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A comprehensive review on skin as a route of administration

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Abstract
At two meters square meters, the skin is the biggest organ in the body. Basically, the epidermis, dermis, and hypodermis are the three separate layers that make up the skin. Protecting the body from unwelcome environmental influences is the skin's natural purpose. For a variety of reasons, the skin presents a particularly alluring substitute delivery system. The skin Ensure that the location where medication is administered is easily accessible and convenient. A desirable substitute for traditional injection for the administration of vaccines and other treatments is the use of transdermal drug delivery systems, which relate to the passage of medication via the skin. Patient acceptance and compliance with transdermal drug administration devices are good. Pharmaceutical delivery that is painless and less invasive is made possible via transdermal drug delivery system. Moreover, it prevents the first-pass action of the liver and GIT degradation, which are frequently linked to oral prescription. Because of its permeability and ability to shield the body from outside agents, the stratum corneum, the top layer of the epidermis, is primarily composed of lipids. Not only is skin noninvasive and convenient, but it also acts as a reservoir to maintain delivery over several days. In comparison to traditional drug administration methods, the transdermal route offers no benefits, such as avoiding the first pass impact. Improved patient compliance, painless medication delivery, increased bioavailability, and simple patch removal in the event of toxicity.

Keywords: Epidermis, skin, transdermal, first pass effect etc

Introduction

Parenteral and oral routes are the most popular for administering medications, with oral delivery being the usual method for small molecules. Oral administration offers benefits such as patient self-administration, portability, and pre-determined dosages [1, 2]. The most practical method of administering medication is still orally due to this reason. As stated in [3, 4], oral delivery is not used for the majority of therapeutic peptide or protein. The stomach's quick deterioration and the epithelium's size restriction caused this. The main, though not perfect, method of delivering macromolecules is by injection. A qualified administrator is also necessary due to the intrusive nature of injections, which cause discomfort and decrease patient acceptance or compliance [6].

Many disadvantages of traditional oral drug administration techniques include poor drug solubility, unfavorable p' kinetics, lack of selectivity, and substantial side effects. Numerous tactics have been devised to enhance patients' pharmacotherapy [7]. Skin provides a convenient and easily accessible site for medicine delivery [8]. Skin preparation for medicinal purposes has been used for as long as medicine has existed. There is a good description of the evolution of penetration research across time. With time, the skin has emerged as a significant drug delivery pathway with topical, regional, and systemic effects [9]. With a surface area of over 2 m^2 and making up more than 10% of the body mass, the skin is the biggest organ in the human body [10].

Transdermal drug delivery refers to the topically applied administration of medications in the form of patches at a preset and controlled rate to achieve systemic effects. For the delivery of vaccines and other medicines, transdermal drug delivery which is the administration of pharmaceuticals through the skin offers an alluring substitute to traditional injection. It provides painless, minimally intrusive drug delivery along with enhanced self-administration convenience. Additionally, it prevents GIT deterioration that overcomes the liver's first-pass impact, which is frequently linked to oral administration. The Nanoparticle, Transferosome, Ethosome, and Niosome Path [16]. When looking for transdermal medication delivery, liposomes and nanoemulsions are currently the main topics of discussion [11]. Water is the most widely utilized donor and receptor fluid because it enhances skin penetration. To make medication delivery easier, improve skin penetration substantial research on compounds such as alcohol (ethanol), fatty acids, surfactants, and dimethyl sulfide (DMSO) [18]. To improve the effectiveness of material transmission across the intact skin, numerous chemical and physical techniques have been used to date.Innovative technologies for enhancing transdermal permeability include ultrasound, electroporation, iontophoresis, and microneedles that open up the skin. For a number of reasons, the skin presents a very alluring option to oral medication administration [9]. It provides a number of benefits over oral and parenteral administration; also, skin plays a crucial function in maintaining homeostasis (avoidance of bodily dehydration) [19].

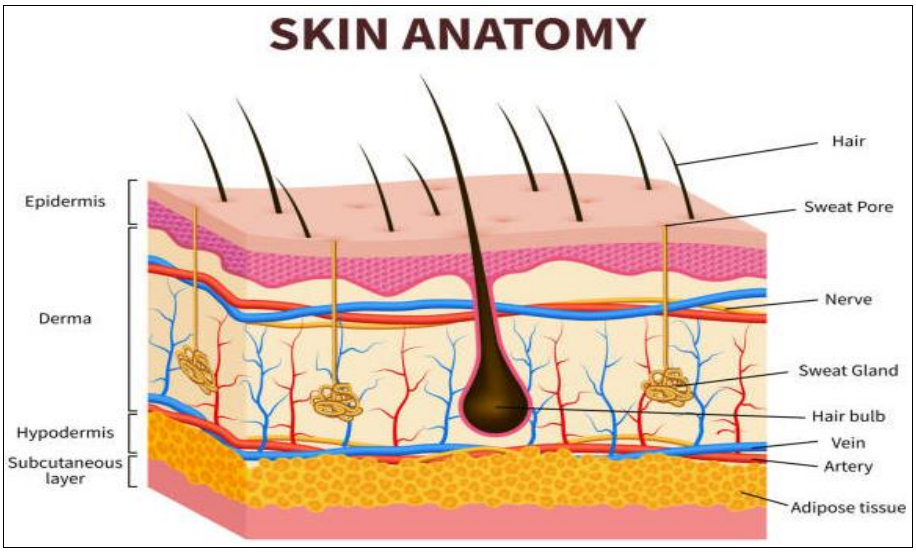

Fig 1: Structure of skin

The skin, with its surface area of approximately 2 m², is the biggest organ in the body. The skin makes up over ten percent of the body [9]. Its primary duty is to shield the organism from the environment's unwanted effects. In general, skin consists of three separate layers, which are as follows:

- Skin Layer
- Dermis
- Hypodermis

The dermis stays continuous with subcutaneous and adipose tissue, while the basement membrane divides the epidermis from the dermis. The skin's barrier function is performed by the stratum corneum, the topmost layer of the epidermis [20].

- **Epidermis**

1. **Stratum Corneum:** It is the diverse outermost layer of the epidermis and has a thickness of roughly 10–20 µm. There are roughly 15 to 25 layers of flattened, stacked, hexagonal, and cornified cells that make up the stratum corneum. Contained within the intercellular matrix. But there is a continuous structure made up of these lipid domains. Therefore, they are thought to be essential in maintaining the skin barrier, which prevents Transepidermal water loss [21].

2. **Dermis:** The dermis is composed of 70% collagenous and elastin fibers, and it is 0.1 to 0.5 cm thick. Peptide and glycosaminoglycan's, also known as acid mucopolysaccharides, are covalently bound. Chain to produce proteoglycans, the foundational molecules that support skin suppleness an enormous vascular network that supports heat exchange, immunological response, skin nourishment restoration, and thermal regulation is found within the dermis. The dermis contains embedded sweat glands and other epidermal appendages like hair follicles [21].

3. **Hypodermis:** This is the skin's lowest layer. It serves as an energy storage zone, a shock absorber, and a heat insulator. A fat cell networked in lobules and connected to the dermis by nectin and elastin fibers makes up this layer. Fibroblasts are among the other primary cells. This layer arranges fat cells in a network.by connecting collagen and elastin fibers, in lobules and connected to the dermis. Skin is roughly 2-3 mm thick overall, although the stratum corneum is roughly 10-15 um thick [21].

Skin as an Administrative Route

Skin provides a handy and easily accessible location for medicine delivery [8]. As old as medicine itself is the practice of using skin preparation for therapeutic purposes. There is a good description of the evolution of penetration research throughout history. Topical, regional, and pre-systemic effects are provided by the skin, which has grown in importance as a drug delivery vehicle throughout time [9]. The biggest organ in the human body is the skin [10].

Transdermal Drug Delivery System Definition

Transdermal drug delivery refers to the topical administration of medications in the form of patches at a regulated and preset rate, which has systemic effects. When it comes to administering vaccinations, transdermal drug delivery—which is the administration of medication through the skin—offers an alluring substitute to traditional injection [14].

Transdermal Drug Patches History

TDDS is another name for patches. It is intended to spread a therapeutically effective dosage of medication across the skin of the patient [19]. in 1970, transdermal patches were created. The FDA authorized the first TDDS patch in 1979 to treat motion sickness. Nitroglycerin patches were authorized in 1981 [20]. Many patches, such as those for clonidine, lidocaine, nicotine, testosterone, etc., are available today [21].

The Ideal Characteristics of TDDS are as Follows [22].

1. M.W. less than around 1000 Dalton
2. Up to two-year shelf life
3. The medication must not cause irritation or adverse reactions.
4. The drug's M.P. (200 0 C) should be low.
5. The drug's half-life should be brief.
6. The ideal partition coefficient is necessary for the therapeutic action of medications.

Benefits of Transdermal Drug Delivery [22].

1. Medication for self-administration.
2. Prevent the first pass effect.
3. Boost bioavailability
4. Decrease the frequency of dosing
5. Patients who are unable to take oral dosage forms can be accommodated with transdermal medication delivery as an alternate mode of administration.
6. Preserves blood levels that are steady, consistent, and under control for extended periods of time.
7. Compared to traditional therapy, a smaller daily dosage of the medication is needed.
8. Drug therapy can be quickly stopped by removing the application from the skin's surface.

Transdermal Drug Delivery System Disadvantages [22].

1. At the application site, contact dermatitis occurs in some patients.
2. An increased price.
3. Could result in allergic responses.
4. Only few strong medications are suitable for transdermal treatment.
5. Ionic medications are not suitable for transdermal treatment.
6. It is unable to provide medication in a pulsatile manner.

Transdermal Drug Delivery System Limitations [22].

1. Limited permeability of the skin.
2. Limited to powerful medications
3. Not suitable for big molecules (>500 Dalton)
4. Notable latency
5. Adhesion difficulties.
6. Disparities in the effectiveness of absorption at various skin locations.
7. The skin degrades the medication.

Drug Penetration Pathways [21]

Drugs can permeate the skin through the skin's appendages and unbroken epidermis by diffusion. Only 1% of the whole skin is made up of these skin appendages, which are sweat glands and hair follicles that create a shunt conduit across intact epidermis (all it is limited by stratum corneum) two methods:

1. The intercellular lipid pathway (between corneocytes)
2. The Trans cellular route (crossing through corneocytes) can be recognized through an unbroken barrier.

1. Intercellular Lipid Route

The stratum corneum interlamellar regions, which include linker regions, have more flexible hydrophobic chains and less organized lipids. This explains the nonplanar gaps that exist between the outer membranes of neighboring cells and crystalline lipid lamellae. The skin barrier's fluid lipids play a critical role in the Trans epidermal diffusion of lipidic and amphiphilic molecules by creating the necessary gaps for their insertion and migration through the lipid layers that separate cells. In order to achieve a systemic effect, the hydrophilic molecules diffuse before 2. Transport through the skin, primarily "laterally" along the surfaces of the less common water-filled interlamellar spaces or through such volumes; polar molecules can also use the free space between a lamella and a corneocyte outer membrane for the same purpose" [9].

2. Transdermal Lipid Route

Intracellular macromolecular matrix within the SC abounds in keratin, which does not contribute directly to the skin diffusive barrier but supports mechanical stability and thus intactness of the SC. Transcellular diffusion is practically unimportant for transdermal drug transport "The narrow aqueous transepidermal pathways have been observed using confocal laser scanning microscopy. Here, regions of poor cellular and intercellular lipid packing coincide with wrinkles on skin surface and are simultaneously the sites of lowest skin resistance to the transport of hydrophilic entities. This lowest-resistance pathway leads between clusters of corneocytes at the locations where such cellular groups show no lateral overlap [9].

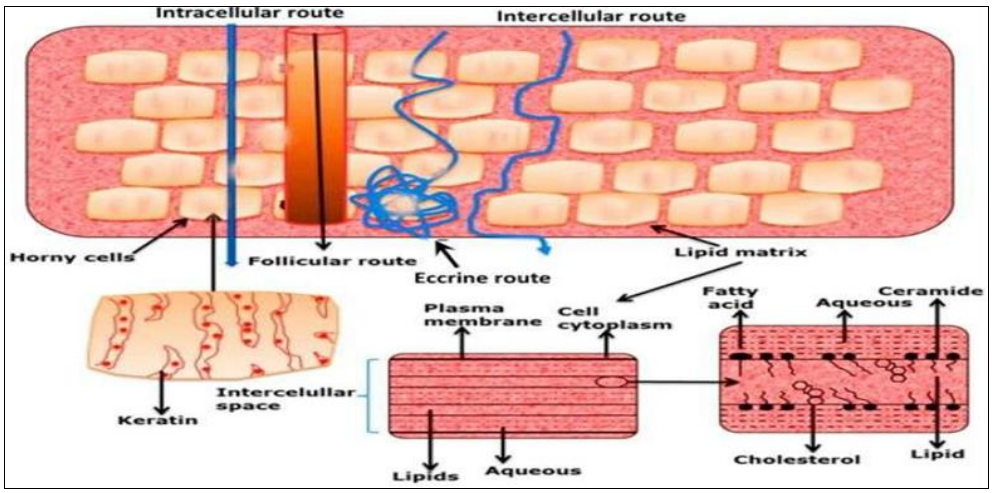

Fig 2: Routes of penetration of drug

Affectors on Tdds [23]

A. Factors related to biology

- **Skin Age**

Younger and adult skin is more permeable than that of elderly people. The study claims that because the child's skin has a larger surface area relative to body weight, it exhibits a hazardous effect. Some compounds have significant adverse effects, such as hexachlorophene, boric acid, and strong steroids.

- **Skin difference**

Disparities between species Different animals have different levels of skin appendage density, thickness, and keratinization, which can affect how well TDDS drugs penetrate the skin.

- **Skin condition**

Drugs with low acidity can easily pass through the skin since the skin has a weak acidity. Fast drug molecule penetration occurs once the top layer of skin cells is damaged by methanol, chloroform, and other solvents.

- **Blood flow**

One element influencing the absorption of medications for TDDS is the circulation of peripheral blood. The rapid absorption of TDDS is caused by an increase in blood flow.

B. Physiochemical Factor

- **Skin Temperature**

Skin temperature affects the diffusion coefficient, which measures how well drugs absorb. Low diffusion coefficients brought on by low temperatures result in reduced TDDS absorption.

- **Skin PH**

The skin's lipid membrane is only readily permeable to unionized medication molecules. Fast drug absorption occurs when the skin's pH matches that of the medication.

- **Drug molecular size**

Penetration of the larger molecular medication is quite challenging. In comparison to big drugs, small-molecule drugs penetrate more quickly.

- **Partition coefficient**

A significant physiological component influencing drug absorption is the partition coefficient. Good drug absorption requires the optimal partition coefficient; pharmaceuticals with a lower partition coefficient value shouldn't be taken. Indicates a reduced TDDS absorption rate.

- **Skin Hydration**

When our skin is wet with water, its permeability increases. Skin cells enlarge and become mushy in hydrated conditions. Drug molecules are easily able to cross the skin's membrane under certain circumstances. TDDS is formulated with certain moisturizing ingredients, such as humectant.

C. Environmental Factor

- **Air Pollution**

The drug release may slow down if an accumulation of air pollutants forms on the skin's surface. The presence of different chemicals in the air can react with the drug and lessen its efficiency, and germs in the air can easily interfere with skin health.

- **Cold season**

Dry and itchy skin is a result of the chilly weather. Since the water level of the skin is so low at that point, moisturizing agents can both promote the drug's penetration into the skin and improve its drying impact.

- **Sunlight**

Straight sunlight shining on the skin's surface thins the blood vessel wall. Internal bleeding happens when exposed to more sunshine. Drug absorption may change at that point. Increased pigmentation also decreases the body's absorption of drugs.

Permeation Enhancer

Drug candidates reach higher therapeutic levels when permeation enhancers are utilized to increase the permeability of the stratum corneum (SC) layer. Permeation enhancers facilitate interactions between the stratum corneum's structural elements, such as proteins and fats. Uplift permeability results from chemically changing the skin barrier function, which is where the change in the protein and lipid packaging of SC is caused by permeation enhancers.

Tdds Permeability Enhancers Example [24]

1. Solvents: methanol, ethanol, and dimethyl sulfoxide
2. Anionic surfactant is sodium lauryl sulfate.
3. Aleuronic F68 and F128 are non-ionic surfactants
4. Essential oils, including menthol, lemon oil, cardamom, and caraway

Conclusion

In conclusion, this comprehensive review on skin as a route of administration gives information regarding anatomy of skin, advantages, ideal characteristics of transdermal drug delivery and permeability enhancer. The Skin is the largest organ of the body with a surface area about 2 m^2. Skin Offer an accessible and convenient site for the administration of medication. Transdermal drug delivery systems refer to the delivery of drugs across the skin, is an attractive alternative to conventional Injection for delivery of vaccine and other therapeutics. Transdermal Drug delivery systems has good acceptance and compliance by patient. TDDS offer minimally invasive, painless delivery of drugs with added ease of self-administration. It also avoids degradation in GIT overcoming first pass effect of liver, which are commonly associated with oral administration.

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