Transdermal Drug Delivery system

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ABSTRACT

Transdermal medication delivery is the application of drug on the skin surface so that it can penetrate through the skin and enters the systemic circulation. Drug transport through the skin is made possible by the skin's 10–70 hair follicles and 200–250 sweat ducts per centimeter. It was acknowledged as a drug delivery method many years ago, although drug penetration is hampered by the stratum corneum of the skin. Transdermal route has a number of advantages over conventional drug delivery routes such as avoidance of first pass effect, enhanced bioavailability, patient compliance, steady state plasma drug level, painless delivery of drugs, ease of application and easy removal of patch in case of toxicity. A transdermal patch is put to the skin, stays in place for a predetermined amount of time—hours, days, or weeks—and releases the medication during that time. There are three ways that drugs can be absorbed through the skin: trans appendageal, intracellular, and intercellular. After being released from the transdermal patch, the medication must travel through several layers of the skin. Permeation enhancing strategies can help overcome the stratum corneum's barrier to drug penetration, which is the main issue with transdermal medication delivery. The backing membrane, medication reservoir, adhesive layer, release control membrane, liner, and other components make up a transdermal patch.

KEY WORD: TDDS, Patch, Transdermal, Drug, Skin.

1. INTRODUCTION

One particularly efficient method of administering medication is by cutaneous delivery. Due to its many advantages over alternative drug delivery methods, the transdermal drug delivery system (TDDS) is a novel strategy in the pharmaceutical industry for medication administration (1). Larger doses and longer regimens are needed for conventional drug delivery system formulations to have therapeutic effects, and long-term regimens may result in significant side effects and eventually low patient compliance (2). An organism's skin is thought to be its first line of defines, shielding it from environmental viruses, toxic substances, and harmful infections (3). The upper strata (15 µm) of the skin contain surrounded keratinocytes and many layers of lipid matrix that serve as a barrier (4). Additionally, the skin is the primary barrier that prevents the majority of medications from entering (5).The Polaris Market Research research claims that (6). By 2032, the global TDS market is expected to have grown from its 2023 valuation of $27.42 billion to $40.01 billion. According to a new Persistence Market Research report, the market for transdermal microneedles (MNs) is predicted to grow to $10.9 billion by 2033 (7).

2. Anatomy and physiology of the skin layer

The best design and development of reliable methods for drug delivery systems might result from an understanding of the anatomy and physiology of the skin. The greatest portion of the human body is the skin. About one-third of the blood that flows through the body is contained within the 20 square feet of human skin (8). Additionally, the skin's high melanin content shields the body from the sun's ultraviolet (UV) rays (9). The skin's ability to maintain homeostasis through the thermoregulation system is another crucial function (10). One such thermoregulation process carried out by human skin is sweating (11).

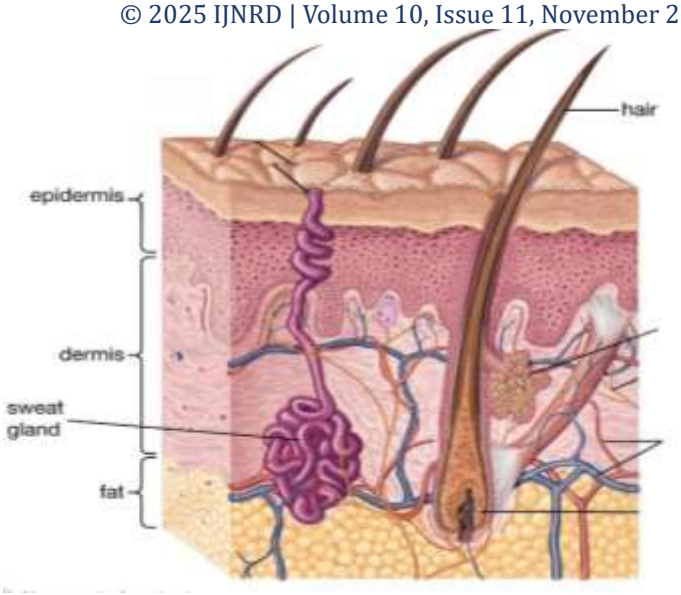

Figure 1. Skin Anatomy

2.1 Epidermis

The thickness of the multilayered epidermis varies from 0.8 mm on the palms and soles to 0.06 mm on the eyelids, depending on the size and number of cell layers (12). corneum stratum. This is the skin's outermost layer, sometimes referred to as the horny layer. When dry, it is around 10 mm thick, but when fully hydrated, it swells to several times this thickness. Ten to twenty-five layers of corneocytes—dead, keratinised cells are present (13). Although it is somewhat impermeable, it is flexible. The main obstacle to drug penetration is the stratum corneum. It is possible to model the horny layer's architecture as a wall-like structure (14). The keratinised cells in this concept act as lipid "mortar" encased in protein "bricks." There are several bilayers of lipids.

It again have 5 different sub layers:-

I. Stratum Corneum
II. Stratum Lucidum
III. Stratum Granulasum
IV. Stratum Spinosum
V. Stratum Basale

2.2 Dermis

The dermis is a layer that is three to five millimeters thick and is made up of a matrix of connective tissue that includes nerves, blood vessels, and lymph vessels. The cutaneous blood supply plays a crucial role in controlling body temperature (15). Additionally, it removes waste and pollutants from the skin while supplying nutrients and oxygen (16). The majority of molecules that penetrate the skin barrier find a sink in capillaries, which extend to within 0.2 mm of the skin's surface. The majority of molecules that penetrate the skin barrier find a sink in capillaries, which extend to within 0.2 mm of the skin's surface. Thus, a permeates dermal concentration is kept extremely low by the blood supply, and the ensuing concentration differential across the epidermis provides the necessary concentration gradient for transdermal permeation (17).

2.3 Hypodermis

The dermis and epidermis are supported by the hypodermis, or subcutaneous fat tissue. It acts as a place to store fat. This layer offers mechanical protection, nutritional support, and aids in temperature regulation. It may have sensory pressure organs and transport the main blood vessels and nerves to the skin. While just penetration through the stratum corneum is necessary for topical drug administration, and drug retention in skin layers is encouraged, transdermal drug delivery requires the drug to pass through all three of these layers and enter the systemic circulation (18).

3. Function of Skin

- Protect body from harm Condition UV radiation pathogen & gives a skin color.
- Supports & protect skin and deeper layer assist in thermoregulation.
- Remove toxin & provide nutrient, O2 skin.
- Regulate body temperature.
- Provide nutritional & membrane support store fat.

3.1 permeation of drug through skin

Addition of transdermal patch on skin

↓

Release of drug from the patch

↓

Diffusion of drug through Stratum Corneum

↓

Then diffuse the epidermis then into the dermis

↓

Migration towards affected area

4. Principle of Transdermal Permeation

In the past, skin was thought to be an impermeable protective barrier, however further research demonstrated the skin's usefulness as a systemic delivery route (19).

Because barely a millimeter of tissue separates the skin's surface from the underlying capillary network, the skin is the body's most intensive and easily accessible organ. The following are the many stages that go into moving a medication from a patch into the systemic circulation: (20).

- Drug diffusion from the drug reservoir to the membrane that controls the pace.
- Drug diffusion from the rate-limiting membrane to the stratum corneum.
- Penetration through living epidermis and absorption by the stratum corneum.
- Drug absorption through the dermal papillary layer's capillary network.
- Impact on the intended organ.

5. kinetics of Transdermal Permeation

The successful development of transdermal medicinal systems depends on an understanding of skin penetration kinetics. The following procedures are involved in a drug's transdermal penetration (21):

i. Stratum corneum sorption
ii. drug penetration through the skin.
iii. medication absorption through the dermal papillary layer's capillary network.

Only if the medicine has specific physiochemical characteristics will this penetration be feasible. The following formula provides the rate of penetration through the skin:

$$dQ/dt = Ps\,(Cd - Cr)$$

Where,

Cd and Cr represent the skin penetrant concentrations in the donor compartment, stratum corneum surface, and the receiver compartment, or body, respectively.

Ps is the skin tissue's total permeability coefficient to the penetrant. The connection provides this permeability coefficient.

$$Ps = Dss\ Ks/\ hs$$

Where,

Dss is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues

hs is the total thickness of skin tissues,

Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum. (22)

A skin penetrant's coefficient Ps can be regarded as constant. The aforementioned equation makes it evident that only when Cd >> Cr. that is, when the drug concentration at the stratum corneum surface Cd is constantly and significantly higher than the drug concentration in the body Cr. can a constant rate of drug permeation be achieved. The formula turns into:

$$dQ\ /dt = Ps\ Cd$$

As long as the amount of Cd stays relatively constant during the skin penetration process, the rate of skin penetration is constant. The drug should be released from the device at a rate Rr, which is either constant or higher than the rate of skin uptake Ra, i.e., Rr >> Ra, in order to maintain a constant Cd. The drug concentration on the skin's surface is kept at a level equivalent to or higher than the drug's equilibrium solubility in the stratum corneum Cs because Rr >> Ra, i.e. Cd>>Cs. Consequently, the equation yields a maximum rate of skin penetration.

$$(dQ/dt)m = Ps\ Cs$$

The maximal rate of skin penetration is dependent on the skin permeability coefficient (Ps) and equilibrium solubility in the stratum corneum (Cs), as can be observed from the above equation. Thus, skin penetration seems to be restricted to the stratum corneum**.**

6. Factor Affecting Transdermal

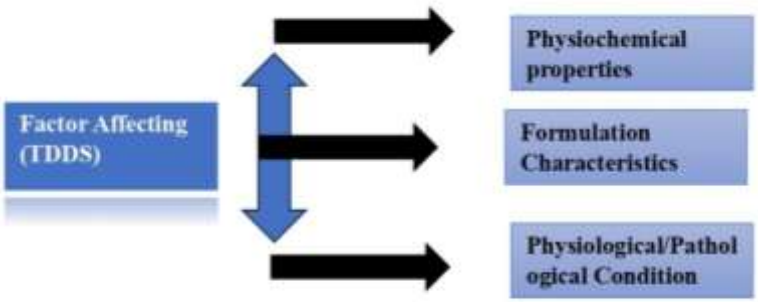

Figure 2. Factor Affecting TDDS

6.1 Physiochemical Properties of drug

a. Size of Drug molecules and molecular weight

Molecular weight and drug absorption are negatively correlated, with small molecules penetrating more quickly than large ones (23).

b. Partition coefficient and solubility

For the best transdermal permeability, the lipid/water partition coefficient must typically be 1 or higher. b. It can be changed chemically without changing the drug's pharmacological action (24).

c. Drug concentration

Passive diffusion controls how medications are absorbed through the skin. The drug travels from high concentration to low concentration in accordance with the concentration gradient. Therefore, the rate of drug diffusion across the skin is determined by the concentration of the medication in the formulation put over the skin. The permeability will increase with concentration.

d. PH condition

Acidic and basic medication absorption rates are mostly influenced by pH, while the unaltered version of the drug has a higher penetrating capacity. Ionizable species transport from aqueous solutions exhibits a significant pH dependence (25).

6.2 Formulation Characteristics

a. Release rate of the drug

The carrier's affinity for the drug in the formulation and the drug's physiochemical characteristics, such as its solubility in a solvent and its interfacial partitioning from the formulation to the skin, determine how quickly the drug is released from the formulation (26).

b. Presence of permeation enhance

To improve a drug's penetration into the skin, various types of permeation enhancers are employed. These briefly modify the skin's integrity (physicochemical and physiological alteration) and allow absorption through the skin's pores. Permeation enhancers can be either chemical substances that work chemically or physical substances that interact physically with the integrity of the skin.

6.3 Physiological and Pathological Condition of the skin

a. Hydration skin

The stratum corneum of the skin swells as a result of hydration, which also gives the skin some mobility. Additionally, hydration improves partitioning from the vehicle to the membrane and permeant solubility. Therefore, medication molecules can easily penetrate the moist skin (27). Hydrated skin increases permeability and dry skin decreases.

b. Skin temperature

The fluidization of lipids and vasodilation of the blood vessels that are in contact with the skin cause the percutaneous absorption of the drug to increase when the skin's temperature rises; consequently, an increase in blood flow to the skin increases the absorption through the skin. Increases temperature increases blood flow and diffusion rate

c. Skin age

Younger skin is more porous than older skin. Children are especially susceptible to pollutants being absorbed via their skin. Therefore, one of the factors influencing medication penetration in TDDS is skin age.

d. Blood flow

Greater blood circulation enhances absorption an drug removal from site.

Advantage

- Drug breakdown in acidic and basic environments is avoided by chemically hastening the GI environment.
- There is no GI distress, and unlike the oral route, this route is unaffected by factors like gastric emptying, intestinal motility, and transit time.
- Therefore, a smaller dose is required to avoid considerable presystemic metabolism (degradation in the GIT or by the liver) (28).
- Enables the efficient use of medications with brief biological half-lives

- Decreased variability within and between patients (29).
- Easy to use.
- Reducing frequency of dosing.
- Optimize the blood concentration-time profile to improve therapeutic efficacy and minimize fluctuations (fast spikes in low and high blood levels) (30).
- Improving patient compliance and lowering the frequency of doses

Disadvantage

- Hydrophilic drug are can be use.
- Large doses, such as more than 10 mg daily, are challenging to deliver.
- Ionic medications cause issues.
- Substances larger than 500 Dalton are not appropriate for TDDS (31).
- High concentrations of drugs might irritate the skin (32).
- Achieving a high plasma medication concentration is challenging.
- Patients experience discomfort due to long-term adherence.
- Medications having a high or extremely low partition coefficient are unable to enter the systemic circulation (33).

7. Approaches to design Transdermal Patch:-

A) Polymer membrane permeation control TDDS –

In this type of TDDS drug reservoir is place between impermeable backing layer. The drug release only through the rate controlling membrane. It can be micropores or nor porous. Drug can be in the form of solution, suspension, gel.

The release rate of the drug from this type system can be control variable polymer composition permeability coefficient or thickness of rate controlling membrane. A constant release rate of drug the release rate is given by

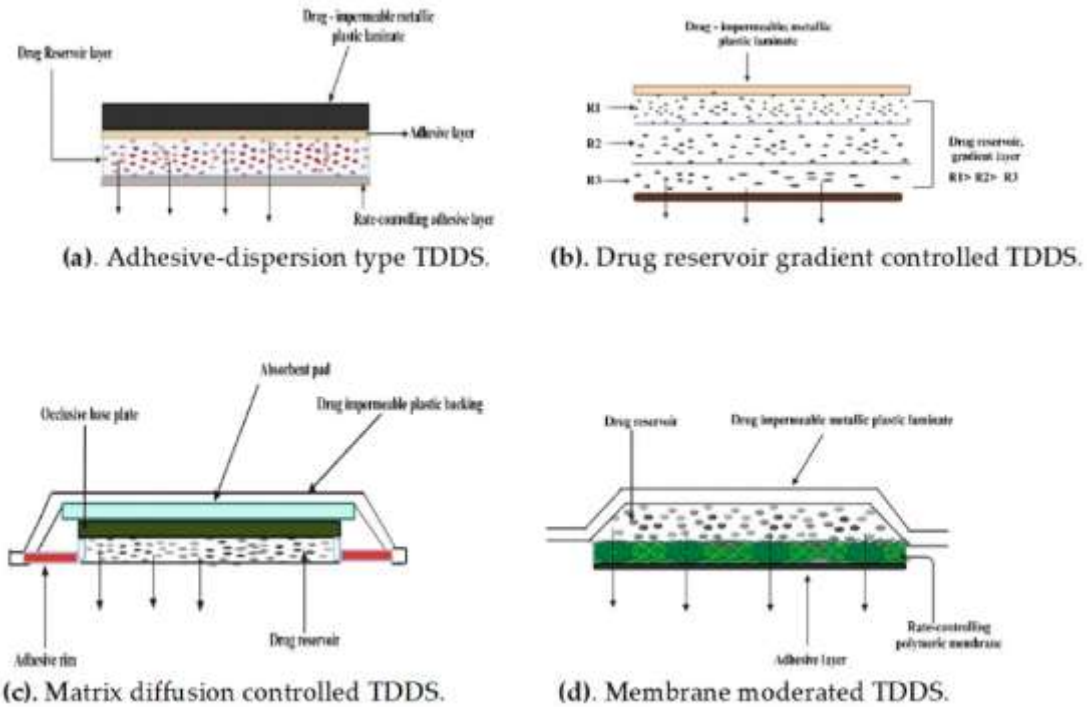

Figure 3. Approaches to design Transdermal Patch

$$(dQ)/(dt) = [\, K\ m/r\ K\ a/m\ D\ a\ D\ m\ K\ m/r\ D\ m\ h\ a + K\ a/m\ D\ a\ h\ m\,]\ C\ R$$

Where,

dQ/dt Rate of drug diffuse

cR Conc. Of drug reservoir

Ka/m Partition coefficient of drug from reservoir to membrane

Km/r Diffusion coefficient in membrane

Dm Diffusion coefficient in adhesive

ha Thickness in adhesive layer

hm Thickness of membrane

B). Adhesive Dispersion type TDDS-

In this type drug reservoir is property by directly dispersing the drug in adhesive.

The drug reservoir is covered by a non-medication rate controlling polymers of constant thickness to produced on adhesive diffusion controlling drug delivery system. The rate of drug release is given as

$$\frac{DQ}{Qt} = Kan\frac{Da}{ha}$$

C) Polymer matrix diffusion controlling TDDS-

Drug reservoir is prepared by dispensing the drug homogeneously in hydrophilic& lipophilic polymer matrix. The resultant medication polymer is the molecule on medicated disc of defined surface thickness

$$\frac{dQ}{dt} = (Acp.Dp/2t)$$

D). Micro Reservoirs type TDDS-

A combination of reservoir & matrix diffusion type DDS. A drug reservoir is formed by first suspending solid drug in solution of water soluble polymer. This drug suspension in homogeneous dispersion in lyophilic polymer by high energy dispersion techniques. This form the microscopic pore of drug reservoir which are supportive in aculasive pad & are thermodynamically constable stabilization by cross linking polymer chain in insitu using cross linking agent. It can further coated with a layer of bio compatible polymer to improve drug release.

7.1. Transdermal patch is used when (34)**.**

- When a patient requests an alternative drug delivery method because they are unable to take oral medication due to dysphagia and have unbearable side effects, such as constipation (35).
- where dependable administration could enhance pain management. Patients with cognitive impairment or those who are unable to self-medicate with their analgesia for various reasons may find this helpful.
- It can create synergistic benefits when combined with other enhancement techniques.

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