Transdermal therapeutic systems, characterization. 
Advantages, disadvantages. 
Enhancers of penetration.

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CONTENT

- Introduction, history
- Advantages & disadvantages
- Structure of the skin
- Permeation through skin
- Factors affecting permeation
- Basic components of TTS
- Permeation enhancers
- Formulation approaches used in development of TTS
- Advanced research of TTS
Transdermal therapeutic system was first introduced more than 20 years ago. The technology generated tremendous excitement and interest amongst major pharmaceutical companies in the 1980s and 90s. First transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness. The FDA has approved, throughout the past years, more than 35 transdermal patch products, spanning 13 molecules.
INTRODUCTION

• **Definition:**

  Transdermal drug delivery or TTS is defined as a self contained discrete dosage form, which when applied to the intact skin, will deliver the drug at a controlled rate to the systemic circulation.
ADVANTAGES

• Easy to use.
• Avoid GIT absorption problems of drugs.
• Avoid FP hepatic metabolism of drugs.
• More improved and convenient patient compliance.
• Rapid termination in case of toxicity is possible.
• Self medication is possible.
• Reduces frequency of dosing.
• Maintains therapeutic level for 1 to 7 days.
• Controlled delivery resulting in more reliable and predictable blood levels.
DISADVANTAGES

• Daily dose of more than 10 mg is not possible.
• Local irritation is a major problem.
• Drugs requiring high blood levels are unsuitable.
• Drug with long half life can not be formulated in TTS.
• Uncomfortable to wear.
• May not be economical.
• Barrier function changes from person to person and within the same person.
• Heat, cold, sweating (perspiring) and showering prevent the patch from sticking to the surface of the skin for more than one day. A new patch has to be applied daily.
STRUCTURE OF SKIN

- **Epidermis:**
  - Stratum corneum (Horny cell layer)
  - Stratum lucidum (Clear layer)
  - Stratum granulosum (Granular Layer)
  - Stratum spinosum (Prickly layer)
  - Stratum germinativum

- **Dermis**
- **Hypodermis or Subcutaneous layer**
STRUCTURE OF SKIN

EPIDERMIS:

- The *stratum corneum* (STC) forms the outer layer (10-15µm thick) which consists of many layers of compacted, flattened, dehydrated keratinized cells.

- *Stratum corneum* layer forms permeability barrier for external environment.
Water content of *stratum corneum* is around 20%.

The moisture required for *stratum corneum* is around 10% (w/w) to maintain flexibility and softness.

It consists of ceramides and neutral lipids such as sterols, free fatty acids and triglycerides.

The *stratum corneum* is responsible for the barrier function of the skin and behaves as a primary barrier to the percutaneous absorption.
DERMIS:

- The dermis is made up of a regular network of robust collagen fibers.
- This network or the gel structure is responsible for the elastic properties of the skin.
- It is supplied by blood to transport nutrients, remove waste & regulate body temp.
- Drug is well absorbed by this route.
STRUCTURE OF SKIN

SUBCUTANEOUS TISSUE:

This is a sheet of the fat known as the superficial fascia attaching the dermis to the underlying structures.

SKIN GLANDS:

Glands produce sweat of pH 4-6.8 & absorb drugs, secrete proteins, lipids and antibodies.

HAIR FOLLICLES:

They have sebaceous glands which produces sebum which includes glycerides, cholesterol and squalene.
Mechanism of absorption through skin

Mechanism involved is passive diffusion

This can be expressed by **FICK’s LAW** DIFFUSION

\[
\frac{dq}{dt} = \frac{D K A (c_1 - c_2)}{h}
\]

\[
\frac{dq}{dt} = \text{rate of diffusion}
\]

\[
D = \text{diffusion coefficient}
\]

\[
K = \text{partition coefficient}
\]

\[
A = \text{surface area of membrane}
\]

\[
h = \text{thickness of membrane}
\]

\[
c = \text{concentration}
\]
Routes of drug absorption through skin

- Transfollicular route
- Transepidermal route
Routes of drug absorption through skin

**Transfollicular route:**

- Skin area available through this route is 0.1 %
- Human skin contains 40-70 hair follicles, 200 to 250 sweat glands on every sq.cm. of skin area.
- Mainly water soluble substances are diffused faster through appendages than that of other layers.
Routes of drug absorption through skin

**Transepidermal route**
- Epidermal barrier function mainly resides in horny layer
- The viable layer may metabolize, inactivate a drug or activate a prodrug.
- It contains many capillaries and thus residence time of drug is only one minute.
- Within *stratum corneum* molecule may penetrate either transcellularly or intercellularly.
- Intracellular region is filled with lipid rich amorphous material.
Schematic Skin absorption of drug
Topical application-absorption & action of drugs

DRUG IN DELIVERY SYSTEM
   
   RELEASE
   
DRUG IN SKIN SECRETION FLUIDS, SWEAT, SEBUM, pH 4.5--5.5

ABSORPTION

LOCALIZED

TOPICAL

DRUG IN TARGET TISSUE

PHARMACOLOGICAL RESPONSE

DISTRIBUTION

DRUG IN BLOOD CIRCULATION

ELIMINATION

SYSTEMIC

TRANSDERMAL
FACTORS AFFECTING TRANSDERMAL PERMEABILITY

 PHYSICOCHEMICAL PROPERTIES OF PARENT MOLECULE

- Solubility and partition coefficient

- pH condition

- Penetrant concentration

PHYSICOCHEMICAL PROPERTIES OF DRUG DELIVERY SYSTEM

- Release characteristic

- Composition of drug delivery system

- Permeation enhancers used
Physiological and pathological condition of skin

- Lipid film
- Skin hydration
- Skin temperature
- Effect of vehicle
- Pathological injury to skin

Biological factors

- Skin age
- Thickness of STC
- Skin condition
Solubility and partition coefficient:

- Solubility of a drug influences its ability to penetrate the skin.
- pKa is index of solubility of drug in vehicle and STC and has influence on transfer of drug from vehicle to skin.
- Drug solubility determines concentration presented to absorption site which will effect rate and extent of absorption.
- Skin permeation can be enhanced by increasing lipophilic character of drug, so that drug penetrates through STC but not through epidermis due to decreased water solubility.
- Drug which is lipid & water soluble is favored.
**pH & penetration concentration:**

- Moderate pH is favorable because if solutions with high or low pH will result in destruction to the skin.
- Higher the concentration of the drug in vehicle, faster the absorption.
- At higher concentrations than solubility, solid drug will have a function as a reservoir and helps to maintain a constant drug concentration for prolonged period of time.
Physicochemical properties of drug delivery system

**Release characteristic**
- Solubility of drug in vehicle determines the release rate.

**Composition of drug delivery system**
- It not only effects the rate of drug release but also the permeability of STC by means of hydration mixing with skin lipids. Example methyl salicylate is more lipophilic than its parent acid (Salicylic acid). When applied to skin from fatty vehicle methylsalicylate yielded higher absorption.
Physiological and pathological condition of skin

**Lipid film:**
It acts as protective layer to prevent removal of moisture from skin. Defeating of this film will decrease TD absorption.

**Skin hydration:**
It can be achieved by covering skin with plastic sheeting, which leads to accumulation of sweat, condensed water vapors and increase hydration.
Biological factors

Skin age:
Skin of foetus, young ones and elders is more permeable than adult tissue.

Skin metabolism:
Viable epidermis is more metabolically active than dermis. If topically applied drug is subjected to biotransformation during permeation local and systemic bioavailability is affected.
BASIC COMPONENTS OF TTS

COMPONENTS OF A TRANSDERMAL DEVICE INCLUDE:

1) POLYMER MATRIX
2) DRUG
3) PERMEATION ENHANCERS
4) OTHER EXCIPIENTS
Basic components of TTS with membrane

clear backing
drug reservoir
drug-release membrane
contact adhesive
Transdermal patch designs

Matrix

Reservoir

Multilaminate

Drug in adhesive

Backing

Drug

Membrane

Adhesive

Liner / skin
Backling membrane

☞ Is flexible and provide a good bond to the drug reservoir, prevent the drug from leaving the dosage form through top.

☞ It is an impermeable membrane that protects the product during the use on the skin.

☑ Contains formulation throughout shelf-life and during wear period

☑ Must be compatible with formulation (non adsorptive)

☑ Printable

☞ E.g.: Metallic plastic laminate, plastic backing with adsorbent pad and adhesive foam pad.
POLYMER MATRIX

Following criteria to be considered in selection of a suitable polymer:

- Molecular weight of polymer must allow diffusion of drug at desired rate.

- Polymer must be non-reactive, inert, non-toxic, easy to manufacture, inexpensive.

- It should not decompose on storage of the device & not deteriorate when large amount of active ingredient is incorporated into it.
LIST OF POLYMERS USED

**NATURAL POLYMERS:**
Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Gums & Natural rubber

**SYNTHETIC POLYMERS:**
Polyvinylalcohol, Polyvinylchloride, Polyethylene, Polypropylene, Polyurea, Polyvinylpyrrolidone, Polymethacrylate, Polysiloxane, Silicon rubber, Nitrile, Acrylonitrile, Butyl-rubber, Styrene-butadiene-rubber.
For successful developing of a TTS, drug should be chosen with great care.

**Important physicochemical properties:**

1. Mol. wt. less than 1000 Daltons
2. Affinity for both lipophilic & hydrophilic phase
3. Drug should have low melting point
✓ It should be potent with daily dose of few mg/day.
✓ Half life of drug should be short.
✓ Non irritant to skin.
✓ Drug with ‘first pass effect’ and which degrade in GIT are ideal candidate.
## Ideal properties of a drug candidate

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>PROPERTIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Sh’d be low ( &lt; 20mg/day)</td>
</tr>
<tr>
<td>Half life</td>
<td>10 or less</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>&lt; 400</td>
</tr>
<tr>
<td>Skin permeability coefficient</td>
<td>$&gt; 0.5 \times 10^{-3}$ cm/hr</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>Non irritating &amp; non sensitizing</td>
</tr>
<tr>
<td>Oral Bioavailability</td>
<td>low</td>
</tr>
<tr>
<td>Therapeutic index</td>
<td>low</td>
</tr>
</tbody>
</table>
PERMEATION ENHANCERS

- These are the agents which promote the skin permeability by altering the skin as a barrier to the flux of desired penetrant.

- Flux $J$ across the skin can be given by
  \[ J = D \cdot \frac{dc}{dx} \]
  
  $D =$ diffusion coefficient
  
  $C =$ concentration
  
  $x =$ Spatial coordinate

- $D$ is function of size, shape, flexibility of diffusing drug molecule
Activity of penetration enhancers

- Interaction with the polar head groups of lipid via hydrogen and ionic bonding.
- Change in hydration sphere of lipids and affect the packing at the head region.
- Increase volume of the aqueous layer: swelling and hydration.
- Protein modification - open up the dense keratin structure and make it more permeable.
IDEAL CHARACTERISTICS OF PENETRATION ENHANCERS

1) IT SHOULD BE INERT
2) NON-TOXIC, NON-IRRITATING
3) ACTION SHOULD BE IMMEDIATE & PREDICTABLE
4) SHOULD NOT CAUSE REMOVAL OF BODY FLUID
5) SHOULD BE COMPATIBLE WITH DRUG & EXCIPIENTS
6) COSMETICALLY ACCEPTABLE
7) ODORLESS, TASTELESS, COLORLESS & CHEAP
SOLVENTS

The compounds increase penetration possibly by swelling the polar pathway and fluidizing the lipid e.g. methanol, ethanol, DMSO, propylene glycol, glycerol etc.

SURFACTANTS

They enhance polar pathway transport of hydrophillic drugs
ANIONIC SURFACTANTS -
Dioctylsulpho-succinnate

CATIONIC SURFACTANTS -
Pluronic F127, pluronic F58
BINARY SYSTEMS

- These systems open up the multilaminate pathway as well as the continuous pathway
  e.g. propylene glycol-oleic acid
  1,4-butandiol-linoleic acid

MISCELLANOUS CHEMICALS

e.g. urea
  N,N- dimethyl m-toluamide
FORMULATION APPROACHES FOR DEVELOPMENT OF TRANSDERMAL THERAPEUTIC SYSTEMS
1. POLYMER MEMBRANE PERMEATION CONTROLLED SYSTEM

Diagram:
- **Drug reservoir**
- **Drug impermeable metallic plastic laminate**
- **Rate-controlling polymeric membrane**
- **Adhesive layer**
1. POLYMER MEMBRANE PERMEATION CONTROLLED SYSTEM

- RCM made up of EVA copolymer

- A thin layer of (with drug compatible) hypoallergenic adhesive polymer e.g. silicon or polyacrylate adhesive may be applied to the external surface.

- Rate of drug release affect by varying:
  - the polymer composition,
  - permeability coefficient
  - and thickness of rate limiting membrane and the adhesive.
1. POLYMER MEMBRANE PERMEATION CONTROLLED SYSTEM

- Accidental breakage of the rate controlling membrane can result in dose dumping or a rapid release of the entire drug content.

  - Nitroglycerine releasing transdermal system for once a day medication for angina
  
  - Scopolamine-releasing transdermal system for 72 hr. prophylaxis of motion sickness.
  
  - Clonidine releasing transdermal system for 7 day therapy of hypertension.
  
  - Estradiol-releasing transdermal system for treatment of menopausal syndrome for 3-4 days.
The intrinsic rate of the drug release from this type of drug delivery system is defined by

\[
\frac{dq}{dt} = \frac{C_R}{1/p_m + 1/p_a}
\]

\(p_m\) and \(p_a\) respectively defined as....
1. POLYMER MEMBRANE PERMEATION CONTROLLED SYSTEM

- $p_m$ and $p_a$ respectively defined as....

$$p_m = \frac{k_{m/r} \cdot D_m}{h_m}$$

$$p_a = \frac{k_{a/m} \cdot D_a}{h_a}$$
1. POLYMER MEMBRANE PERMEATION CONTROLLED SYSTEM

Where,

- $k_{m/r}$ and $k_{a/m}$ are the partition coefficient for the interfacial partitioning of the drug from reservoir to the membrane and from the membrane to adhesive layer respectively.

- $D_m$ and $D_a$ are diffusion coefficients and

- $h_m$ and $h_a$ are the thickness
Substituting the $p_m$ and $p_a$ equation in equation 1

\[
\frac{dq}{dt} = \frac{k_{m/r} \cdot K_{a/m} \cdot D_m \cdot D_a}{k_{m/r} \cdot D_m \cdot h_a + k_{a/m} \cdot D_a \cdot h_m} \quad C_r
\]

Which define the intrinsic rate of drug release from a membrane moderated drug delivery system.
2. ADHESIVE DISPERSION-TYPE SYSTEM
2. ADHESIVE DISPERSION-TYPE SYSTEM

- Adhesive polymer is poly(isobutylene) or poly(acrylet) adhesive

- isosorbide dinitrate releasing transdermal therapeutic system for once a day medication of angina pectoris

- It is used for the administration of verapamil
The rate of drug release in this system is defined by:

\[ \frac{dq}{dt} = k_{a/r} \cdot D_a \cdot \frac{c_r}{h_a} \]

where,

\( K_{a/r} \) is partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.
3. GRADIENT CONTROLLED TTS

Drug – impermeable metallic plastic laminate

Drug reservoir gradient layers $R_1 > R_2 > R_3$
The rate of drug release from this drug reservoir gradient controlled system is given by:

\[
\frac{dq}{dt} = \frac{k_{a/r} \cdot D_s}{h_a(t)} A(h_a)
\]

Thickness of the adhesive layer for drug molecules to diffuse through increases with time \( h(t) \)

Nitroglycerine TTS patch
4. POLYMER MATRIX DIFFUSION CONTROLLED TTS SYSTEM
4. POLYMER MATRIX DIFFUSION CONTROLLED TTS SYSTEM

- Nitro-dur I and Nitro-dur II for continuous transdermal release of nitroglycerine at a daily dose of 0.5 mg/cm² for therapy of angina pectoris.

- Nitro dur II is modified version of I in which the drug is dispersed in acrylic based polymer adhesive with a resinous cross linking agent which result in much thinner and more elegant patch.
4. POLYMER MATRIX DIFFUSION CONTROLLED TTS SYSTEM

- The rate of drug release from this type of system is defined as:

\[
\frac{dq}{dt} = \left[ \frac{AC_p D_p}{2t} \right]^{1/2}
\]

- A is the initial drug loading dose dispersed in the polymer matrix and \( C_p \) and \( D_p \) are the solubility and diffusivity of the drug in polymer respectively.

- Since only the drug dissolved in the polymer can release.
5. MICRORESERVIOR TYPE OR MICROSEASELED DISSOLUTION CONTROLLED SYSTEM
Silicon elastomer - the lipophillic polymer is used for dispersion technique to form microscopic sphere of drug reservoir.

The quick stabilization occur by cross linking of the polymer chain which produced medicated polymer disc with a constant surface area and fixed thickness according to requirement of drug release.
5. MICRORESERVIOR TYPE OR MICROSEALED DISSOLUTION CONTROLLED SYSTEM

- It is successfully utilized in the preparation of Nitro-disc, a nitroglycerine releasing transdermal therapeutic system used in angina pectoris.

- This system followed zero order release of drug without the danger of dose dumping.
6. OTHER TTS

- **IONTOPHORESIS**
  - Built-in battery layer
  - Comparable in size to a normal transdermal patch
  - The Lectro Patch, General Medical Co.
  - Treatment time: 20 min
  - Recommended maximum current: 4mA
  - Lidocaine (local anesthesia), dexamethasone (arthritis), hydrocortisone (arthritis), acetic acid (calcified tendinitis) etc.
IONTOPHORESIS

[Diagram showing the process of iontophoresis]

- Drug reservoir
- Electrodes
- Reference reservoir
- Battery Microcomputer
- Skin
- Blood vessel
- Tissue
- Cl⁻, Na⁺, D⁺, Cl⁻ movement
Sonophoresis:
- The application of high frequency ultrasound to enhance drug penetration.
  Examples: lidocaine, hydrocortisone, salicylic acid.

Electroporation:
- Transient high-voltage electrical pulses, to cause rapid permeabilization of the *stratum corneum* through which large and small peptides, oligonucleotides and other drugs can pass in significant amounts.
# Transdermal Controlled-Release Products and Devices

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Type of Devices</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine</td>
<td>Transderm-Scop</td>
<td>Reservoir</td>
<td>Motion sickness</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Transderm-Nitro</td>
<td>Reservoir</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Nitro-Dur</td>
<td>Monolithic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrodisc</td>
<td>Monolithic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>Estraderm</td>
<td>Reservoir and ethanol enhancer</td>
<td>Hormone treatment</td>
</tr>
</tbody>
</table>
Recently approved transdermal contraceptive

- Recently approved by FDA (Ortho-McNeil)
- Once a week for three weeks, fourth week patch free
- 99 percent effective when used as directed
- Combination estrogen and progestin
- One-and-three-quarter inch square applied to the lower abdomen, buttocks or upper body.
- Skin irritation or detachment reported in 2-5% of patients
Advanced micro-needle Patch transdermal system allowing continuous delivery through the skin of proteins and water-soluble drugs.
MICROARRAY NEEDLE

• The device creates painlessly micropores in the S.C. known as microstructured arrays or microneedles.
• These devices have about 400 microneedles.
• The solid silicone needles (coated with drug) or hollow metal needles (filled with drug solution) penetrate the horny layer without breaking it or stimulating nerves in deeper tissues.
• Flux increase up to 1,00,000 fold are reported.
Multidose Transdermal Drug Delivery System

- It is comprises a laminate composite with a plurality of compartments.

- Each compartment is a reservoir for a unit dose of a drug active to be transdermally administered.

- Individual seals are provided for resealably enclosing the drug active in each of the reservoirs.

- The individual enclosing seals are removable to release the unit dose into contact with the skin of the patient and are able to control the transdermal absorption of the drug.
Applications:

- Delivery of large proteins, fragile antibodies, and hormones.
- Delivery of small molecules, particularly those with difficulty diffusing through skin layers.
- Delivery of vaccines, both conventional and DNA-based.
- Fluid sensing of glucose, hormones, blood gases, and therapeutic drug levels.
Crystal reservoir technology

- This system makes oversaturation of adhesive polymer with drug forcing partial crystallization.

- Presence of both molecular and solid state, allow higher conc. & consistent supply of drug.

- As skin absorbs dissolved drug, crystals re-dissolve to maintain drug at solubility limit (max. thermodynamic activity) at the site of contact.

- This results in smaller thinner patches with better patient acceptability. Clinical trials with this technology with $\beta_2$ adrenergic agonist tulobutanol confirmed superiority of TDDS formulation over oral formulation.
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