A Comprehensive Review of Transdermal Drug Delivery Systems
- Mechanisms, Advancements, and Future Frontiers

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ABSTRACT: Currently, approximately 74% of medications are administered orally, but they often fall short of achieving optimal effectiveness. To address these limitations, the transdermal drug delivery system has emerged as a promising solution. This method involves delivering drugs through the skin to achieve systemic effects, distinguishing it from traditional topical drug delivery. This approach offers several advantages, such as prolonged therapeutic effects, minimized side effects, enhanced bioavailability, improved patient compliance, and convenient termination of drug therapy. The stratum corneum is recognized as the primary barrier affecting the transdermal permeation of most molecules. The process of transdermal drug delivery involves three main routes of drug penetration: appendageal, transcellular, and intercellular. Factors like skin age, condition, physicochemical properties, and environmental influences must be considered when delivering drugs through this route. Key components of transdermal drug delivery systems (TDDS) include a polymer matrix membrane, the drug itself, penetration enhancers, pressure-sensitive adhesives, backing laminates, and a release liner. Transdermal patches are categorized into reservoir systems, matrix systems, and micro-reservoir systems, each designed to introduce active ingredients into the circulatory system through the skin. 

Keywords: transdermal drug delivery, transdermal patches, systemic blood circulation, skin.

I. INTRODUCTION:
Conventional dosage forms often result in significant fluctuations in plasma drug concentrations, leading to undesirable outcomes such as toxicity or diminished effectiveness. These issues, coupled with challenges like repetitive dosing and unpredictable absorption, spurred the development of controlled drug delivery systems. Such systems release one or more drugs continuously in a predetermined pattern over a fixed period, either systemically or targeting a specific organ. The primary goals of controlled drug delivery are to enhance drug safety, improve efficacy, and ensure patient compliance by achieving better control over plasma drug levels and reducing dosing frequency. One prominent example of controlled drug delivery is the Transdermal Therapeutic System (TTS), which refers to self-contained discrete dosage forms applied to intact skin. These systems deliver drugs at a controlled rate through the skin to the systemic circulation. The pioneering Transdermal Drug Delivery (TDD) system, Transdermal-Scop, was developed in 1980 to treat motion sickness using scopolamine. Employing a membrane-modulated approach, this system features a microporous polypropylene film as the membrane and a drug reservoir containing a solution of the drug in a mixture of mineral oil and polyisobutylene. The controlled release is maintained over a three-day period, showcasing the potential of this innovative drug delivery technology. 

The Transdermal Drug Delivery System presents several advantages:

- The frequency of dosing can be significantly reduced.
- Improved bioavailability allows for a reduction in drug concentration.
- Escaping first-pass metabolism by the liver enhances drug effectiveness.
- Issues related to gastrointestinal medication absorption, such as those arising from stomach pH, enzymatic activity, and interactions with food or other orally administered pharmaceuticals, can be avoided.
- Lowering plasma concentration levels of drugs leads to decreased side effects.
- Non-invasive nature eliminates the need for parenteral therapy, streamlining the drug administration process.
Enhanced compliance is achieved compared to previous dosage forms, as longer therapy is provided with a single application.

Rapid termination of drug therapy is possible by simply removing the application from the skin's surface.

Self-administration is facilitated by these systems.

Systemic drug interactions are reduced.

Extended duration of action is a key feature of transdermal drug delivery, offering prolonged therapeutic effects. \(^2\)

**Anatomy and physiology of skin**

The skin is primarily made up of three layers. The upper layer is the epidermis, the layer below the epidermis is the dermis, and the third and deepest layer is the subcutaneous tissue.

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**Fig 1. Structure of skin \(^3\)**

- The epidermis, the outermost layer of skin, provides a waterproof barrier and contributes to skin tone.
- The dermis, found beneath the epidermis, contains connective tissue, hair follicles, blood vessels, lymphatic vessels, and sweat glands.
- The deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue.

The epidermis is further divided into five layers on thick skin like the palms and soles (stratum basal, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum), while in other places, the epidermis only has four layers, lacking the stratum lucidum.

The dermis is divided into two layers, the papillary dermis (the upper layer) and the reticular dermis (the lower layer). \(^4\)

**The functions of the skin include:**

- Protection against microorganisms, dehydration, ultraviolet light, and mechanical damage; the skin is the first physical barrier that the human body has against the external environment.
- Sensation of pain, temperature, touch, and deep pressure starts with the skin.
• Mobility: The skin allows smooth movement of the body.
• Endocrine activity: The skin initiates the biochemical processes involved in Vitamin D production, which is essential for calcium absorption and normal bone metabolism.
• Exocrine activity: This occurs by the release of water, urea, and ammonia. Skin secretes products like sebum, sweat, and pheromones and exerts important immunologic functions by secreting bioactive substances such as cytokines.
• Immunity development against pathogens.
• Regulation of Temperature. Skin participates in thermal regulation by conserving or releasing heat and helps maintain the body’s water and homeostatic balance. (45)

Classification of Transdermal Drug Delivery System-
Classification of transdermal drug delivery systems has proceeded through three generation on the basis of drug molecule Size and the presence of penetration enhances material.

1. First-generation transdermal delivery systems- The majority of transdermal patches currently in clinical use belong to the first generation of transdermal delivery systems. Recent advancements and increased public acceptance have led to a surge in the market availability of these first-generation patches. However, this trend is expected to slow down as drugs suitable for these systems become less available. First-generation candidates are typically low-molecular weight, lipophilic, and effective at low doses. Transdermal delivery is preferred when oral bioavailability is low, there’s a preference for less frequent dosing, a need for steady delivery profiles, or other relevant factors. (5)

2. Second-generation transdermal delivery systems-The second generation of transdermal delivery systems acknowledges the importance of enhancing skin permeability to broaden the range of transdermal drugs. An ideal enhancer in this generation should (i) temporarily disrupt the stratum corneum structure to increase skin permeability, (ii) provide an additional force for transport into the skin, and (iii) avoid causing harm to deeper living tissues. However, methods developed in this generation, like conventional chemical enhancers, iontophoresis, and non-cavitational ultrasound, have faced challenges in finding the right balance in increasing delivery across the stratum corneum while safeguarding deeper tissues from damage. (6)

Basic Components of Transdermal Drug Delivery Systems-
1. Polymer matrix or matrices.
2. The drug
3. Permeation enhancers
4. Other excipients

1. Polymer Matrix: The Polymer controls the release of the drug from the device. Possible useful polymers for transdermal devices are:
   • Natural Polymers: e.g., cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.
   • Synthetic Elastomers: e.g., polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenbutadiene rubber, Neoprene etc.
   • Synthetic Polymers: e.g., polyyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polycrlylate, Polyamide, Polyurea, Polyvinyl pyrrolidone, Polymethylmethacrylate, Epoxy etc. (7)

2. Drug: For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

3. Permeation Enhancers: These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. These may conveniently be classified under the following headings:
   • Solvents: These compounds increase penetration possibly by swelling the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alky methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetalamide and dimethyl formamide; pyrrolidones- 2 pyrrolidone, N-methyl, 2-pyrroliodine; laurocapram (Azone), miscellaneous solvents-propylene glycol, glycerol, silicone fluids, isopropyl palmitate.
   • Surfactants: These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length. Anionic Surfactants: e.g. Dioctyl sulpho-
succinate, Sodium lauryl sulphate, Decodecyl-methyl sulphoxide etc. Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc. Bile Salts: e.g. Sodium ms taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

Binary system:
- Miscellaneous chemicals: These include urea, ahydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents. Some potential permeationenhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-n-methyl-ß-cyclodextrin and soyabean casein. (8)

4. Other Excipients:
a. Adhesives: The fastening of all transdermal devices to the skin have so far been done byusing a pressure sensitive adhesive which can be positioned on the face of the device and inthe back of the device and extending peripherally. Both adhesive systems should fulfill the following criteria:
- Should adhere to the skin aggressively, should be easily removed.
- Should not leave an unwashable residue on the skin.
- Should not irritate or sensitize the skin.
- The face adhesive system should also fulfill the following criteria;
  - Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
  - Permeation of drug should not be affected.
  - The delivery of simple or blended permeationenhancers should not be affected.

Role of adhesion in drug delivery- In TDDS, main principle is it selectively adhere the skin and providedrug release. Drug delivery is varied in age and gender function. Because in this system drug release is through the skin and also younger and older patient having different skin nature. Younger skin is greater dehydrated while aged skin has less moisture content so youger skin have more elastic than aged skin so we carefully select the adhering material for the drug release. This type of condition role of adhesion is very important. Here, drug absorption based on the drug partition between TDDS and skin. Good permeation and action is depending on the proper adhesion of patch. After the application of patch, the adhesion covers the particular effective area, that area only provides greater action. And also, so many factors are affecting the drug absorption such as thickness of skin, skin temperature, bloodflow, no. of hair follicles, skin cleansing, sweat gland function, pH of skin surface, and body temperature. After the application of patch, it warms the skin temperature that lead to increase the flow of drug to skin. During the gradually increasing of skin temperature swells the polymerand sustained release of drug to stratum corneum. (9)

b. Backing membrane: Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosag eform through the top, and accept printing. It is impermeable substance that protec ts the product during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminum foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminum foil disc). (10)

Transdermal patch-
A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. An advantage of a transdermal drug delivery route over other types of medication delivery (such as oral, topical, intravenous, or intramuscular) is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. (11)

Types of transdermal patches:
a) Single layer drug in adhesive: In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layerstogether and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.
b) Multi-layer drug in adhesive: This type is also similar to the single layer but it contains a immediate drug release layer and other layer will be controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.
c) Vapour patch: In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves as release vapour. The vapour patches are new to the market.
commonly used for releasing of essential oils
indecongestion. Various other types of vapor
patches are also available in the market which are
used to improve the quality of sleep and reduces the
cigarette smoking conditions.

d) Reservoir system: In this system the drug
reservoir is embedded between an impermeable
backing layer and a rate controlling membrane.
The drug releases only through the rate-controlling
membrane, which can be micro porous or non-
porous. In the drug reservoir compartment, the drug
can be in the form of a solution, suspension, gel or
dispersed in an insoluble polymer matrix. Hypoallergenic
adhesive polymers can be applied as outer surface
polymeric membranes which is compatible with drug.

e) Matrix system:
i. Drug-in-adhesive system: In this type the drug
reservoir is formed by dispersing the drug in an
adhesive polymer and then spreading the medicated
adhesive polymer by solvent casting or melting (in
the case of hot-melt adhesives) on an
impervious backing layer. On top of the reservoir,
unmediated adhesive polymer layers are applied for
protection purpose.

ii. Matrix-dispersion system: In this type the drug is
dispersed homogeneously in hydrophilic or
lipophilic polymer matrix. This drug containing
delivery system is a combination of reservoir and
matrix-dispersion system. The drug reservoirs
formed by first suspending the drug in an
aqueous solution of water-soluble polymer and then
dispersing the solution homogeneously in a
lipophilic polymer to form thousands of
unreachable, microscopic spheres of
drug reservoirs. This thermodynamically unstable
dispersion is stabilized quickly by immediately
cross-linking the polymer in situ by using cross
linking agents.

Factors affecting transdermal drug delivery-
(15,16,17)

1. Skin condition- The intact skin itself acts as a
barrier, but many agents like acids and alkali cross
the barrier cells and penetrate through the skin.
Many solvents open the complex dense structure of
the horny layer: solvents like methanol and
chloroform remove the lipid fraction, forming
artificial shunts through which drug molecules can
pass easily.

2. Skin age- It is seen that the skin of adults and
young ones is more permeable than that of the older
ones. But there is no dramatic difference. Children
show toxic effects because of the greater surface
area per unit body weight. Thus, potent steroids,
boric acid and hexachlorophene have produced
severe side-effects.

3. Physicochemical factors-
- Hydration of skin- Generally, when water
saturates the skin, it swells tissues, softens
wrinkles on the skin and its permeability
increases for the drug molecules that penetrate
through the skin.
- Temperature and pH of the skin- The
penetration rate varies if the temperature varies
and the diffusion coefficient decreases as the
temperature falls; however adequate clothing
on the body prevents wide fluctuations in
temperature and penetration rates. According
to pH, only unionized molecules pass readily
across the lipid membrane, and weak acids and
bases dissociate to different degrees according
to their pH and pKa or pKb values.

4. Environmental factors-
- Sunlight- Because of sunlight, the walls of
blood vessels become thinner, leading to
bruising, with only minor trauma in the sun
exposed areas. Also, pigmentation, the most
noticeable sun-induced pigment change, is a
freckle or solar lentigo.
- Cold season- The cold season often results in
itchy and dry skin. The skin responds by
increasing oil production to compensate for the
weather’s drying effects. A good moisturizer
will help ease symptoms of dry skin.
- Air pollution- Dust can clog pores and increase
bacteria on the face and the surface of skin,
both of which lead to acne or spots, which
affects drug delivery through the skin.
- Invisible chemical pollutants in the air can
interfere with the skin’s natural protection
system, breaking down the skin’s natural oils
that normally trap moisture in the skin and
keep it supple.

US FDA approved transdermal drugs.
This list includes transdermal patches and
delivery systems approved by the FDA. Only the
first approved product for a given drug or drug
combination administered by a given delivery
method is shown. Topical creams, ointments, gels and sprays are not included.\(^{(18)}\)

Table No. 1 US FDA approved transdermal drugs.\(^{(19)}\)

<table>
<thead>
<tr>
<th>Approval year</th>
<th>Drug</th>
<th>Indication</th>
<th>Product Name</th>
<th>Marketing company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>Scopolamine</td>
<td>Motion sickness</td>
<td>Transderm-Scop</td>
<td>Novartis Consumer Health (Parsippany, NJ)</td>
</tr>
<tr>
<td>1981</td>
<td>Nitroglycerin</td>
<td>Angina pectoris</td>
<td>Transderm-Nitro</td>
<td>Novartis (East Hannover, NJ)</td>
</tr>
<tr>
<td>1984</td>
<td>Clonidine</td>
<td>Hypertension</td>
<td>Catapres-TTS</td>
<td>Boehringer Ingelheim (Ridgefield, CT)</td>
</tr>
<tr>
<td>1986</td>
<td>Estradiol</td>
<td>Menopausal symptoms</td>
<td>Estraderm</td>
<td>Novartis (East Hannover, NJ)</td>
</tr>
<tr>
<td>1990</td>
<td>Fentanyl</td>
<td>Chronic pain</td>
<td>Duragesic</td>
<td>Janssen Pharmaceutica (Titusville, NJ)</td>
</tr>
<tr>
<td>1991</td>
<td>nicotine</td>
<td>Smoking cessation</td>
<td>Nicoderm, Habitrol, ProStep</td>
<td>GlaxoSmithKline (Philadelphia, PA), Novartis Consumer Health (Parsippany, NJ), Elan (Gainesville, GA)</td>
</tr>
<tr>
<td>1993</td>
<td>Testosterone</td>
<td>Testosterone deficiency</td>
<td>Testoderm</td>
<td>Alza, Mountain View, CA</td>
</tr>
<tr>
<td>1995</td>
<td>Lidocaine/epinephrine (iontophoresis)</td>
<td>Local dermal analgesia</td>
<td>Iontocaine</td>
<td>Iomed (Salt Lake City, UT)</td>
</tr>
<tr>
<td>1998</td>
<td>Estradiol/norethindrone</td>
<td>Menopausal symptoms</td>
<td>Combipatch</td>
<td>Novartis (East Hannover, NJ)</td>
</tr>
<tr>
<td>1999</td>
<td>Lidocaine</td>
<td>Post-herpetic neuralgia pain</td>
<td>Lidoderm</td>
<td>Endo Pharmaceuticals (Chadds Ford, PA)</td>
</tr>
</tbody>
</table>
II. CONCLUSION-

The transdermal drug delivery system (TDDS) review articles offer useful insights on the transdermal drug delivery systems and its evaluation procedure as a handy reference for the research scientist working on TDDS. The information above demonstrates that TDDS have significant potentials, since they can be used to create promising deliverable medications from both hydrophobic and hydrophilic active substances. More knowledge of the various biological interactions and polymer mechanisms is needed to optimize this drug delivery technology. The next generation of drug delivery systems, TDDS, has a realistic, practical use.

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REFERENCE-


