Transdermal Drug Delivery System

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Abstract
Non-invasive method of drug administration are transdermal patches, it is an adhesive patch designed to deliver a specific dose of medication through the skin and into the bloodstream through the body, it has so many advantages over other routes of administration, for instance it is less invasive patient friendly and has the ability to bypass 1st pass metabolism and the destructive acidic environment of the stomach that occurs upon the oral ingestion of drug's.

Keywords: Transdermal, drug delivery, medicinal patches, Skin.

Introduction
Transdermal = Trans (Cross) + Dermal (Skin).
Transdermal drug delivery system are optically dosage form which deliver the drug through a skin. The drug are in the form of patches which applied on the skin to deliver a specific dose of drug into the systemic circulation through the skin. For outcome of ideal therapeutic action require not only proper drug selection but also required drug delivery more effectively for drug delivery human skin is a casually accessible surface, over the past three decades developing controlled drug delivery has become increasingly important in the Pharmaceutical industry.
The pharmacological response concentration of the drug at the site of action give both desire therapeutic effect and undesired adverse effect which in turn depends upon the dosage form and the extent of absorption of the drug at the site of action.
The traditional way to take medications is tabletes and injects but now new option are becoming increasingly popular. Transdermal drug delivery method is one of the highly successful alternative drug delivery method. Skin of average adult body covers a surface of approximately 2 m² and receive one ³ of blood circulating through the body. The deliver a drug into the body through transdermal layer of skin it is necessary to understand about the skin.

TDD system which is a technique that provide drug absorption through the skin. Drug administered by intravenous route or oral route. Intravenous for systemic and oral administration for local drug delivery. TDD is painless method of delivering drug. By applying a drug formulation on to intact and healthy skin. When drug reaches the into the dermal layer then it becomes available for systemic absorption.
The first transdermal system (TDD) Developed in 1980 contained drug for the treatment of motion sickness, TDD Is membrane moderated system. TDDS are adhesive drug containing system. TDD device, which may be an active or passive design, is a device provide alternative route for administrating medications. These device allow for pharmaceutical to be delivered across the skin barrier. Transdermal drug use in treating conditions like hypertension, pain, migrating etc. compared to oral dosage system. Transdermal drug delivery system controlled release of drug through skin into patient which reduce first pass metabolism effect.
Advantages:
- It increases patient compliance, avoid first pass metabolism.
- It is non-invasive and avoids the inconvenience of parental therapy.
- Easy to use.
- Self medication is possible.
- Drug therapy can be terminated rapidly by removal of the application from the skin surface.
- Transdermal drug reduces side effects.
- It has no interaction with gastrointestinal fluids.
- It has stable blood level.
- It increases the flexibility of termination.
- It is more comfortable than other drug delivery systems.
- Self administration is used or possible.

Disadvantages:
- It may cause dermatitis at the site of application in some patients.
- Don’t provide long term adherence.
- Potent drug can be formulated in patches.
- In some cases it placed behind the ear making it uncomfortable for the patient.
- It shows high cost.
- Some time it was cause uncomformability or local irritation cause.
- In this no ionic drug delivery take place.
- In this low drug level in blood/plasma
- It shows molecular size restriction.
- Variation in barrier functions are found.
- In this drug are no rapidly released.

Anatomy and physiology of the skin
The skin covers the body and protects it from the external environment.
It is a protective barrier.
It also prevents:
- Water loss
- Sensory function
- Body temperature
- Thermoregulation

The skin is composed of 2 layers – outer layer epidermis and deeper layer dermis.
The dermis is connected to underlying structure via a subcutaneous tissue the hypodermis which is not technically considered part of the skin.
The epidermis provides barrier and protection it consists mainly of the protein keratin a tough and water-insoluble structural protein.
Epidermis = Barrier – Keratin
The dermis constitutes the bulk of the skin, it provides support and flexibility.
Dermis = Support, flexibility.
Collagen = Elastic
The dermis consists mainly of collagen and to a lesser extent, elastic fibers. Loss of collagen and elastic, such as with aging, causes the skin to slack. The boundary surface between the epidermis and dermis is not flat but wavy meaning the 2 tissues interblock strengthening their connection. With age this boundary flattens and the skin becomes more fragile. The dermis is well vascularized and contains

1. Sensory nerves
2. Hair follicles
3. Sebaceous glands and
4. Sweat glands

It has 2 zones, the upper papillary dermis with losses connective tissues and the lower reticular dermis with dense connective tissue. The dermis houses immune cells and allows inflammatory response to activate upon exposure to invading organisms. The hypodermis is composed of loose connective and adipose tissues. This is where most of the body fat is stored. The hypodermis provides thermal insulation padding and serves as the body main energy storage

Hypodermis = Subcutaneous fat, insulation padding, energy storage.

The thickness and proportion of the epidermis and dermis vary greatly depending on their location on the body but the skin is classified as thick or thin based on the thickness of the epidermis. Thick skin is found only in areas where there is a lot of abrasion: Palms, soles, digits and has epidermal layers. Thin skin is everywhere else and has 4 epidermal layers. Most cells of the epidermis are keratin producing cells or keratinocytes New cells are constantly produced by mitotic cell division in the basal layer. They then move towards the skin surface as they age and differentiates changing shape, form cuboidal to flat. The distinct epidermal layers represent different stages of keratinocytes differentiation form their birth to their death. The spinous layer is characterized by presence of abundant desmosomes which connect keratin. Filaments of adjacent cells, anchoring them together, providing resistance to physical stress. The granular layer is loaded with keratohyaline granules. These granules release several substance that cross link keratin filaments, converting them into an impermeable keratin matrix. This process known as cornification or keratinization, the result of which is the most superficial layer the cornified layer about 30 cells thick. These fully keratinized dead cells form the skin barrier. They are shed periodically form the surface as new cells are moving up. The entire epidermis is replaced every 30 to 40 days. The renewal process becomes slower with age but faster in injured skin, when cell proliferation

Epidermis = Mostly keratinocytes (80%)
Renewal rate = 30-40 days
Slower in animal skin. Faster in injured skin.
Is accelerated for wound healing.

The epidermis also contains immune cell touch sensory cells and melanocyte. Melanocyte produce the pigment melanin and transfer it to keratinocytes. The amount of melanin produced is the major determinant of skin colour. Melanin synthesis is stimulated by UV light and thought to be a protective mechanism against UV radiation damage. Being a largest organ it’s very fitting that it’s part of system with a very long word.

Integumentary system: Skin and structures associated with it – make up the integumentary system.

Why do we admire skin so much?
Well skin is critical for homeostasis because it helps maintain internal body temperature and fluid balance. As a physical barrier, it protects from invasion of pathogens like bacterial or fungi, for example skin in where vitamin D is produced, skin also has sensory function. Example if a ladybug lands on your arm, you are usually aware of it.

The integumentary system which includes skin has some depth to it, this system has layers, layers of different tissues and cell types and you’ll find major layers can be divided into smaller layers as well as we were going to take a little explanation on this and a reminder.

**Epidermis:** The epidermis is the most superficial layer of the skin and provides the first barrier of protection from the invasion of substances into the body. First I want to mention cell that can be found in different locations in the epidermis called keratinocytes. These are cells that make keratin. Keratin is actually a protein that helps cell to be water resistant and tough. Keratinocytes are produced at the bottom layer of epidermis which we’ll get to on tour and they get pushed upward to the top, superficial layer of the epidermis where they are considered cornified cell are hardened, flattened and tough. They’re also dead, they’ve loss their organelles and just full of keratin. Now before we start exploring the layers of the epidermis, i think it’s really helpful to have mnemonic to remember the different layers of the epidermis from the outer layer to the inner layer. Here’s an epidermis mnemonic can temurs get some bamboo? I may or may not have made that mnemonic up and there are probably better ones out there but many lemurs do like bamboo something to do said for factual mnemonics.

**Dermis**

Base layer of the epidermis will be bonded to the dermis which we’ll move into right now. The dermis unlike the epidermis you will find blood vessels in the dermis. The dermis is a type of connective tissue which is a non-epidermal type of tissue that connects things together in the body. You’ll also find sweat gland hair follicles and nerves in the dermis. The dermis has fibres of two type of proteins collagen providing support and elastic which gives it elasticity. These proteins are made by specialized cells in this layer called fibroblasts.

The dermis has two general layer a papillary layer which has connective tissue that is more loose and a deeper reticular layer where connective tissue is more tightly packed. Now before we move to one more layer this is a good time to mention scars. Many cuts that are isolated the epidermis won’t scar but if cut makes it to the dermis it can often scar.

**Fundamentals of skin permeation**

Before the adverse devolpment of pharmacy or until the last century everyone suppose that the skin was impermeable to drug or other substance except gases but now in the current century the study indicated the permeability to liquid soluble drugs. Also it was recognized that various layers of skin are not equally permeable.

Epidermis layer of skin is less permeable than the dermis layer of skin. The doubts about stratum corneum permeability were removed after a large controversy and it also remove doubts about using isotopic tracers. It was suggested that stratum corneum greatly hamper permeation.

1. Stratum corneum as skin permeation barrier
2. Intracellular verses transcellular diffusion
3. Permeation pathways
1. **Stratum corneum as skin**

Per square centimeter an average human skin contains 40-70 hair follicles and 200-250 sweat ducts. In this ducts especially water soluble substance pass faster than lipid soluble substance. Still these ducts don’t contribute much for skin permeation. Therefore most neutral molecules pass through stratum corneum by passive diffusion.

**Series of steps in sequence:**

a) On surface layer of stratum corneum sorption of a penetrant molecule take place.

b) Diffusion through it and viable epidermis and finally reaches to dermis

c) The molecule is taken up into the microcirculation for systemic distribution.

2. **Intracellular vs transcellular diffusion**

Lipid rich amorphous material was failed in intracellular region’s of stratum corneum. In dry stratum corneum intracellular volume may be 5% to 10% in full hydrated stratum corneum.

3. **Permeation pathway**

Permeation pathway is divided into 2 routes

A) **Appendageal route**

In this route transport of drug take place by sweat glands and their follicles with their associated sebaceous gland. Appendageal route is also known as shunt routes because these routes circumvent penetration through the stratum corneum. Appendageal route is considered to be of minor important because of it’s relatively small area approximately 0.1% of total skin area

B) **Epidermal route**

Epidermal route is a permeation pathway of transdermal drug delivery system.

It divided into following parts

i) **Transcellular:**

Transcellular route or pathway is simply define as the transport of molecules across epithelial cellular membrane. These include passive transport of small molecules, active transport of ionic and polar compounds and endocytosis and transcytosis of macromolecules.

ii) **Paracellular**

Paracellular pathway is simply define as the transport of molecules around or between the cells. Tight junctions or similar situation exist between the cell.

Mainly partition coefficient that means log K was decided principle pathway percentage

**Ideal molecular properties for transdermal drug delivery system**

For drug delivery, drug show some properties if that properties help to penetrate drug into body then we can assay that

1. The PH of saturated solution must be between 5 to 9.
2. Optimum partition coefficient is required for good therapeutic action.
3. Melting point of drug is low than 200°C.
4. An adequate solubility in lipid and water is necessary for better penetration of drug (1mg/ml).

**Design of transdermal delivery system**

Drug dissolved or dispersed in an inner polymer matrix. It is a basic components of any transdermal delivery system that provide support and platform for drug release

1. **Matrix**
2. **Reservoir**
1. **Matrix**: It is also known as monolithic. It is a inner polymer matrix binds with the drug and controls it’s release from device.

2. **Reservoir**: It is also known as membrane. The polymer matrix does not control drug release.

**Reference**


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