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Overview Of Transdermal Drug Delivery System.

Mohammed Jahid Halder[1], Dr. Mohammad Wais[2], Mohammad Anas Khan[3]

[1](H.K. College Of Pharmacy, Jogeshwari (West), Mumbai – 400102.
Email: mohdjahid.halder@hkcp.edu.in)

[2](H.K. College Of Pharmacy, Jogeshwari (West), Mumbai – 400102
Email: mohd.wais@hkcp.edu.in).

[3](H.K. College Of Pharmacy, Jogeshwari (West), Mumbai – 400102.
Email: mohdanas.khan@hkcp.edu.in)

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ABSTRACT

Transdermal drug delivery system (TDDS) has emerged as a potential novel drug delivery system within the last 30 years to boost the therapeutic efficacy and safety, maintain steady state plasma level of drugs and overcome important drawbacks of the traditional oral dosage forms and parenteral preparations. TDDS is ideally fitted to diseases that demand chronic treatment with frequent dosing. This review deals with a brief insight on the formulation aspects, the physical and chemical enhancers being explored to enhance the transdermal delivery of drugs across the stratum corneum, the evaluation parameters (physicochemical, *in vitro, in vivo* studies) and therapeutic applications of TDDS.

Keywords — **Novel drug delivery, Formulation aspects, Physical & Chemical enhancer, Evaluation parameters.**

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Introduction

Transdermal drug delivery systems (TDDS) are topically applied designed to deliver a therapeutically effective quantity of drug across a patient's skin at controlled rate for systemic effect. The key objective for topical drug delivery is that the low diffusion rate of drugs across the relatively impermeable, outer skin layer, the stratum corneum. The aim is to deliver drugs through skin in a predetermined and controlled release, it is known transdermal drug delivery system. It contains drug either in a reservoir with a rate – controlling membrane or spread in polymer matrix.

Advantage

- Reduces first pass metabolism effect.
- Sustains therapeutic drug level.
- Permits self – administration.
- Non – invasive. (No needles or injection)
- Improves patient compliance.
- Reduce side effects.
- Long acting drug delivery.
- Maintains therapeutic level for 1 to 7 days.

Disadvantage

- Poor diffusion of large/huge molecules.
- Skin irritation.
- Only suitable for very potent drugs.
- Drug with long half-life cannot be formulated in TDDS.
- More expensive than oral drugs.

Structure of skin

It is divided into three layers

- Epidermis

It is the outer layer. It comprises of stratum corneum. Water content of stratum corneum is around 20%. Stratum corneum is responsible for the

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barrier operates the skin and behaves as primary barrier to the percutaneous absorption.

- Dermis

It is made of robust collagen fibers. Below the dermis there is a fat containing subcutaneous tissue.

- Subcutaneous tissue

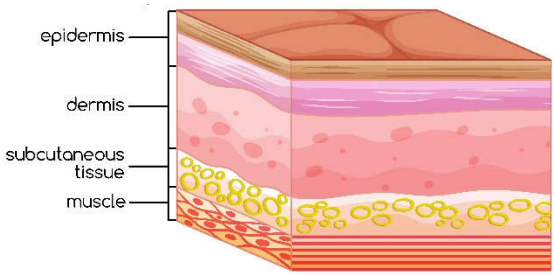
It is a sheet of the fat containing areolar tissue. Attaching the dermis to the underlying structure.

- Skin appendages

Sweat glands produce sweat of pH 4 – 6.8 & absorbs drugs, secretes proteins, lipids and antibodies. Its function is to control heat.

- Hair follicles

They have sebaceous gland that produces sebum and includes glycerides, cholesterol and squalene.



Routes of drug absorption through skin

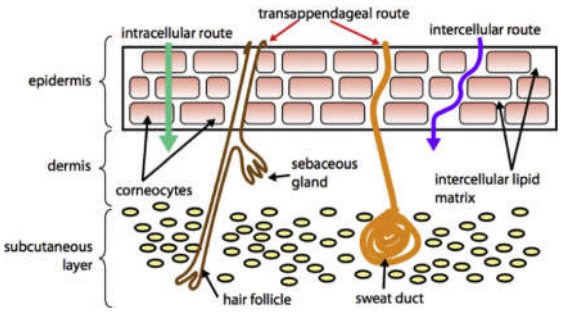
It occurs by the following routes are

- Transepidermal absorption

Stratum corneum is the main route for absorption. Permeation involves partitioning of the drug into the stratum corneum. Permeation depends upon o/w distribution tendencies of drug. Permeation through the dermis is through the interlocking channels of the ground substance.

- Transfollicular absorption

Skin appendages (sebaceous) are considered as absorption by passing the stratum corneum Follicular route is important for permeation because the opening of the pore is relatively huge and sebum aids in the diffusion. Partitioning into the sebum followed by the diffusion to the depths of the epidermis.



Factor affecting transdermal permeation

Physicochemical property of drug molecule

1) Partition co - efficient.

The optimal partition coefficient (K) is needed for good action. (Between 1 - 4)

2) pH condition.

The pH of the skin is mostly acidic i.e. 4 – 6. This pH is responsible for regulating permeability of drug. According to pH penetration hypothesis, only the unionised type of drug can permeate through lipid barrier.

3) Drug concentration.

The flux is proportional to the concentration gradient across the barrier and concentration gradient are higher if the concentration of drug will be more across the barrier.

4) Molecular weight & size.

Drug with high molecular weight have low permeation. Smaller particle size have more permeability than the large particles.

Physicochemical property of drug delivery system

1) Release characteristics.

Solubility of drug in dosage form determines the release time.

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2) 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.

Pathophysiological condition of skin

1) Hydration of skin.
Hydration is most important factor increasing the permeation of skin.

2) Lipid film.
The lipid film on the skin surface acts as a protecting layer to stop the removal of moisture from the skin and helps in maintaining the barrier function of stratum corneum.

3) Effect of vehicle.
A vehicle will influence absorption by its effect on physical state of drug and skin.

4) Pathological injury to skin.
Injuries that disrupt the continuity of the stratum corneum will increases permeability due to increased vasodilatation.

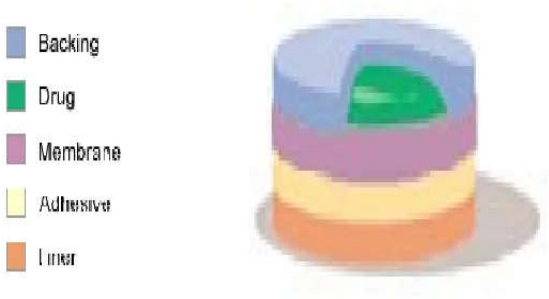
Biological factors

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

2) Skin metabolism
Viable epidermis is metabolically active than dermis. If topically applied drug is subjected to biotransformation throughout permeation local and systemic bioavailability is affected.

3) Regional skin sites
Thickness of skin, nature of stratum corneum & density of appendages very site to site. These factors affect penetration.

Basic components of transdermal permeation.



1) Drug
It should have compatible with polymer and excipient.
Drug selection criteria

- Dose must be less than 10mg per day.
- Molecular weight less than 1000 daltons.
- Aqueous solubility > 1mg/ml
- Drug should not be an irritant to skin.
- Drug should be potent and have short half-life.
- Drug should not stimulate an immune reaction in the skin.

2) Polymer matrix
It controls the release of drug. Polymer matrix should be compatible with drug and excipient. Stable at skin and body temperature. They must not damage skin. Example: - Gelatin, Neoprene, Polyethylene

3) Release liner
During storage the patch is covered by a protecting liner that is removed and discharged immediately before applying the patch to skin. It is a part of primary packaging. Example:-Polyethylene, Polyvinylchloride.

4) Penetration Enhancers
These are substances which improves penetration of drug through skin

- Organic solvent
- Polar solvent
- Binary example - propylene glycolic acid
- Surfactant Anionic example – SLS. Non - ionic example - pluronic F- 27, f - 68

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- Miscellaneous example - urea, N - N – dimethyl.

5) Adhesives

It helps in maintaining an intimate contact between the transdermal system and skin surface. Compatible with drug. It should have sensation free. It should be allergic free. Example: - Polyacrylates, Silicones.

6) Backing laminate

Hold and protect the drug reservoir from exposure to atmosphere. Avoid loss of drug. High flexibility. Example: - vinyl, polyethylene.

Classification of TDDS

1) Membrane permeation – controlled

Drug reservoir (homogenous dispersion of drug with polymeric matrix or suspension of drug in unleachable viscous liquid medium like silicone fluid) is encapsulated within drug impermeable metallic plastic laminate and a rate controlling polymeric membrane (ethylene vinyl acetate co polymer). The cross sectional view of this system is shown in the following Fig.1. A thin layer of silicone or poly acrylate adhesive may applied to the external surface of the rate controlling membrane to achieve intimate contact of the TDDS and the skin surface. Release rate of this TDDS depends upon the polymer composition, permeability coefficient and thickness of the rate controlling membrane and adhesive.

The rate of drug release from this TDDS is calculated by the following

$$\frac{dq}{dt} = \frac{\frac{Cr}{1}}{Pm} + \frac{1}{Pa}$$

C = concentration of drug in the reservoir compartment

Pm = permeability coefficient of rate controlling polymeric member

Pa = permeability coefficient of adhesive

Example: - nitro-glycerine – releasing transdermal system (transderm - nitro) for once a day medication in heart condition.

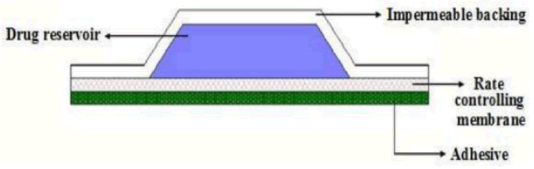

Figure 1: Membrane permeation controlled system

2) Matrix diffusion – controlled

Drug reservoir. Homogenous dispersion of drug with hydrophilic or lipophilic polymer matrix by anyone of the following methods. Homogenous dispersion of finely ground drug particles with liquid polymer or highly viscous base polymer followed by cross linking of polymer chains. Homogenous mixing of drug solid with polymer at an elevated temperature. Dissolving the drug and polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature. Medicated polymer is moulded in to desired surface area and controlled thickness. This medicated polymer disc is pasted on to an occlusive base plate with impermeable plastic backing. Then the adhesive polymer is spread along the circumference to form a strip of adhesive rim around the medicated disc. The rate of drug release from this system is calculated by

$$\frac{dq}{dt} = \frac{(A\ Cp\ Dp)^{1/2}}{2t}$$

A = initial drug loading

Cp & Dp = solubility & diffusivity of drug in polymer matrix

Example: - estradiol di acetate releasing TDDS

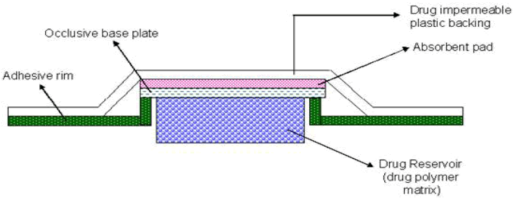

Figure 2: Matrix diffusion-controlled system

3) Adhesive diffusion – controlled

Drug reservoir. Homogenous dispersion of drug with adhesive polymer (poly (isobutylene) or polyacrylate). Then spreading of this medicated adhesive polymer on flat sheet of drug impermeable

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metallic plastic backing to form thin drug reservoir layer. On top of the drug reservoir layer, thin layers of rate controlling adhesive polymer of specific permeability and constant thickness are applied to produce an adhesive diffusion/dispersion-controlled TDDS. The cross sectional view of this system is shown in the following Fig. 3. The rate of drug release in this system is calculated by

$$\frac{dq}{dt} = \frac{\frac{Ka}{r}.Da}{ha} \quad \text{Cr}$$

Ka/r = partition co – efficient of drug between adhesive layer & reservoir layer
Da = diffusion co – efficient of drug in the adhesive layer
ha = thickness of adhesive layer
Example: - Iso sorbide dinitrate releasing TDDS

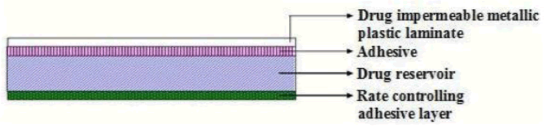

Figure 3: Adhesive dispersion-type system

4) Micro reservoir dissolution – controlled

It is the combination of the reservoir and matrix diffusion. Drug reservoir. Homogenous dispersion of drug suspension in a lipophilic polymer (silicone elastomer). As a result discrete unleachable microscopic spheres of drug reservoir is formed which is stable by cross linking. Medicated polymer is moulded in to desired surface area and controlled thickness. This medicated polymer disc is pasted on to a base plate with impermeable plastic backing. Then the adhesive polymer is spread along the circumference to form a strip of adhesive rim around the medicated disc. The cross sectional view of this system is shown in the following Fig.4.
Example: - Nitro glycerine releasing TDDS.

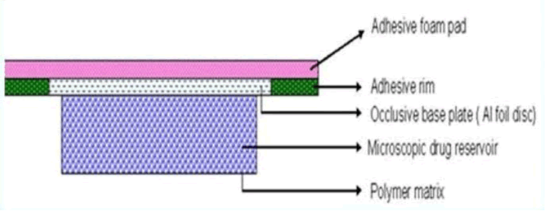

Figure 4: Microreservoir dissolution controlled system

Evaluation of TDDS

- Physical appearance/texture.

Clarity, colour, flexibility & smoothness.

- Thickness of the patch

The thickness of the drug prepared patch is measured by using a digital micrometer at completely different purpose of patch and determines the average thickness and standard deviation for the same to make sure the thickness of the final prepared patch.

- Weight uniformity

The final prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

- Folding endurance

Repeatedly folding at same point until it breaks. The number of time it could be folded is its folding endurance value.

- Water vapour permeability (WVP) evaluation

WVP=W/A
W is the amount of vapour permeated through the patch expressed in gm/24 hrs and A is the surface area of the exposure samples expressed in m

- Drug content

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug contain with the suitable method (UV or HPLC technique).

- Percentage elongation break test

Elongation percentages = L1 - L2x100 / L2
Where,
L1= is the final length of each strip
L2= is the initial length of each strip

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- Percentage moisture content

$$\% \text{ moisture content} = \frac{final\ weight - initial\ weight}{initial\ weight} \times 100$$

Where,
Final and initial is of the patch

- Content uniformity test

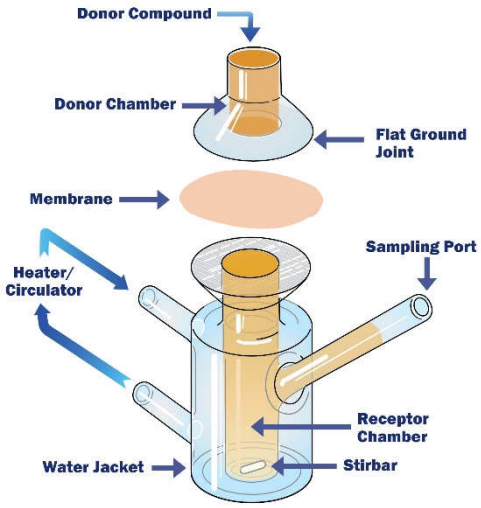
10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then the test pass. But if 3 patches have content in the range of 75% to 125% then additional 20 patches are tested. If these 20 patches have range from 85% to 115%, then the test pass.

- In vitro drug release studies

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples are withdrawn at a time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

- In vitro skin permeation studies

In-vitro permeation study can be carried out by using Franz Diffusion cell with an effective permeation area and receptor cell volume of 1.0 cm^2 and 10 ml respectively. The temperature is maintained at 32°C. The receptor compartment is filled with 10ml phosphate buffer solution and is constantly stirred in a magnetic stirrer at 100rpm. The skin is then mounted on receptor compartment with stratum corneum side facing upward into the donor compartment. The transdermal patch is then applied on the skin in donor compartment. Samples are withdraw through sampling port of the diffusion cell at predetermined time interval over 24 hr and are analysed. The receptor phase is immediately replenished with equal volume of fresh diffusion buffer. Flux can be determined directly as the slope of the curve between steady state values of amount of drug permeated vs time in hours.



Conclusion

TDDS a practical application as it is the next generation of drug delivery system. Due to recent advance in technology of the drug to the site of action without rupturing the skin membrane transdermal route is turning into the most widely accepted route of drug administration. As we known, the basic function of skin is protection and hence it is difficult to target the skin for drug delivery. Because skin having many layers, but using novel techniques in TDDS we have successfully penetrate the drug into systemic circulation.

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