal patch was segmented into three longitudinal strips corresponding to the left, right, and central regions. The initial length (L_1) and the final length (L_2) of each strip were recorded. The degree of

contraction was determined using the following equation:

Contraction = $[(L_1 - L_2) / L_1] \times 100$

This assessment serves to verify that the patch preserves consistent dimensional stability, exhibiting no substantial shrinkage or deformation.[11]

CONCLUSION

Transdermal Drug Delivery Systems (TDDS) represent a sophisticated, non-invasive, and controlled approach for administering pharmaceuticals through the skin into systemic circulation. These systems address the limitations associated with oral and parenteral administration routes, including first-pass hepatic metabolism, degradation within the gastrointestinal tract, and issues related to patient adherence. TDDS facilitates sustained drug release, decreases dosing frequency, and enhances bioavailability, thereby contributing to improved therapeutic efficacy. Nonetheless, their application is confined to drugs possessing appropriate molecular size, lipophilicity, and pharmacological potency. Despite these constraints, TDDS continues to be a promising modality in contemporary drug delivery, offering advantages in terms of patient convenience, safety, and therapeutic effectiveness, and is progressively advancing in parallel with innovations in formulation technologies.

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Cite: Ruchita Phalaskar*, Tanvi Salunkhe, Nidhi Zendekar, Arya Niwate, Muskan Darekhan, A Systematic: Review Article on Transdermal Drug Delivery System, Int. J. Med. Pharm. Sci., 2026, 2 (3), 400-406. https://doi.org/10.5281/zenodo.19228353