



# THE SKIN: A PROMISING ROUTE FOR DRUG DELIVERY

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## **Abstract -**

The skin is one of the biggest and easiest organs in the human body to access. There are three primary layers that make up skin: Epidermis, Dermis, Hypodermis or subcutaneous fat layer. The primary three roles of the skin are sensibility, regulation, and protection. The term "Percutaneous absorption" refers to the process by which chemicals enter the body through the skin and enter the systemic circulations. There are three possible points of entrance into the skin: transcellular, intercellular and transfollicular routes. Several factors affect transdermal permeability like biological factors, physicochemical factors and formulation characteristics. The current review tries highlights some basics of skin and drug absorption through the skin with factors affecting the same.

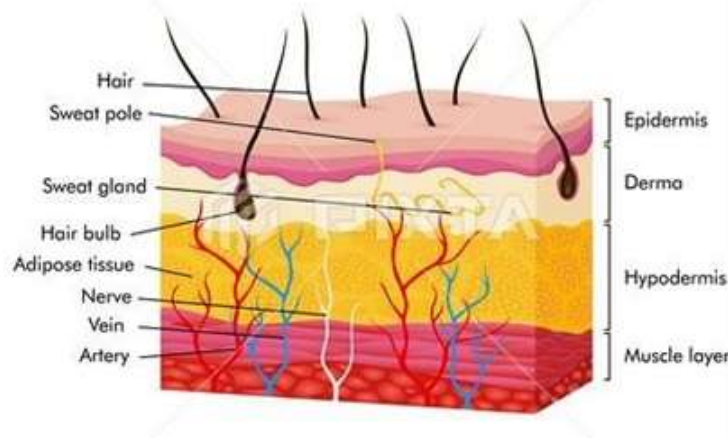
**Keywords:** Skin, Epidermis, Protection, Percutaneous Absorption.

## **Introduction**

The skin acts as a very effective barrier to prevent bacterial infections. Despite the fact that many bacteria come into touch with or live on the skin, they typically cannot cause an infection. In the event that bacterial skin infections do develop, they can impact any area of the body, no matter how big or tiny. Depending on how severe they are, they could be harmless or even deadly. Bacteria that can cause bacterial skin infections commonly enter the body through hair follicles and microscopic skin rips from wounds, burns, sunburns, animal or insect bites, and pre-existing skin diseases. Several activities, including swimming in contaminated ponds, lakes, or oceans and gardening on contaminated soil, can lead to bacterial skin infections in humans.

### **1. Skin**

The largest organ in the body, the skin, is thought to function as an exterior defensive system. It envelops the body's exterior and functions as a mechanical barrier to keep the inside of the body sealed off from the outside environment in addition to acting as a protective mechanism.<sup>1</sup> The Figure No. 1.1 shows structure of skin.



**Figure No. 1.1 Structure of skin**

Your first line of protection against infection is your skin. Different forms of protection are offered by multiple layers of skin. Your skin's epidermis, the first layer, houses your immune system.

Your body is shielded by your immune system from the influx of adjacent infectious bacteria, viruses, yeasts, parasites, and fungus. The dermis, the second layer of skin, provides nourishment and strengthens your skin's surface by supporting it. The subcutaneous zone is the skin's third and bottom layer. This layer of fat serves as a shock absorber, energy reserve, and temperature regulator. Your skin's layers cooperate to prevent skin infections.<sup>2</sup>

The skin is one of the biggest and easiest organs in the human body to access. An average person's skin weighs between 4 and 5 kg, or about 16 percent of their overall weight, and has an area of roughly 2 square meters. Furthermore, one third of the blood supply is given to it. Human skin varies in thickness, measuring 0.5 mm on the eyelids and 4 mm on the heels.<sup>3</sup>

The skin serves as a protection against chemical and physical assaults, a thermostat controlling body temperature, and a barrier against microbial invasion. Additionally, it separates the surrounding environment from the blood circulation network underneath.<sup>4</sup>

### 1.1 Anatomy of the Skin:

Anatomically stratified, the skin is a multilayered histological organ. The skin makes up 16–18% of the average body weight and serves as an anatomical barrier between the body and its surroundings. There are three primary layers that make up skin:

1. Epidermis
2. Dermis
3. Hypodermis or subcutaneous fat layer

#### Epidermis:

It is the outermost layer of skin made up of stratified squamous epithelial cells. Its thickness varies according to its location within the body. The thickest layer is found on the soles of the feet and the palms of the hands. The epidermal layer is devoid of nerve endings and blood vessels. The skin's unique integrity is derived from the incredibly intricate interlocking bridge that holds the epithelial cells together. The primary cell types that comprise the epidermis are Merkel's cells, Langerhans cells, melanocytes, and keratinocytes. The skin's epidermis aids in temperature regulation. There are 25 to 30 layers of dead cells in the epidermis outer most layer.

Main layers of the skin were depicted in Figure No. 1.3.

There are five structural layers that comprise the epidermis.

a) The stratum spinosum

b) The stratum lucidum

- c) The stratum granulosum
- d) The stratum corneum
- e) The base stratum

The outermost layer of the epidermis, known as the stratum corneum, is made up of thin, dead cells that lack nuclei and have keratin in place of protoplasm.<sup>5</sup>

Longitudinal section of skin was depicted in Figure No. 1.2

### **Dermis:**

The dermis lies directly below the epidermis layer. The dermis, which makes up most of the skin, is 1/8<sup>th</sup> of a centimeter thick. There is a range of 2000 to 3000 m in dermal thickness. It consists of an unidentified powder substance loosely attached to a fibrous protein matrix. The dermis has flexibility and extensibility due to collagen.

The fibrous tissue develops beneath the dermis and unites with the tissue that contains subcutaneous fat. The ridges that extend into the epidermis are called papillae, or the top layer of the dermis.

The following structures make up the skin's dermis:

1. A blood vessel
2. Vessel for lymph
3. Neuronal sensory end
4. The channels that connect sweat glands
5. Hair follicles, hair roots, and hairs
6. The sebaceous gland

Two zones can be distinguished structurally within the dermis: the papillary region, which is close to the epidermis, and the reticular region, which is deeper and thicker.<sup>6</sup>

### **Papillary region:**

Labile connective tissue and areolar connective tissue make up the papillary area. Projections that resemble fingers and extend toward the epidermis are referred to as "papillae". The skin on the palms, fingers, soles, and toes has friction ridges because of papillae activity on the epidermis. Because friction ridges form according to patterns that are determined by both genetics and epigenetics, each human fingerprint or footprint may be identified uniquely.

### **Reticular region:**

Deep within the papillary zone, the reticular region is frequently noticeably thicker. The elasticity, flexibility, and strength of the dermis are attributed to these protein fibers. Blood arteries, sweat glands, sebaceous glands, receptors, and hair roots are also situated in the reticular area.<sup>7</sup>

### **Hypodermis:**

It is made up of fat and elastic fibers mixed with loose, rough, white fibrous connective tissue. About thirty percent is water. It is noticeably thicker than the dermis despite variations in thickness. It is widely distributed in blood and lymphatic arteries. This layer contains the cutaneous nerves, the secretory component of the sweat gland, and the base of the hair follicle. Half of the body's fat is found in the hypodermis, where the three main cell types are adipocytes, macrophages, and fibroblasts. The body uses fat as insulation and a cushion.

### **Percutaneous absorption:**

The term "Percutaneous absorption" refers to the process by which chemicals enter the body through the skin and enter the systemic circulations. This meticulous procedure is broken down into three stages.

1. The entrance of a material into a certain stratum is known as penetration.
2. The infiltration of one layer into another is called penetration, and it differs from the preceding layer both structurally and functionally.
3. Absorption is the process by which a substance enters the bloodstream.

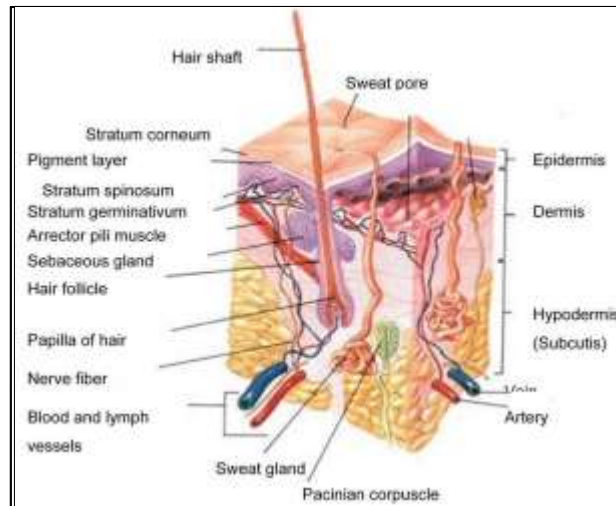


Figure No.1.2: Longitudinal section of skin<sup>8</sup>

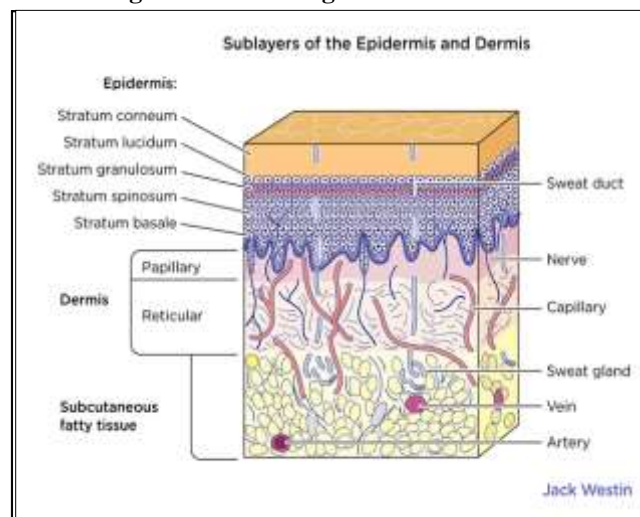


Figure No.1.3: The skin showing the main layers of the epidermis<sup>9</sup>

## 1. 2 Functions of the skin:

The primary three roles of the skin are sensibility, regulation, and protection.

### Protection:

The skin acts as a barrier, providing defense against chemical and radiation exposure, pressure changes, mechanical shock, attacks by tiny organisms, and temperature swings. Skin's main purpose is to shield the body from dangerous substances outside of it.

### Regulation:

Numerous physiological processes, including the regulation of body temperature through sweating and hair growth, are largely dependent on the skin. The skin produces vitamin D. It also acts as a store for vitamin D production.

### Sensation:

The skin's vast nerve cell network enables it to monitor and communicate changes in its surroundings. Various heat, cold, touch, and other senses have various pain receptors. Neuropathy, which is defined by a loss of feeling in the afflicted areas of the skin, is the result of damage to these nerve cells. Neuropathy patients are more likely to sustain a serious wound or have an existing wound worsen because it's possible that they won't feel pain or other emotions when hurt.<sup>10</sup>

### 1.3 Drug Penetration Routes via the Skin

Since the 1800s, scientists have been enthralled with the skin's complex structure. Hmalle and Duriau conducted early studies that identified the different levels of permeability in the skin's dermis and epidermis. In a series of investigations conducted between 1924 and 1929, Hermann Rein was the first to use the physical characteristics of isolated human skin to demonstrate that the stratum corneum and viable epidermis are separated by a barrier.<sup>11,12</sup>

To reduce the skin barrier in a way that is practically viable, safe, and efficient, a diverse group of scientists with skills in engineering, pharmaceutical sciences, physics, chemistry, biology, and medicine are working together. Over the past ten years, there have been some exciting developments in the field of better skin permeability thanks to the cooperation of professionals from different fields.<sup>13</sup>

It is commonly known that the stratum corneum serves as the primary rate-limiting barrier to molecular diffusion via the mammalian epidermis.<sup>14</sup>

The therapeutic drug's release from a topical formulation and its passage into the blood stream entail numerous procedures, such as

- (i) The formulation's internal and external disintegration
- (ii) Accessing the stratum corneum (SC), the skin's topmost layer
- (iii) Diffusion via the SC, mostly via a lipidic intercellular pathway (i.e., the rate-limiting step for most patients).
- (iv) Dispersion of the SC into the viable epidermis in water
- (v) Absorbance by the unstable capillary network, which leads to the systemic circulation in the end
- (vi) Diffusion into the higher dermis through the viable epidermis.<sup>15</sup>

There are three possible points of entrance into the skin: transcellular, intercellular and transfollicular routes. Figure No. 1.4 shows routes of drug penetration via the skin.

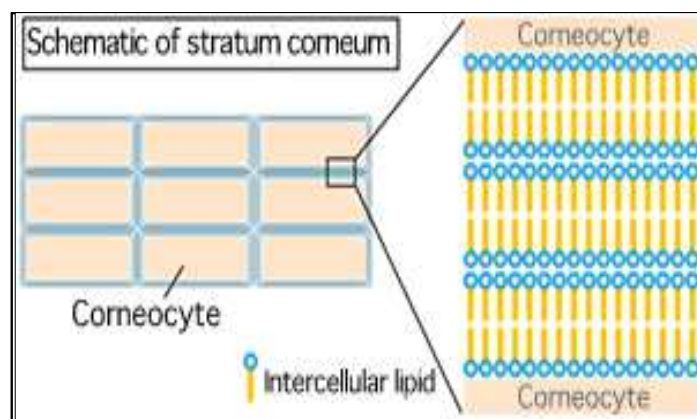


Figure No.1.4: Routes of drug penetration via the skin

#### Transfollicular Route:

There are numerous pores and duct-connected sweat, oil, and hair follicles on the skin's surface. The stratum

corneum can be crossed by drug transport through these ducts, albeit there are a variety of factors that influence this process, including the quantity and makeup of glandular secretion. Nevertheless, the trans-appendageal pathway contributes very little—it makes up only 0.1% of the overall skin surface. Drugs can pass via sebaceous gland cells, the sebaceous gland, or the follicular sheath epithelium because they possess more permeability than corneocytes and can enter the follicle without going via the protective stratum corneum. Even though the shunt route collision area is limited, absorption is aided by the abundant blood supply.

### Transcellular Route:

Erythrocytes allow drugs taken via the Transcellular route in the skin to pass. Hydrophilic medications can pass via the aqueous environment created by highlyhydrated keratin-containing cells. A lipid envelope that attaches to the interstitial lipids protects the cells. Up to 20 lipid bilayers encircle each keratinized skin cell, acting as barriers between the cells. Consequently, many partitioning and diffusion phases are needed for the transcellular route of drug diffusion. The fundamental constituent needs to first penetrate and diffuse into the morewatery corneocytes before exiting via the many lipid bilayers dividing the corneocytes and infiltrating the surrounding lipid envelope. There is significance in the relative capacity to divide into and out of each skin phase. For highly hydrophilic drugs, the transcellular pathway is the most common pathway during steady-state flux.

### Intercellular Route:

As the name implies, the medication diffuses via the intercellular channel, a continuous lipid matrix that separates the cells. This river has a barrier quality because of the complex structure that cyanobacteria have produced. This pathway requires water to travel 50 times farther than previously believed, which makes it perfect for uncharged lipophilic drugs.<sup>16</sup>

The structure of skin with three possible entry points viz 1) via the horny layer that is still intact, 2) via the sebaceous glands that are attached to the hair follicles, or 3) via the sweat glands were shown in Figure No. 1.5.

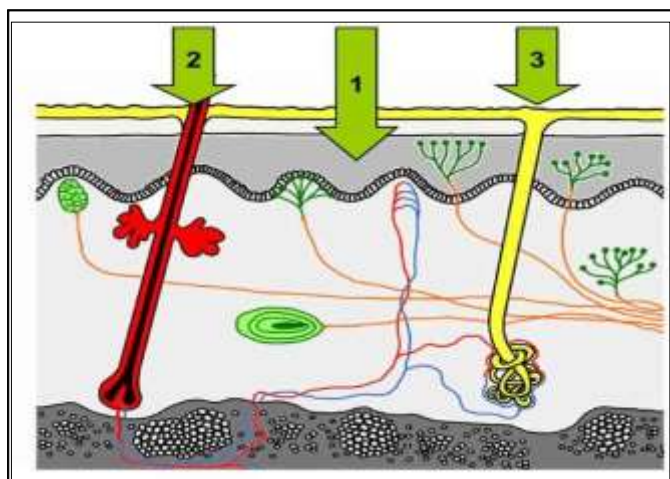


Figure No.1.5: Structure of the skin demonstrating three possible entry points: (1) via the horny layer that is still intact, (2) via the sebaceous glands that are attached to the hair follicles, or (3) via the sweat glands.

### 1.4 Factors Affecting Transdermal Permeability:

Several chemicals are kept from entering the skin by this epidermal barrier which primarily depends on their chemical and physical makeup as well as the skin's natural and altered states.<sup>17</sup>

- **Biological Factors:**

- **Skin Condition:** Solvents like methane and chlorine, acids, alkalis, harm skin cells and promote penetration. Skin conditions are altered by the patient's illness. Although a healthy skin barrier is healthier, the previously listed circumstances can affect penetration.

- **Skin Age and Site:** Children are particularly liable to substances that irritate their skin. Therefore, one factor influencing medication penetration in TDDS is skin age. Studies have indicated that rats' permeability, even once the epidermis seems histologically developed the skin to 5% aqueous triethyl phosphate solution drops quite dramatically over the seven days prior to delivery and more gradually following delivery.

- **Skin Metabolism:** Skin is the organ that breaks down chemicals, hormones, and certain medications. Skin metabolism assesses the potency of medication absorbed via the skin.

- **Species Differences:** Different species have different levels of skin keratinization, thickness, and appendage density, all of which affect penetration. It is established that skin permeability differs between animals. As a result, human skin is less porous than that of guinea pigs and rabbits, respectively. When evaluating the performance of novel candidates in lab settings, this is a factor that must be considered.<sup>18</sup>

- **Physicochemical Factors:**

- **Skin Hydration:** Soaking the skin in water causes it to swell, become softer, wrinkle, and show a noticeable increase in permeability. Hydrating the stratum corneum is one of the most essential strategies to quicken the rate at which most substances enter the skin.

- **Temperature and pH:** When the temperature drops, the diffusion coefficient lowers, which causes a substantial variation in the penetration rate of substance via human skin. As stated by the straightforward formulation of the pH-partition hypothesis, uniformly sized molecules easily cross lipid membranes.

- **Diffusion Coefficient:** The primary factor influencing a molecule's diffusional speed is the medium's state of matter. Diffusivities in skin decrease gradually and attain their minimum levels in the compacted stratum corneum matrix. The characteristics of the drug, the diffusion medium, and their interactions at constant temperature determine a drug's diffusion coefficient in a typical vehicle or in skin.

- **Drug Concentration:** Previous research has shown a connection between the concentration gradient during the barrier phase and the solvent flux. Drug permeation therefore usually obeys Fick's law. Saturation of the density is an essential condition for maximal flux in a thermodynamically stable system. The chemical potential gradient, sometimes called the activity gradient, is actually the most significant element behind diffusion, despite the fact that concentration differentials are commonly thought to serve as the driving force behind diffusion.

- **Partition Coefficient:** The partition coefficient is a crucial factor in controlling the rate at which a drug penetrates. Diffusion resistance originating primarily from the membrane means that the diffusion coefficient is very important. There may be differences between a drug and a vehicle, stratum corneum and vehicle partition coefficient, the first layer of the membrane encounters a high diffusant starting concentration.

- **Molecular Weight:** Drug molecules' sizes vary indirect proportion to how much of them penetrate the skin. Substance molecules more than 500 Daltons may cause issues with peripheral blood circulation. The smaller the absorption, the greater the molecular weight. Therefore, drug molecules shouldn't be so large that they cause issues with absorption.

## • Formulation Characteristics:

These are the different formulation characteristics:

- **Rate of Drug Release:** The physical and chemical qualities of the drug, such as its solubility in solvent, affect how easily it releases from the formulation, the speed at which it engages with skin to determine when to release it, and the carrier's affinity for the drug in the formulation.

- **Formulation Ingredients:** Different excipients and polymers employed in the formulation can change the physical and chemical properties of the medication or the skin's physiology, which can affect the drug's release or persistence through the skin.

- **Presence of Permeation Enhancers:** A number of penetration enhancers are utilized to augment the drug's skin penetration. The skin's physical, chemical, and physiological integrity are momentarily compromised by them, making it more susceptible to absorption. Chemical compounds that function chemically or physical substances that interact physically with the skin's integrity are both considered penetration enhancers.<sup>19</sup>

## Conclusion -

Skin is easily accessible for applying and removing products. The skin is increasingly seen as a promising route for drug delivery due to its accessibility and potential for non – invasive treatments. Overall, skin serves as a highly promising route for delivering both local and systemic therapies, especially with advancements in permeation enhancement technologies.

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