

TRANSDERMAL PATCHES – A REVIEW

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ABSTRACT

Transdermal patches, or drug delivery systems embedded in the skin, offer significant advantages over injections and oral medications. Bypassing needles and first-pass metabolism, they boost patient compliance and provide controlled, continuous drug release. This eliminates the peaks and valleys of traditional methods, minimizing side effects and supporting drugs with short lifespans. However along with all these advantages there are also many limitations with this system. This review on TDDS offers valuable insights for researchers exploring this innovative drug delivery technique.

Keywords: Transdermal Patches, TDDS, Advanced Drug Delivery, Innovative Drug Design

INTRODUCTION

Transdermal patches are employed in cosmetic, topical & transdermal drug delivery systems (TDDS)⁽¹⁾. Commercially, first transdermal drug delivery patch were introduced in 1979 i.e. scopolamine patch & after that it become a striking route for drug transmission delivery plus a demanding area for research.⁽²⁾ TDDS is ideal for self-application & commonly reasonably priced.^(3, 4) thus, in previous years, patches of various drugs like lidocaine, nicotine, methyl salicylate, hormone, fentanyl have been utilized for expansion of product line for treatment of many conditions.

Protein & peptide based therapeutics are rapidly degraded by stomach acid & hindrances of size restriction from the epithelium⁽⁵⁾. Administration of macromolecules by main mode is therefore via injection⁽⁵⁻⁷⁾. But the injection causes pain & decreases acceptance by patients. Hence trained staff for administering injectables is essential^(5, 8). Many of the routes of administration have other such limitations which are overcome by employing the transdermal drug delivery system (TDDS). TDDS additionally avoids first path metabolism, reduces possible systematic side effects, and improves patient compliance and feasibility for unconscious, vomiting, or self-administering patients^(9, 10). Transdermal patches offer controlled release and absorption of medication, maintaining stable plasma concentrations over an extended period^(11, 12). This

success has led to increased research activity and resource allocation, driving further innovation in the field^(13, 14).

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	Combipatch	Menopause
Lidocaine	Lidoderm	Pain relief
Norelgestromin	Ortho Evra	Contraception
Estradiol/levonorgestrel	Climara Pro	Menopause
Oxybutynin	Oxytrol	Overactive bladder
Lidocaine (ultrasound)	SonoPrep	Pain relief
Lidocaine/tetracaine	Synera	Pain relief
Fentanyl HCl	Ionsys	Postoperative pain
Methylphenidate	Daytrana	ADHD
Selegiline	Emsam	Depression
Rotigotine	Neupro	Parkinson's disease
Rivastigmine	Exelon	Dementia

Figure 1: Marketed Products of Transdermal Patches

Generations of TDDS:

TDDS are categorized into three generations. The first generation includes only small drug molecules, with no need of penetration enhancers, that could be topically

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applied. In the second-generation penetration enhancers are involved alongside drug molecules. In the third generation the penetration of the stratum corneum is targeted to allow for the delivery of small drug molecules, protein and peptide based drugs, and different vaccines ^(15, 16).

Advantages of TDDS

Merits of adopting TDDS includes ⁽¹⁷⁻¹⁹⁾:

- Gives continuous drug release for prolong duration.
- Self-application is possible.
- Gives equivalent therapeutic effects comparatively with other dosage form.
- Applicable to emergency condition for comatose & unconscious patient.
- Can easily be used for agents having narrow therapeutic windows.
- Reduces dosing frequency.
- Avoids first pass metabolism and provides superior bioavailability.
- Maintain plasma concentration of potent drug until dosing interval.
- Adulteration in TDDS systems is harder.
- Provides immediate termination of drug delivery by removing the patch from surface of the skin.
- Reduces systemic side effects.
- Provides alternate route to oral drug delivery.
- It is painless, non-invasive, & convenient to patients. Especially for pediatric & geriatric patients.
- Avoids variation in drug levels & improves therapeutic efficacy.

Disadvantages of TDDS:

Limitations of the TDDS includes ^(20, 21):

- Inappropriate for drugs required in higher doses.
- Hydrophilic nature drugs permeate too slowly.
- Sticking capability of patch depends upon type of skin & surrounding environment.
- Irritates skin & causes immune reactions.
- Macromolecules, ionic drugs can't be delivered.

- When patients in shock or have low peripheral blood supply TDDS are unable to provide desired results.

MAJOR COMPONENTS OF TDDS

A. Polymer Matrix

It regulates drug delivery ⁽²²⁾. Table 1 presents more details regarding its types.

Natural polymers

Some of the natural polymers used in patch matrices include cellulose derivatives, gelatin, zein, gums, proteins, starch, shellac, waxes, natural rubber etc.

Synthetic Elastomers

This category includes polybutadiene, nitrile rubber, styrene-butadiene rubber, polysiloxane (silicone rubber), butyl rubber, neoprene, hydriin rubber, etc.

Synthetic polymers

The synthetic polymers commonly used are polyethylene (PE), polymethylmethacrylate (PMMA), polyvinyl chloride (PVC), polyvinylpyrrolidone (PVP), polypropylene (PP), polyvinyl alcohol (PVA), polyurea, polyacrylate, polyamide, epoxy etc.

Table 1: Basic Types of Polymer Matrix ^(15, 22, 23)

B. Drug (Therapeutic Agent)

For effective formulation a TDDS, the drug should be decided with very carefully, the drug must be comparative with relative excipients ^(15, 23).

C. Penetration Enhancers

They flux the preferred drug. They can be of different types chemicals which can broadly be associated into different categories.

Solvents

Solvents act like boosters for drug delivery. They achieve this in two ways: some disrupt the skin's natural barrier, creating a temporary passage for the medication (polar route), while others loosen up the fatty molecules within the skin, allowing the drug to

move more freely between them (fluidizing lipids). E.g. Water-based alcohols like ethanol and methanol; Alkyl homologs such as dimethyl sulfoxide (DMSO), and dimethyl acetamide (DMAc); Pyrrolidones like 2-pyrrolidone, N-Methyl-2-pyrrolidone (NMP); other miscellaneous solvents such as propylene glycol, oleic acid, etc^(15, 23, 24).

Surface Active Agents (Surfactants)

Transdermal patches often include surfactants to act as microscopic helpers for drug delivery. These come in three forms: anionic and nonionic surfactants (like Dioctyl sulfosuccinate or Pluronic F127), which disrupt the skin's barrier to create temporary entry points for the medication, and bile salts (like Sodium taurocholate), which mimic natural digestion to further enhance drug absorption [15, 18].

Miscellaneous chemicals

Transdermal patches may include some additional chemical helpers for specific drugs. These can include urea, a hydrating agent, to improve absorption of water-soluble medications. In some cases, specialized chemicals like anticholinergic agents might be included for targeted effects. Less commonly, some patches might use eucalyptol for potential pain relief, cyclodextrin for improved drug solubility, or casein for better adhesion [15, 18].

D. Adhesive

Tacky to all TDDS devices to skin by pressure sensitive adherent present at the front of the device or backside of devices extending peripherally⁽¹⁵⁾.

E. Backing Membrane

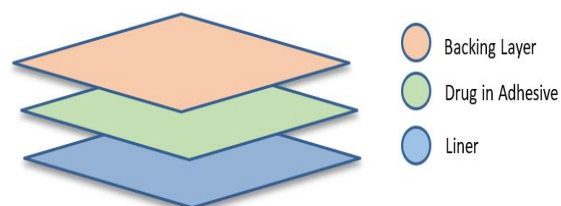
The backing membrane of a transdermal patch acts like a secure, stretchy bandage, adhering to the drug reservoir. Which creates a barrier stopping drug leakage from the top of the patch, both during storage and application. It also shields the patch from contamination and external elements when placed on skin. Common materials include metallic plastic laminates for flexibility, or combinations like plastic backings with absorbent pads and aluminum foil bases for additional protection⁽²⁵⁾.

CLASSIFICATION OF TRANSDERMAL PATCHES

TDDS patches can be broadly classified into four main categories^(15, 16, 23):

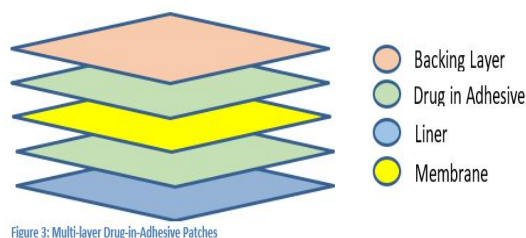
Single-layered Drug-in-Adhesive Patches

The drug is enclosed in the adhesive in contact with the skin. In this design, the adhesives perform two functions. It sticks the patch to the skin. It also manufactures the base to make single backing film (blends drug & excipients). Drug release rate is based on diffusion system transverse to skin.



Multi-layered Drug-in-Adhesive Patches

In this design, multiple layers are present. They either have a membrane layer separating two discrete drug-in-adhesive layers or the placement of multiple drug-in-adhesive layers beneath a single backing film.



Drug Reservoir-in-Adhesive Patches

In this design, a liquid compartment is formed by solution or suspension of a drug that alienates from liner through partially permeable membrane & sticking material (adhesive). The major constituent is adhesive that accounts for skin sticking. The patch can have adhesive in two places: either as a continuous layer between the membrane and the liner, or in a ring-shaped area around the membrane.

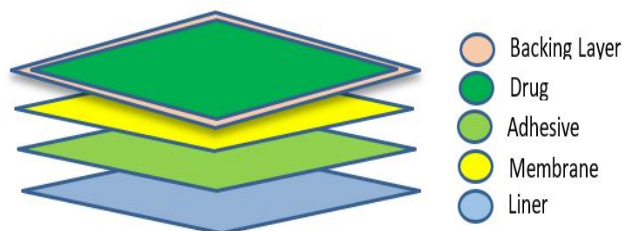


Figure 4: Drug Reservoir-in-Adhesive Patches

Drug Matrix-in-Adhesive Patches

In this design, the drug solution or suspension is enclosed with semisolid matrix which directly connects with liner. Adhesion is a major constituent accountable that superimposes & contains a concentric arrangement in the region of semisolid matrix.

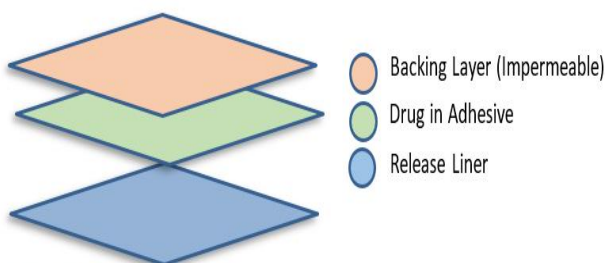


Figure 5: Drug Matrix-in-Adhesive.

OVERVIEW OF SKIN STRUCTURE

The most easily accessible human organ is skin which covers the major surface area of body i.e. 1.7m². Which makes 16% of the total body weight of the typical person ^(26, 27). Major function of skin is shielding and linking the internal body & external atmosphere ⁽²⁸⁾. Skin has three major layers^(29, 30):

1. The outermost layer, the Epidermis, with the stratum corneum acting as a waterproof barrier.
2. The middle layer, the Dermis, a strong and elastic layer.
3. The deepest layer, the Hypodermis, stores fat and helps regulate body temperature.

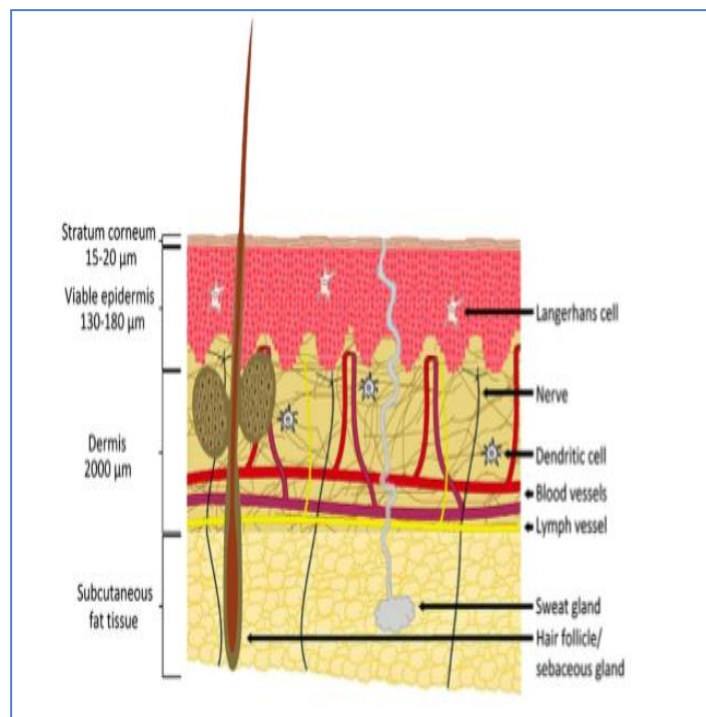


Figure 6: Anatomy of the Skin

Epidermis

- It has multiple layers of epithelial cells. Which vary in width from 0.6mm on surfaces like eyelids to 0.8 mm on the palm & sole ⁽²⁸⁾.
- The major cellular content of epidermis is keratinocytes (approx: 95% of cells). Other cellular contents include melanocytes, Merkel cells, and Langerhans cells ⁽²⁰⁾.
- The superficial layer of epidermis is stratum corneum ^(28, 31, 32). Stratum corneum primarily contain with 70% insoluble keratin & 20% lipid ⁽³³⁾. Presence of water linked to corneocyte keratin, directly connect with exterior area ^(28, 34).

Dermis

- The thickness of this layer is about 2-3 mm , contain 70% collagen and elastin fibers (providing potency & softness) to skin ⁽³⁵⁾.
- The dermis contains macrophages, lymphatic vessels, nerves, and blood vessels. The blood vessels nourish both epidermis and dermis itself ⁽³¹⁾.

Hypodermis

It is the innermost layer of skin. It consists of specialized cells for storing fats. It is a layer that anchors body tissue (muscle & bone) & skin. Major functions are shielding from physical shock and heat insulation. Also maintains & conducts the signals from the skin carried by blood vessels and nerves ^(28, 36). It also contains fibroblasts & macrophages ⁽³⁷⁾.

ROUTES OF DRUG PENETRATION

Two major routes that interact with skin such as transdermal & transappendageal pathways.

Transepidermal Pathway

Molecules from stratum corneum pass through this pathway which has two routes i.e. intra-cellular or inter-cellular routes ⁽³⁸⁾. Intra cellular transportation permits to pass polar molecules through corneocytes. Certain substances can move between cells (intercellular transport). This is because the spaces between cells are filled with a lipid matrix that allows easy passage of oily or non-polar solutes.

Transappendageal Pathway

Sweat glands and hair follicles act like little tunnels for some molecules. These molecules can enter the body through these pathways, along with passing directly through the skin ⁽³⁹⁾.

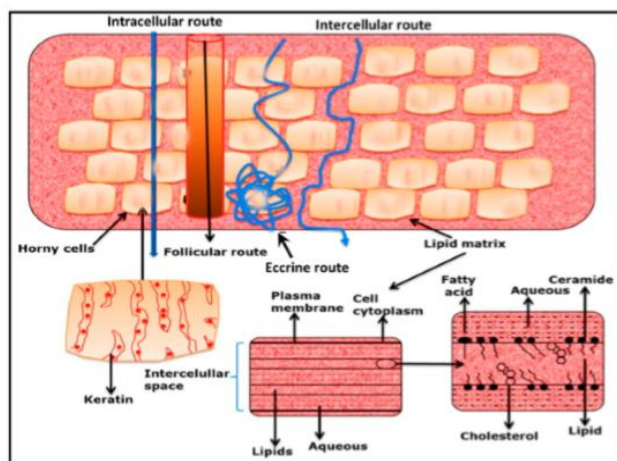


Figure 7: Routes of Drug Permeation

MECHANISM OF SKIN PERMEATION

Most important layers of skin are dermis & epidermis. Epidermis is the most significant layer for transdermal drug delivery system. It keeps the water inside & waste outside of the body. Epidermis has no blood supply while the dermis has systemic capillaries. If a drug is supplied transdermally, it follows passive diffusion. The drug transfers through stratum corneum to the deeper layers from where it absorbs into the blood without accumulating in the skin layers ^(12, 40, 41).

The multifaced configuration of skin forces the permeant to transfer multiple hydrophobic & hydrophilic domains in multiple cases ⁽⁴²⁾. Therefore, the drug used should be comparatively both hydrophilic and hydrophobic to efficiently infiltrate to the skin ⁽⁴³⁾. Drugs can be delivered through transdermal patches in dissolved lipid based form enabling them to produce the required efficacy. Some drug should be combined with comparative substances such as alcohol, increases the penetration power of drug through the skin to the blood stream ^(44, 45). Figure 9 shows the concise flow diagram for the mechanism of drug permeation through the skin layers.

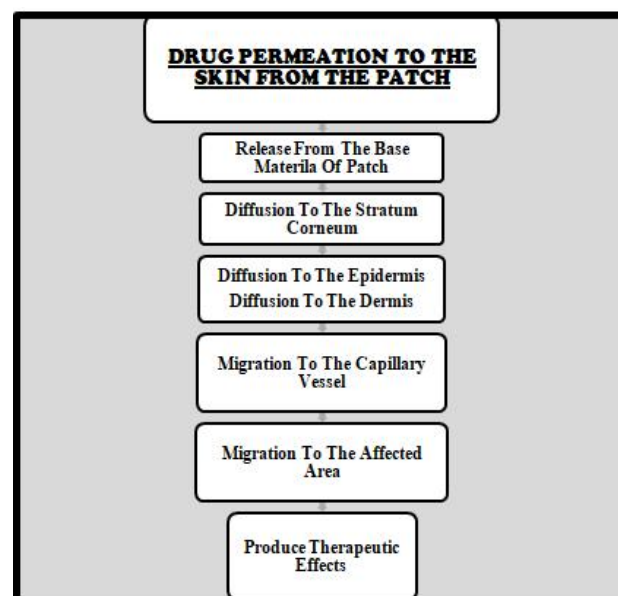


Figure 8: Mechanism of Drug Permeation from the Patch

TDDS KINETICS

The most important step is to evaluate the percutaneous absorption of molecules during the formulation of transdermal patch. The drug absorbs first through the skin layers. From where it permeates into the blood. Which transports it to where the drug can interact with its target ^(46, 47).

The process that involved for drug absorption through percutaneous way includes:

Penetration - Entrance of matter inside the skin.

Partition - Start separating into the aqueous viable epidermis.

Diffusion - Form higher to lower concentration, from epidermis to dermis.

Permeation - Layer to layer distribution of molecule.

Absorption - Drug reaches to blood stream.

Drug molecules are either stored in a reservoir within the TDDS patch or dissolved in a gel-like matrix. Assessing the kinetics, or how the drug moves through the skin, is crucial for optimizing these patches.

The key metric for drug transport is flux, denoted as J and measured in micrograms per square centimeter per hour ($\mu\text{g}/\text{cm}^2/\text{h}$). This represents the rate at which the drug molecule transverses in the skin. This process is governed by Fick's Law of diffusion, stating that drug transport depends on:

Concentration gradient: The difference in drug concentration between the patch and the skin drives the movement. A higher concentration difference leads to faster transport.

Diffusion coefficient: This property of the drug indicates how easily it moves within the skin.

Diffusion length: This is the thickness of the skin barrier that the drug needs to pass through. A thinner barrier allows for faster diffusion. ^(47, 48)

Skin penetration: The medication needs to adequately permeate the skin to access the bloodstream. Factors like solubility in skin layers and interaction with skin components play a role.

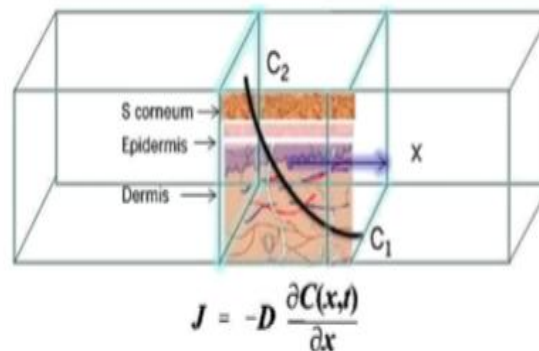


Figure 9: Flux of drug molecule transverse to skin from a transdermal patch. Where, J = drug substance flux, C_2 = active substance concentration in patch, C_1 = active substance concentration in skin, D = diffusion co-efficient, L = thickness (cross sectional) for diffusion, T = time of diffusion

Critical Considerations for Designing Effective TDDS

Thermodynamic driving force: The patch design should provide a strong force to push the drug transdermally (passive diffusion). This is accomplished by maximizing the concentration gradient.

Drug molecule properties: Drugs with suitable characteristics, such as small size and high permeability, are better candidates for TDDS. ⁽⁴⁹⁻⁵¹⁾

The stratum corneum reduces penetration of drug molecules through skin. Drug penetration can now be improved to overcome this barrier by employing various chemical and physical methods. These methods include use of ultrasound, iontophoresis, and a variety of other such techniques and chemical agents. ⁽⁵²⁻⁵⁴⁾

FACTORS AFFECTING TRANSDERMAL PERMEATION

1. Physicochemical Factors:

- **Partition coefficient:** Determines the drug's ability to move between water and lipids, impacting how easily it passes through the skin's layers.

- Molecular size and weight: Smaller molecules generally penetrate better due to easier diffusion through skin layers.
- Concentration of penetrant: Higher concentration usually increases permeation until saturation is reached.
- pH: Affects the ionization state of the drug, influencing its solubility and permeation across skin barriers.
- Solubility: Both drug and vehicle solubility in each other and in skin layers affect permeation.

2. Physiological Factors:

- Barrier properties: Depth, hydration, and integrity of the stratum corneum (outermost layer) significantly impact permeation.
- Skin blood flow: Higher blood flow at the application site can increase drug absorption.
- Age: Permeation tends to decrease with age due to changes in skin barrier properties.
- Skin condition: Skin diseases or injuries can alter barrier function and affect permeation.
- Metabolism: Skin enzymes can metabolize some drugs, reducing their systemic effect.

3. Formulation Factors:

- Vehicle: Type and properties of the carrier system (e.g., gel, patch) influence drug release and skin interaction.
- Penetration enhancers: Certain ingredients in the formulation can temporarily increase skin permeability.
- Adhesives: Used in patches, they should be non-irritating and allow controlled drug release.
- pH: As with skin, formulation pH can affect drug ionization and permeation.
- Additives: Preservatives, antioxidants, and other additives should not compromise skin integrity or drug stability.

4. Additional factors:

- Application site: Different skin regions have varying permeabilities due to thickness, hair follicles, and blood flow.
- Environmental factors: Temperature, humidity, and occlusion (covering the application site) can affect skin properties and permeation.

The specific drug and its formulation affect how much each factor matters.

SKIN PERMEABILISATION ENHANCEMENT TECHNIQUES

Figure 10 illustrates the various approaches used to improve the transdermal drug delivery ⁽⁵⁵⁾. There are two major categories that these methods can be classified into:

1. Passive/Chemical Methods:

- Easy integration with transdermal patches.
- Examples: Chemical enhancers, emulsions.
- Potential lag time in drug release, hinders drugs requiring rapid onset of action (e.g., insulin). ⁽⁵⁶⁾

2. Active/Physical Methods:

- Can overcome limitations of passive methods by actively driving drug delivery.
- Examples: Iontophoresis, microneedles, ultrasound.
- May require specialized equipment or techniques.
- Potential concerns about skin irritation or pain.

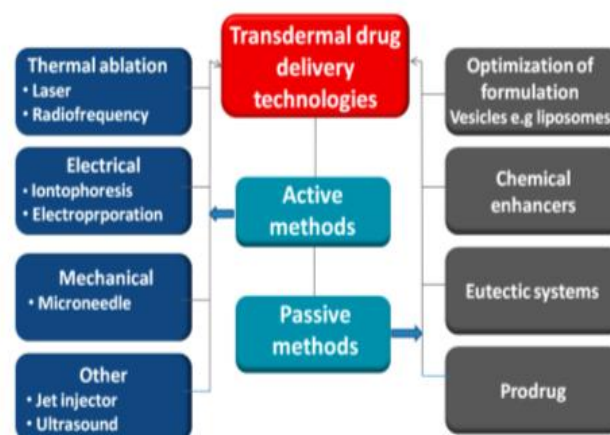


Figure 10: Techniques to improve topical drug absorption ⁽⁵⁵⁾

Mechanisms of Action of Chemical Enhancers:

Chemical enhancers work through various mechanisms to loosen the tight packing of the stratum corneum to allow for better penetration of drugs and facilitate drug delivery. Here are some key mechanisms ^(19, 27):

1. Increased Stratum Corneum Fluidity: Some enhancers, like alcohols and terpenes, can make the

intercellular lipid lamellae of the stratum corneum more fluid, creating larger spaces for drug molecules to pass through.

2. **Intercellular Protein Interaction:** Other enhancers, like sulfoxides and urea, can interact with proteins in the stratum corneum, temporarily disrupting their tight packing and creating pathways for drug diffusion.
3. **Intercellular Lipid Interruption or Extraction:** Some enhancers, like fatty acids and surfactants, can directly interact with and extract lipids from the stratum corneum, creating temporary gaps for drug molecules to pass through.
4. **Enhanced Drug Activity:** These enhancers function by raising the drug's thermodynamic activity, essentially making it more available to pass through the skin's barrier.

Examples of Chemical Enhancers: Sulfoxides, Alcohols, Propylene glycol, Azone, Essential oils, Water, Terpenes, Fatty acids, Terpenoids, Urea, etc.

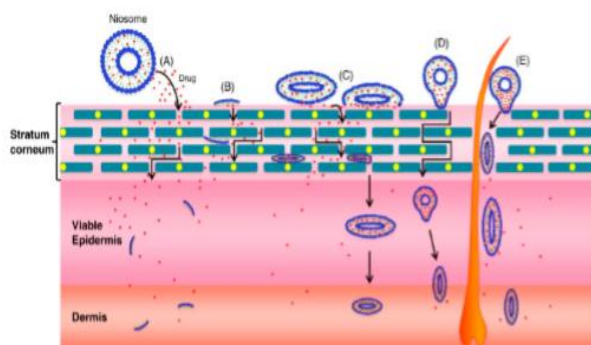


Figure 11: Illustrates the various mechanisms of action of niosomes as permeation enhancers and drug carriers A: niosomes release drug molecules, B: niosomes acts as penetration enhancer, C: adsorption &/or blend with stratum corneum

Limitations and Alternatives:

One major limitation of chemical enhancers is their potential to induce cutaneous irritation, caused by inflammatory responses, erythema, edema, and potential development of dermatitis ^(19, 57, 58). To address this, newer strategies like niosomes and proniosomes are being explored.

1. **Niosomes:** These are non-ionic surfactant vesicles that act as drug carriers and penetration enhancers. Upon hydration, proniosomes transform into niosomes which can diffuse deeper into the skin and release the drug ⁽⁵⁹⁾.
2. **Proniosomes:** These are dry powder forms of niosomes that require hydration before use. They offer improved stability and address the irritation concerns associated with some chemical enhancers ⁽⁵⁹⁾.

Active Methods for Enhanced Drug Delivery Across Skin Layers:

Active methods utilize external energy sources to actively drive drug molecules across the skin, primarily targeting the stratum corneum ⁽⁵⁵⁾. Compared to passive methods that rely on natural diffusion, active methods offer:

- Increased penetration, particularly for large molecules or drugs with poor skin permeability.
- Faster onset of action for drugs requiring rapid delivery.
- Targeted delivery to specific skin layers.
- However, it's important to note that these methods may require specialized equipment and can potentially cause skin irritation in some cases ^(3, 60).

1. Energy-Based Approaches:

- **Ultrasound:** Uses sound waves to create temporary channels in the skin for drug penetration.
- **Electroporation & Iontophoresis:** Employ electric currents to create transient pores or facilitate the movement of charged molecules (ions) across the skin.
- **Lasers & Radiofrequency Heating:** Utilize controlled heat to create temporary pathways for drug delivery.
- **Powder Injection & Jet Injectors:** Utilize high-velocity injections for transdermal drug delivery ^(60, 61).

2. Mechanical Approaches:

- **Microneedles:** Tiny needles pierce the outer skin layer, creating microchannels for drug delivery.

- Tape Stripping: Repeatedly removes the outermost layer of skin, enhancing permeability for a short period ^(62, 63).

Benefits and Market Impact:

These active methods have significantly increased the value and potential of transdermal drug delivery. They enable the delivery of a wider variety of drugs, offer faster and more targeted delivery, and open up new possibilities for treating various skin and systemic conditions ^(18, 27).

Table 2: Ideal Properties of TDDS ⁽²⁵⁾

IDEAL PROPERTIES OF TDDS		
S.no	Properties	Range
1	Packaging properties	Easily removable of release liner
2	Appearance	Clear or white color
3	Dose frequency	Once a day- once a week
4	Patch size	< than 40 cm ²
5	Shelf life	Up to 2.5 years
6	Release properties	Consistent pharmacokinetic & pharmacodynamic profile over time
7	Skin reaction	Non irritant

Table 3: Ideal Properties of Drug for TDDS ⁽²⁷⁾

OPTIMUM PROPERTIES OF DRUG CANDIDATES FOR TRANSDERMAL PATCHES		
S.No	PARAMETER	PROPERTIES
1	Dose deliverable	10mg/day
2	Oral bioavailability	Low
3	Partition coefficient	1-3
4	Skin permeability coefficient	Greater than 0.5x10 ⁻³ cm/hr
5	Molecular weight	Greater than 500 Da
6	T _{1/2}	10 hours or greater
7	Therapeutic index	Low
8	Skin irritation	Non-irritating
9	pH of saturated aqueous solubility	5-9

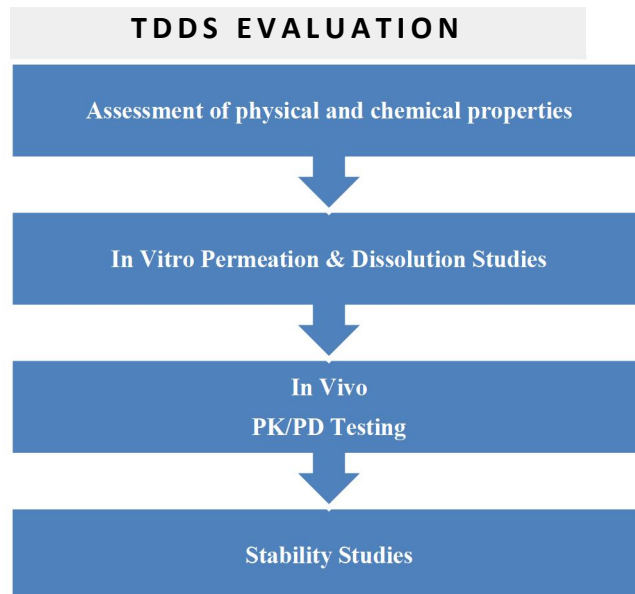


Figure 12: Flow Diagram for Evaluation of TDDS ^(33, 60, 64-66)

PHYSICOCHEMICAL EVALUATION OF TDDS

To ensure their efficacy and safety, a thorough physicochemical evaluation of TDDS is crucial. This evaluation focuses on the physical and chemical properties of the TDDS components and their interaction with the drug itself. By understanding these physicochemical aspects, one can develop TDDS with optimal performance and patient benefit.

Thickness

The preferred method for measuring patch thickness is with a digital micrometer, known for its accuracy and ease of use. To get a representative measurement, the readings are taken at several points across the patch, avoiding the edges where there might be variations. The appropriate acceptance limits must be defined beforehand, considering the specific formulation design and any relevant regulatory requirements. By following these steps, one can ensure an accurate and reliable measurement of patch thickness ^(25, 65, 67).

Weight Variation

Ensuring consistent drug delivery in transdermal patches requires verifying their weight uniformity. Select 10 patches at random, measure their individual

weights with a calibrated balance, and calculate the percentage variation from the average weight. Compare these variations to pharmacopeial guidelines (e.g., USP <5%) to identify any patches with potentially uneven drug content. This single step helps guarantee the quality and safety of your transdermal products ^(25, 67).

Drug Content

Drug content verification entails precise measurement: accurately weigh a representative patch sample (e.g., 100mg), extract the drug with a suitable solvent, and analyze it using a validated method like HPLC or spectrophotometry. Express the extracted drug amount as a percentage of the labeled patch content. Crucially, define acceptable limits based on your specific formulation design and relevant regulations to ensure consistency and quality within those boundaries. This meticulous process guarantees adherence to both internal standards and external mandates, ultimately safeguarding the drug's potency and effectiveness ^(67, 68).

Content Uniformity

Verifying consistent drug distribution within transdermal patches requires individual analysis of 10 samples. Extract the drug from each patch using the established content test method and analyze them individually. Calculate the drug content of each patch and compare them to pharmacopeial guidelines for content uniformity. Typically, USP suggests at least 90% of patches fall within 85-115% of the specified content, with no individual patch exceeding 125% or falling below 75%. This ensures each patch delivers the intended dose within acceptable variability, contributing to product quality and patient safety ^(67, 68).

Folding Endurance

Folding endurance assesses a patch's ability to withstand bending without breaking. Simply fold a patch repeatedly at the same spot until it breaks, recording the number of folds. Repeat this with several patches and calculate the average folds per patch. To determine if the patches pass, define a

minimum acceptable number of folds based on their desired flexibility and intended use. For instance, patches meant for areas with frequent movement might require more folds than those for static areas. This simple test helps ensure patches can conform comfortably to the body and function effectively during wear ^(25, 67).

Flatness

Maintaining a smooth, non-warping patch is crucial for optimal drug delivery. To assess flatness the strips are cut from the center and edges, measuring their initial lengths. They are laid out flat, applied to a light weight (e.g., 10g), and re-measured. The percentage constriction for each strip is calculated, indicating how much they shrunk due to warping. Acceptance limits based on both desired aesthetics and functionality are set, ensuring the patches remain comfortably flat and deliver medication effectively ^(64, 69).

Moisture Content (%)

To assess the potential stability and drug release impact of moisture content in a transdermal patch, measure its weight before placing it in a calcium chloride desiccator at room temperature for 24 hours. After reweighing, calculate the percentage moisture content using the formula $[(\text{Final weight} - \text{Initial weight}) / \text{Initial weight}] \times 100\%$. Compare this value to predefined limits based on your specific formulation and intended storage conditions to ensure the patch meets quality and safety standards. This simple test helps guarantee optimal performance and patient well-being ⁽⁶⁹⁾.

Moisture Uptake (%)

Assessing moisture uptake in transdermal patches follows a similar method to moisture content, but with a key twist. Instead of a calcium chloride desiccator, use one containing a saturated potassium chloride solution, which provides a more humid environment. Place the patch inside for 24 hours at room temperature, then reweigh it. Calculate the percentage moisture uptake using the same formula: $[(\text{Final weight} - \text{Initial weight}) / \text{Initial weight}] \times 100\%$. Compare this value to pre-defined limits considering

your formulation and storage conditions, ensuring the patch remains within acceptable moisture absorption ranges for optimal performance and stability ⁽⁶⁹⁾.

Water Vapor Permeability (WVP)

Assessing a transdermal patch's breathability is key to its performance. The Water Vapor Permeability (WVP) test measures how much water vapor permeates the patch over time. Place the patch in a specialized apparatus and monitor the water vapor transferred in a controlled environment (e.g., 24 hours). Calculate the WVP using the formula: $WVP = W/A \times t$, where W is the weight of water vapor permeated, A is the patch's exposed area, and t is the time. Compare the resulting WVP to predefined limits based on your specific patch design and desired drug release profile. This crucial test ensures the patch allows appropriate moisture exchange while maintaining drug integrity, contributing to optimal drug delivery and patient comfort ⁽⁶⁶⁾.

Tensile Strength

Determining a transdermal patch's tensile strength involves measuring the force required to tear it apart. Employ a suitable tensile strength tester, ensuring proper sample alignment and gripping. Calculate the strength using the formula $Tensile\ strength = F / (a \times b)$, where F is the breaking force (Newtons), a is the sample width (meters), and b is its thickness (meters). Finally, compare the obtained value to predefined limits based on your desired patch integrity and ease of handling during application and use. This assessment helps ensure the patch can withstand everyday wear and tear without compromising its functionality or drug delivery ⁽⁶⁹⁾.

ADHESIVE PERFORMANCE TESTING

Peel Adhesion Test

Measures the strength of the adhesive bond at a specific angle and speed. It is crucial for ensuring patch adherence during wear and activity. There are two main types i.e. 90° peel test and T-peel test. Important factors include polymer molecular weight, tackifiers, pressure-sensitive properties. ⁽⁶⁷⁾.

Tack Tests:

Tack describes an adhesive's ability to form an instant bond with a substrate under light pressure. It's crucial for initial patch application and maintaining adhesion on skin ⁽⁷⁰⁾. Factors affecting tack:

- Higher molecular weight generally leads to higher tack.
- Specific polymer types and their characteristics influence tack.
- These additives increase the surface area and deformability of the adhesive, enhancing tack.
- Roughness and wettability of the substrate affect tack.

Tack measurement methods:

- Thumb tack test: Qualitative assessment of initial force needed to remove adhesive by thumb pressure ⁽⁷⁰⁾.
- Rolling ball test: Measures distance a steel ball rolls on an inclined plane after contacting the adhesive, indirectly assessing softness and tack.
- Quick stick (peel tack) test: Force required to rapidly peel a tape from a substrate at a specific angle and speed ⁽⁶⁷⁾.
- Probe tack test: Force needed to detach a probe with a rough surface away from the adhesive after contact ⁽⁶⁷⁾.

Shear Strength Test:

Measures the cohesive strength of the adhesive itself, resisting internal flow under stress. It ensures patch integrity and prevents delamination during wear. Two main methods shear creep test and shear peel test. Important factors include polymer type, crosslinking density, thickness ^(67, 70).

IN VITRO EVALUATION

Diffusion Studies:

Evaluates the in vitro release kinetics for the transdermal drug delivery system. The kinetic models followed are generally Higuchi model, Peppas & Korsmeyer model, and others depending on release kinetics. Flow-through diffusion cells simulate physiological flow conditions with continuous media flow. A commonly used flow-through cell is the Franz Cell. Drug concentration in the medium is measured

by analytical techniques like HPLC or spectrophotometry^(69, 71, 72).

Skin Permeation Studies:

Assesses the in vivo permeation and systemic absorption of the drug delivered via the transdermal patch. The Franz diffusion cell is a widely used instrument for studying skin permeation. It consists of two chambers: a donor chamber holding the drug formulation and a receptor chamber containing a solution that mimics the bloodstream. These chambers are separated by a membrane that can be either synthetic or actual human or animal skin. Drug concentration in the receptor compartment is measured by analytical techniques such as HPLC^(69, 71, 72).

IN VIVO EVALUATION

Assesses the performance and safety of your transdermal drug delivery system in living organisms. Two primary approaches are used:

Animal models:

The pharmacokinetics, efficacy, and potential side effects of the patch are studied in a controlled environment. Rats, rabbits, mice, pigs (depending on skin similarity and regulatory requirements). The drug remaining in the patch after application to compare release rates with in vitro data is measured. Drug concentration in various body fluids and tissues to understand systemic absorption and metabolism is tracked. Adherence to animal welfare guidelines and regulations must be ensured^(71, 72).

Human volunteer studies:

To assess the safety, efficacy, and user experience of the patch in humans under controlled conditions. Typically conducted in phases (I-IV) with increasing complexity and participant numbers. Like animal studies, but with additional focus on skin reactions, tolerability, and subjective assessments. Strict ethical and regulatory approvals are required before conducting human studies^(16, 73).

EVALUATION OF TDDS STABILITY

Following International Conference on Harmonization (ICH) guidelines, the transdermal drug delivery system (TDDS) underwent a 6-month stability study at a controlled temperature of $40^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity. Samples were withdrawn at predetermined intervals (0, 30, 60, 90, and 180 days) and analyzed for drug content using suitable analytical techniques. This evaluation aimed to assess the potential instability of drug and ensure the TDDS maintains its quality and integrity over the expected shelf life⁽⁶⁾.

CONCLUSION

Technological advancements are paving the way for direct delivery of drugs to drug sites without breaching the skin, making it a rapidly accepted route of administration. TDDS' versatility allows them to handle both hydrophobic and hydrophilic drugs, opening doors for promising new treatments. However, maximizing this system's potential requires a deeper understanding of biological interactions and the development of advanced polymers. With further research, TDDS has the potential to become the most important drug delivery system. The ability to deliver medication painlessly, conveniently, and effectively makes transdermal drug delivery a promising approach. Its diverse benefits include a wider range of deliverable drugs, improved medication absorption, minimized complications and side effects, coupled with affordability and ease of use. Transdermal delivery even bypasses first-pass metabolism for drugs typically administered orally. While transdermal patches are the most established form of TDDS, the stratum corneum, with its low permeability, poses a hurdle for these patches. This hurdle is being tackled through innovative physical and chemical approaches, pushing the boundaries of this promising technology.

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