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Review Article

TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

Verma Sushma and Ojha Abhishek[1]

Corresponding Author:* ***Ojha Abhishek* ✉ *abhishekojhapharma@gmail.com*

Skin is considered as the largest organ of the body and it has many different functions. The skin functions occur in thermoregulation, protection, metabolic functions and sensation. The skin is divided into two main regions, the epidermis, and the dermis, one of each providing a distinct overall role function of the skin. The dermis is mainly attached to an underlying hypodermis, which is also called subcutaneous connective tissue, which generally stores adipose tissue and also recognized as the superficial fascia of gross anatomy. Basically it is composed of three layers. The outer-most layer is called the epidermis, which serves as a barrier and protects the body from any infection. The second layer is called the dermis and consists of connective tissues which cushion the body from stress and strain. Now a day's the transdermal drug delivery system is the most prominent method for the drug delivery. Transdermal drug delivery system is basically the topically administered drug which are generally in the form of patches for the controlled and pre-determined effects of drug. These devices allow the drug to be delivered through the skin barrier or the outer most layer of the skin. Polymers are called backbone for the transdermal drug delivery system.

Keywords: Skin Introduction, Types of skin, Transdermal drug delivery system, Evaluation

INTRODUCTION

Skin

Skin is considered as the largest organ of the body and it has many different functions. The skin functions occur in thermoregulation, protection, metabolic functions and sensation. The skin is divided into two main regions, the epidermis, and the dermis, one of each providing a distinct overall role function of the skin. The dermis is mainly attached to an underlying hypodermis, which is also called subcutaneous connective tissue, which generally stores adipose tissue and also recognized as the superficial fascia of gross anatomy. Basically it is composed of three layers. The outer-most layer is called the epidermis, which serves as a barrier and protects the body

[1] Noida Institute of Engineering and Technology, Pharmacy Institute, 19, Knowledge Park-II, Greater Noida, Uttar Pradesh, 201306.

from any infection. The second layer is called the dermis and consists of connective tissues which cushion the body from stress and strain. The inner-most layer is the fatty subcutaneous tissue called the hypodermis and contains larger blood vessels and nerves; it insulates the body and absorbs shock.

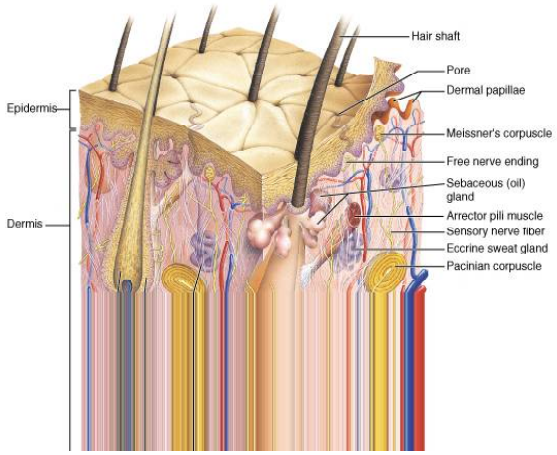
1. **The Epidermis -** The epidermis is composed of the outer-most layers of skin cells. Epidermis means 'upon' or 'over' dermis and normally contains 4 layers. It does not contain any blood vessels and therefore the cells obtain diffused oxygen from the surrounding air. The outer-most cell layer is known as the stratum corneum and is composed mostly of corneocytes, which are keratinocyte cells that are in their last stage of differentiation. Keratinocyte cells constantly migrate from the stratum basale layer of the epidermis, become differentiated into corneocytes and reach the skin surface. These cells are continuously sloughed off from the skin surface by the rubbing or washing process.
2. **The Dermis** - The dermis is the skin's second layer which is thick, fibrous and elastic (made mostly of collagen, elastin and fibrillin), and gives the skin its flexibility and strength. It protects the epidermis and contains the nerve endings, sweat glands, oil (sebaceous) glands, hair follicles and blood vessels. The dermis is mainly divided into two layers; the papillary dermis or stratum papillare and reticular dermis or stratum reticulare. The superficial layer forms conic projections alternating with epidermal rete ridges, which increases the contact surface area between the dermis and epidermis enabling better adhesion between these two layers. This layer consists of loose bundles of collagen and thin elastic fibres which stretch perpendicular to the dermo-epidermal junction.
3. **The Subcutaneous Fat** - The lowermost layer of skin is the subcutaneous fat layer and is also called the 'hypodermis' meaning 'beneath the skin'. It consists of loose connective tissue, elastin and cells such as fibroblasts, macrophages and adipocytes. This layer mainly consists of fat cells (50% adipocytes) and plays an important role in our body by attaching the dermis to the muscles and bones via a special connecting tissue called septa, which consists of blood vessels, nerve cells and collagen.

FUNCTIONS OF SKIN

1. The primary function of skin is to act as a protective barrier of the body against mechanical, thermal and physical injury, and noxious agents.
2. It prevents loss of moisture (dehydration) and protects against the harmful effects of UV radiation from sun; it acts as a sensory organ, regulates temperature control and plays a significant role in immunological surveillance.
3. The skin synthesizes vitamin D3 and also has cosmetic, social and sexual associations. Vitamin D3 is made when 7-dehydrocholesterol, present in skin, reacts with ultraviolet light (via natural daylight) that falls onto the skin; it is produced at the stratum basale and stratum spinosum.
4. The destruction of microorganisms and interaction with the body's immune system is performed by Langerhans cells, phagocytic cells and epidermal dentritic cells.
5. Langerhans cells are dentritic cells found in all layers of the epidermis, but mostly in the

stratum spinosum; they are also found in the papillary dermis around the blood vessels. During skin infections, the Langerhans cells take up and process microbial antigens to become fully functional antigen-presenting cells. These cells secrete a variety of cytokines which are important in the pathogenesis of contact dermatitis, atopic dermatitis, histiocytosis X, human immunodeficiency virus-type 1 and skin graft rejection.

Figure 1: Structure of Skin



TRANSDERMAL DRUG DELIVERY SYSTEM

Now a day's the transdermal drug delivery system is the most prominent method for the drug delivery. Transdermal drug delivery system is basically the topically administered drug which are generally in the form of patches for the controlled and pre-determined effects of drug. These devices allow the drug to be delivered through the skin barrier or the outer most layer of the skin. Polymers are called backbone for the transdermal drug delivery system.

ADVANTAGES OF TDDS

1. Avoids chemically hostile GI environment (drug degradation in acidic and basic environments is prevented).

2. No GI distress and the factors like Gastric emptying, intestinal motility, transit time, donot effect this route as in oral route.

3. Avoidance of significant presystemic metabolism (degradation in GIT or by the liver) and therefore need lower doses.

4. Allows effective use of drugs with short biological half-life.

5. Allow administration of drugs with narrow therapeutic window because drug levels are maintained within the therapeutic window for prolonged periods of time.

6. Reduced inter and intra patient variability.

7. Reduction of dosing frequency and enhancement of patient compliance.

8. Provides controlled plasma levels of very potent drugs.

9. Can provide adequate absorption of certain drugs.

10. Avoids the risk and inconveniences of parenteral therapy (Painless method of drug administration).

11. Drug input can be promptly interrupted simply by removal of the patch when toxicity occurs.

12. Provides suitability of self medication.

DISADVANTAGES OF TDDS

1. Drugs that require high blood levels cannot be administered – limited only to potent molecules, those requiring a daily dose of 10mg or less.

2. Transdermal administration is not a means to achieve rapid bolus type drug input, rather

it is usually designed to offer slow, sustained drug delivery.

3. Adequate solubility of the drug in both lipophilic and aqueous environments, to reach dermal microcirculation and gain access to the systemic circulation.

4. The molecular size of the drug should be reasonable that it should be absorbed percutaneously.

5. Tolerance inducing compounds are not an intelligent choice for this mode of administration unless an appropriate wash out period is programmed in between the dosing regimen.

6. Difficulty of permeation of the drug through human skin –barrier function of the skin.

7. Skin irritation or dermatitis due to excipients and enhancers of drug delivery system used for increasing percutaneous absorption is another major limitation.

8. Adhesive may not adhere well to all types of skin.

Ideal properties of transdermal drug delivery system

1. The shelf life should be upto to 2.5 years.

2. The patch size should be less than 40 cm^2.

3. The dose frequency should be once a daily-once a week.

4. They should be clear or white color.

5. They should be non-irritating to the skin.

6. Release properties- should have consistent pharmacokinetic and pharmacodynamic profile over the time.

Formulation approaches used in the development of TDDS

1. Membrane permeation – controlled systems.
2. Adhesive dispersion – type systems.
3. Matrix diffusion - controlled systems.
4. Microreservoir type or Microsealed dissolution - controlled systems.
5. Poroplastic – type systems.
6. Transdermal delivery of Macromolecules.

Factors Affecting Transdermal Permeability

1. Physico chemical properties of parent molecule

· Solubility and partition co- efficient.

· pH condition.

· Penetrant concentration.

2. Physico chemical properties of drug delivery system

· Release characteristic.

· Composition of drug delivery system.

· Permeation enhancer used.

3. Physiological and pathological condition of skin

· Lipid film

· Skin hydration

· Skin temperature

· Effect of vehicle

· Pathological injury to skin

4. Biological factors

· Skin age

· Thickness of Stratum Corneum

· Skin condition

5. 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 the excess solid drug will function as a reservoir and helps to maintain a constant drug constitution for prolonged period of time.

BASIC COMPONENTS OF TDDS

- Polymer matrix
- The drug
- Permeation enhancers
- Other excipients

1. Polymer matrix

Ideal polymer

- MWT, and chemical functionality of the polymer should not affect the diffusivity of drug and its release
- Stable
- non reactive
- easily manufactured
- easily fabricated into desired product
- Inexpensive
- degaradation product must be non toxic or non antagonistic to the host
- Should retain its mechanical properties when the large amount of drug is loaded in to it.

Polymers used in TDDS

Natural Polymers

Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums, Natural rubbers, starch.

Synthetic elastomers

Polybutadiene, hydrin rubber, polysiloxone, silicone rubber, nitrile.

2. Suitable drug candidate

Physico chemical properties of drug

- Should have MW less than 1000 daltons(800-1000).
- Should have affinity for both lipophilic and hydrophilic phases.
- Should have low melting point.

Biological properties of drug

- Should be potent(less than 20mg).
- Half life should be short.
- Must not induce a cutaneous irritant or allergic response.
- Drugs which degrade in the GI tract or inactivated by hepatic first pass effect are suitable candidate.
- Tolerance to the drug must not develop.
- Drugs which has to be administered for a longer period of time can be formulated.
- Drugs which cause adverse effects to non target tissues can also be formulated.

3. Permeation enhancers

Solvent

Increases penetration by swelling the polar pathway transport or fluidising lipids. Eg. water, ethanol, methanol, DMS, homologs of methyl sulphoxide, dimethyl acetamide, and DMF, 2-pyrrolidone, N-methyl, 2-pyrrolidone, laurocapram, PG, glycerol, silicone fluids, isopropyl palmitate.

Surfactant

Enhances the polar pathway transport of hydrophilic drugs

Anionic surfactant

Dioctyl sulpho succinate,SLS,deco decylmethyl sulphoxide etc.

Non ionic surfactant

Pluronic F127,Pluronic F68,etc.

Bile salt

Sodium taurocholate,sodium deoxy cholate,sodium tauroglycocholate.

Binary systems

Propylene glucol-oleic acid and 1,4-butane diol-linoleic acid

Miscellaneous

Urea-hydrating and keratolytic agent,N,N-dimethyl-m-toluamide,calcium thioglycolate,anti cholinergic agents

Potential permetion enhancer

Euclyptol,di-o-methyl-ß-cyclodextrin and soyabean casein

4. Other excipients

Adhesives

- pressure sensitive polymeric adhesive .
- Serves to adhere the components of the patch together along with adhering
- the patch to the skin.

Ideal properties

- It should not irritate or sensitize the skin or affect normal functions of the skin
- It should adhere to the skin aggressively
- It should be easily removed
- It should not leave an unwashable residue on the skin
- It should have an intimate contact with the skin
- It should be compatible with the drug,excipients and permeation enhancers
- Permeation of drug should not be affected

EVALUATION METHODS

The evaluation methods for transdermal dosage form can be classified into following types: Physicochemical evaluation, *In vitro* evaluation and *In vivo* evaluation

Physicochemical Evaluation

Interaction Studies

The drug and the excipients must be compatible with one another to produce a product that is stable. The interaction between drug and excipients affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are taken out by Thermal analysis, Fourier transform infrared spectroscopy (FTIR), ultra violet (UV) and chromatographic techniques by comparing their physicochemical properties like assay, melting point, wave numbers, and absorption maxima.

Thickness of the Patch

The thickness of the drug prepared patch is measured by using a digital micrometer at different point of patch and this determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

Weight Uniformity

The prepared patches are to be dried at 60°C for 4 h before testing. A specified area of patch is to

be cut in different parts of the patch and weighed in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Folding Endurance

A specific area of strip is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking gave the value of folding endurance.

Percentage Moisture Content

The prepared patches are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature. After 24 h, the films are to be reweighed and the percentage moisture content determined by below formula:

Percentage moisture content (%) = [Initial weight - Final weight / Final weight] ×100

Percentage Moisture Uptake

The prepared patches are to be weighed individually and to be kept in a desiccator containing saturated solution of potassium chloride in order to maintain 84% Rhesus factor (RH). After 24 h, the films are to be reweighed and the percentage moisture uptake determined by the formula:

Percentage moisture uptake (%) = (Final weight - Initial weight / initial weight) × 100

Water Vapour Permeability (WVP) Evaluation

Water vapour permeability can be determined by a natural air circulation oven. The WVP can be determined by the following formula:

$WVP = W/A$

where, WVP is expressed in g/m^2 per 24 h, W is the amount of vapour permeated through the patch expressed in g/24 h, A is the surface area of the exposure samples expressed in m^2.

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 the drug content analyzed with the suitable method (UV or HPLC technique).Then, the average of three different samples is taken.

Content Uniformity Test

Ten (10) patches were selected and content 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 transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75 to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85 to 115%, then the transdermal patches pass the test.

In Vitro Skin Permeation Studies

An *in vitro* permeation study can be carried out by using diffusion cell on thick abdominal skin of male Wistar rats weighing 200 to 250 g. Hair from the abdominal region is removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment, and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece was mounted between the

compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume was removed from the receptor compartment at regular intervals, and an equal volume of fresh medium was replaced. Samples were filtered through filtering medium and analyzed spectrophotometrically or using HPLC. Flux was determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm2) versus time in hours, and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm^2).

In Vivo Evaluation

Skin irritation study

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50 cm2) of the rabbit is to be cleaned and the hair removed from the clean dorsal surface by shaving and the surface cleaned by using rectified spirit with the representative formulations applied over the skin. The patch is to be removed after 24 h and the skin observed and classified into 5 grades on the basis of the severity of skin injury.

CONCLUSION

Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin, membrane transdermal route is effective. This article provides valuable information regarding the formulation and evaluation aspects of transdermal drug delivery systems. TDDS is a realistic practical application as the next generation of drug delivery system.

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