Chapter-07

AN INTRODUCTION TO TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

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INTRODUCTION

The skin is the largest organ of the human body, on an average consists 10% of the body mass and covered nearly $2m^2$ of the body surface area (**Figure 7.1**). It regulates number of important functions includes protection against external physical, chemical and biological assailants, as well as prevention of excess water loss from the body and plays a vital role in thermoregulation. Skin gives the largest interface between the human body and the external environment and its most important functions is to regulate what enters the body via the skin, as well as what exits. Skin provides a barrier to water loss and pathogens. It also protects against diverse forms of trauma which may be due to ultraviolet radiations. It helps to enhance the metabolic functions as well as synthesizing vitamin D. Skin is composed of three layers that are epidermis, the dermis, and the subcutaneous tissue (**Figure 7.2**).

LAYERS OF HUMAN SKIN

Epidermis*:* Epidermis is the outer layer of the skin that defines the stratified squamous epithelium, consists of keratinocytes in the progressive stages of differentiation. It is also known as protective layer. The average thickness of the layer is 0.1mm. It is the avascular layer, having no blood vessels. It has rigid and patterned surface that can see clearly on the fingertips. Commonly the epidermis layer divided into five sub-layers, they are as follows (**Figure 7.3**):

Dermis: This layer is the thick, fibrous, filamentous layer beneath the epidermis. It contains the epidermally derived appendages, fibroblasts, macrophages, and mast cells. It helps the membrane to cover the organs underneath and protect them from damage. Dermis composed of nerves and blood vessels and one living cell type: fibroblasts that produce the fibrous material.

Hypodermis: Also known as the subcutaneous layer, directly below the dermis and serves to connect the skin to underlying fibrous tissue of bones and muscles. It holds the fat tissues and acts as a support membrane for both epidermal and dermal layer of skin. It has its own importance in transdermal drug delivery.

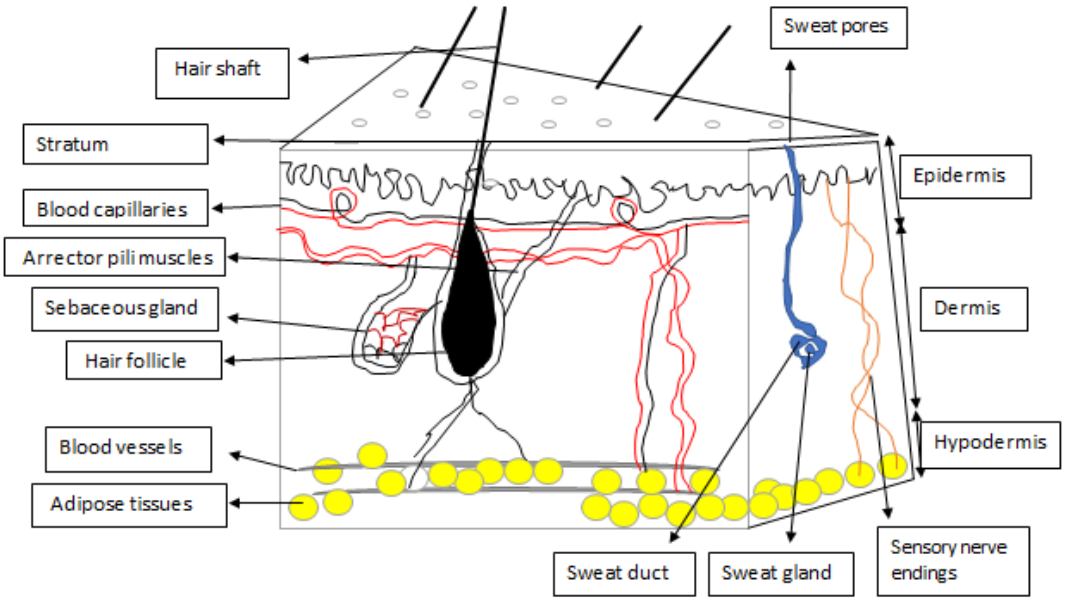

Figure 7.1: Structure of Human Skin

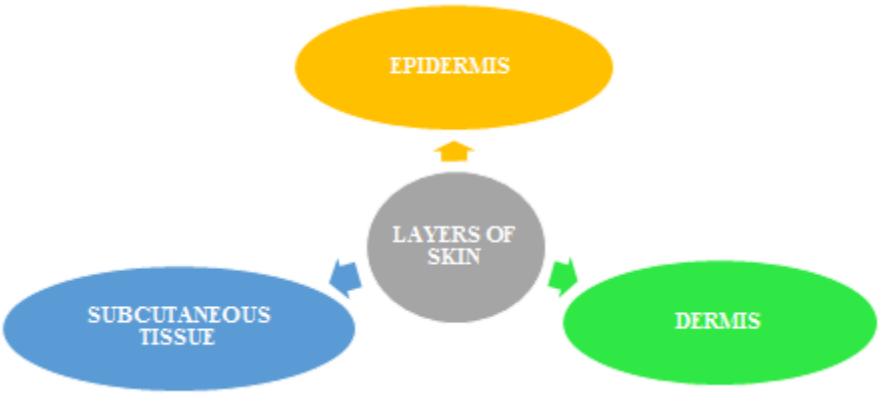

Figure 7.2: Layers of Skin

Drug Penetration Pathway: In the epidermis layer and the appendages of skin the drugs are penetrate through the skin using the method of diffusion. Drug can be penetrated by three pathways such as transcellular route, paracellular lipid route and transappendgeal route (**Figure 7.3**).

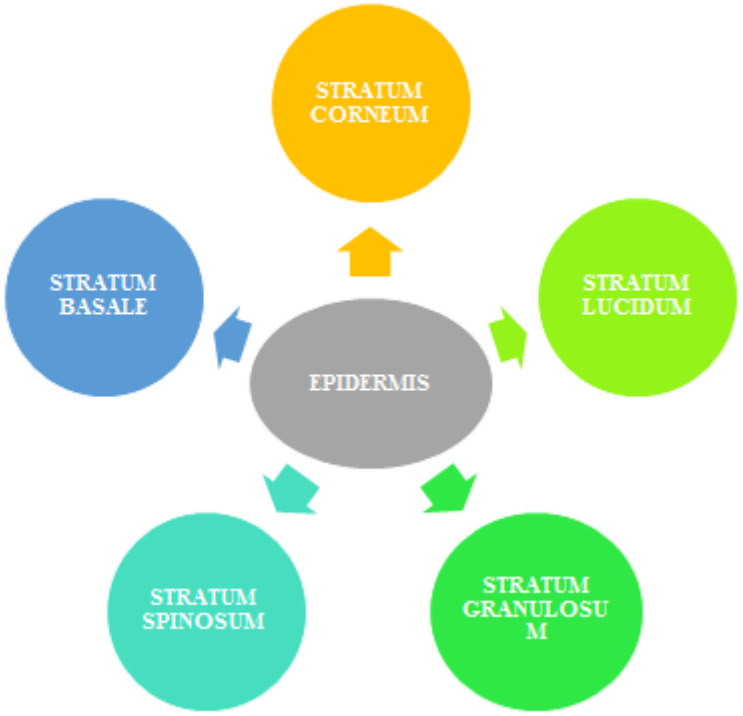

Figure 7.3: Layers of Epidermis

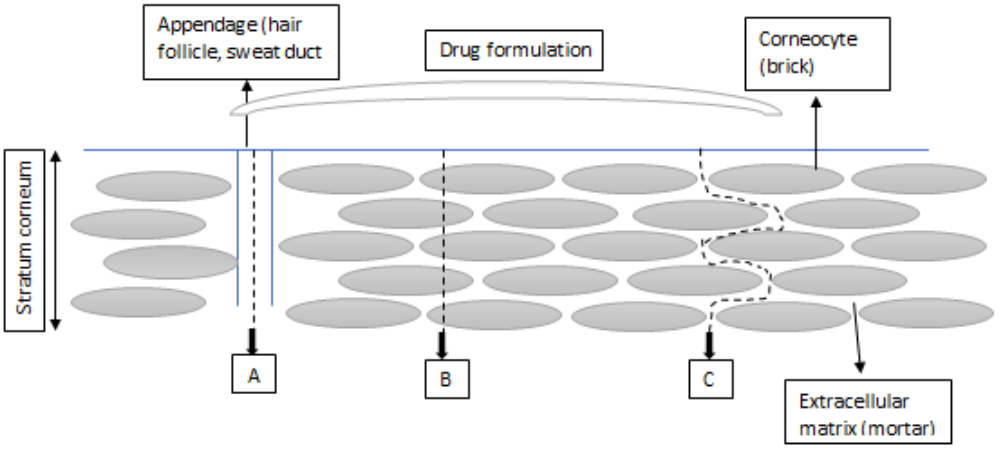

Figure 7.4: Drug Penetration Pathways

(a) The appendageal route, (b) The transcellular route, and (c) The tortuous extracellular route

Transcellular route: In the transcellular route, the drug crosses the skin by directly passing through both phospholipid membranes and the cytoplasm of the dead keratinocytes which constitute the stratum corneum. To cross this pathway, drug molecules should partition into cell membranes at the apical side to enter the cytoplasmic domain. After that the drug molecules partition into the other cell's membrane at the basolateral side for the access to the systemic circulation. These pathways are for the penetration of small (<500Da) and the moderately lipophilic (log p=1-3) molecules. Hence, the penetration of the highly lipophilic and large molecules is limited through the stratum corneum.

Paracellular route: It is the most common pathway for the penetration of the drug molecules. It allows the permeation of the hydrophilic molecules which are not able to transport through lipid membrane by the transcellular route of absorption. The drug molecules remain in the lipid moiety and stay around the keratin in such type of pathways.

Transappendgeal route: It is also called as shunt route, transport the large and water-soluble drugs molecules. Only 0.1% of the area of skin surface, comprises this route of transport. This route makes continues channel for the permeation of drug, but it hindered easily because of presence of hair follicles and sweat ducts. This route is to be mostly important for ions and large polar molecules that hardly permeate through the *stratum corneum*.

Structure of Human Skin: Skin is the largest and heaviest organ of body to provide the largest interface between the human body and the external environment. Therefore, one of its most important functions is to regulate what enters the body via the skin, as well as what exits. On an average an adult has skin surface area of about $2m^2$. It receives approximately 1/3 of all blood circulating through the body.

pH of human skin is 5.5

Anatomically the human skin consists of following:

1. **The Epidermis:** The epidermis is itself a complex multiply layered membrane, yet varies in thickness from around 0.06 mm on the eyelids to around 0.8 mm on the load-bearing palms and soles of the feet. It contains four histologically distinct layers which, from the inside to the outside, are the stratum germinativum, stratum, spinosum, stratum granulosum and the stratum corneum and fifth layer, the stratum lucidum, is sometimes described but is more usually considered to be the lower layers of the stratum corneum.

- **The stratum germinativum - It is also called as basal layer and contains following cells:**
  - **Keratinocytes:** It acts like proteinaceous anchors for these lowest layer cells.
  - **Melanocytes:** Synthesize the pigment melanin from tyrosine.
  - **Langerhans cells:** These are recognised as the major antigen-presenting cells of the skin.
  - **Merkel cells:** They have a role in cutaneous sensation
- **The Stratum Spinosum-** This layer consists of two to six rows of keratinocytes in which the keratinocytes begin to differentiate and synthesize keratins.
- **Stratum Granulosum-** In this layer the keratinocytes continue to differentiate, synthesize keratin and start to flatten. And, it also contains enzymes that begin degradation of the viable cell components such as the nuclei and organelles.
- **The Stratum Lucidum-** The Stratum Lucidum is the layer in which the cell nucleus disintegrates and increases the keratinization of the cells concomitant with further morphological changes such as cell flattening
- **Stratum Corneum –** The cells of the basal layer (stratum germinativum) divide and migrate upwards to produce the Stratum Corneum or horny layer. It is composed by layers of corneocytes, which are hexagonal flat cells without a nucleus, held together by lipids. Functions of Stratum Corneum - as protective physical, chemical barrier, retards water loss from underlying tissues, minimize UV light penetration and limit the entrance of micro-organism.
- **Constituents of Stratum Corneum-** Protein-70-80%, Lipids-10-15% with 5-10% unidentified on the basis of dry weight

2. **Dermis:** The dermis is typically 3–5 mm thick and is the major component of human skin. This layer is often viewed as essentially gelled water, which provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules. The dermis contains following:
   - **Blood vessels:** It is essential for regulation of body temperature and the vasculature is also important in wound repair.
   - **Lymphatic vessels:** It is important in regulating interstitial pressure,

facilitating immunological responses to microbial assault and for waste removal; the lymphatic vessels may also remove permeated molecules from the dermis – hence maintaining a driving force for permeation.

- **Hair follicles:** It is responsible for the presence of hairs found at different area of skin.
- **Sebaceous glands:** It secretes sebum; this is composed of free fatty acids, waxes and triglycerides which lubricate the skin surface and help to maintain the surface pH at around 5.
- **Sweat glands:** eccrine and apocrine
  - **Eccrine -** Secreting sweat, a dilute salt solution at a pH of around 5, these glands are stimulated in response to heat and emotional stress.
  - **Apocrine –** These are located near the dermo-epidermal layer but are limited to specific areas of the skin including the axillae, nipples and ano-genital regions. The lipoidal and 'milk' protein secretions are primarily responsible for imparting the odour of 'sweat'.

3. **Subcutaneous fat layer hypodermis:** It bridges the gap between the overlying dermis and the underlying body constituents. In most areas of the body this layer is relatively thick typically in the order of several millimeters. And it is absent in areas like eyelids.
4. **Function:** This layer of adipose tissue principally serves to insulate the body and to provide mechanical protection against physical shock.
5. **Epidermal enzyme systems:** Skin contains all the major enzymes responsible for the Metabolism of the topically applied compounds but the activity of these enzymes in skin has found to be less as compared to liver.

Function of Human Skin:

1. **Barrier function:** It protects the internal body organs and fluids from external influences as well as prevents loss of endogenous water and nutrients (humans are approximately 70% water) and protects against many unwanted toxic substances and pathogenic microorganisms.
2. **Temperature control:** The skin plays an essential role in the control of body temperature, which is regulated by sweating and arteriovenous thermoregulation.
3. **Defence and repair:** It provides the ability for defence and repair, such as touch sensitivity (Merkel cells, nociceptors), immunity (Langerhans cells), and protection against UV radiation (melanocytes), wound healing and cutaneous

metabolism. Repair occurs automatically through the continuous turnover of the skin but this mechanism can be accelerated via cytokine release following insult or injury.

Routes of Permeation of Topical Drug into Skin

1. **Trans Cellular-** The chemical moieties are transported through keratin packed corneocytes via portioning into and out of the cell membrane
2. **Intra Cellular-** The molecule transported around the corneocytes in the lipid rich extracellular region
3. **Transappendageal –** This transport supported by sweat glands, sebaceous glands and hair follicles

The permeation of drugs through Intra Cellular or Trans Cellular is highly dependent on their relative ability and portioning in each phase. Thus the hydrophilic and lipophilic drugs follow separate pathways to transport across the skin layers. Hence the non-ionic and lipophilic compound are easily permeated while skin appendages such as sebaceous glands, hair follicles, sweat glands act as diffusional shunt through rate limiting barrier, facilitating the absorption of topically applied (for ions and large polar molecules that struggle to cross intact Stratum Corneum). This Transappendageal absorption may be a dominant pathway of dermal permeation, in case slowly diffusing molecules.