

## Recent Advancement on TDDS (Transdermal Drug Delivery System)

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www.jrasb.com || Vol. 1 No. 5 (2022): December Issue

Received: 28-10-2022

Revised: 18-11-2022

Accepted: 28-11-2022

### ABSTRACT

The creation of a transdermal drug delivery system (TDDS) has been one of the most sophisticated and innovative approaches to drug delivery. The transdermal drug delivery system has attracted considerable attention because of its many potential advantages, including better patient compliance, avoidance of gastrointestinal disturbances, hepatic first-pass metabolism, and sustained delivery of drugs to provide steady plasma profiles, particularly for drugs with short half-lives, reduction in systemic side effects and enhanced therapeutic efficacy. This review article covers a brief outline of the transdermal drug delivery system; Highlight the restrictions, drawbacks, shortcomings, and Versatile benefits of delivery systems.

**Keywords-** In vivo as well as in vitro release analysis, a mechanism for transdermal drugs, Transdermal patch, permeation enhancers, skin, TDDS.

## I. INTRODUCTION

Drug delivery system (DDS) is a generic term for a series of physicochemical technologies that can control delivery and release of pharmacologically active substances into cells, tissues and organs, such that these active substances could exert optimal effects [1, 2]. In other words, DDS covers the routes of administration and drug formulations that efficiently deliver the drug to maximize therapeutic efficacy while minimizing any side effect [3,4,5]. Depending on the delivery route, there are many types of administration modalities, such as oral administration, transdermal administration, lung inhalation, mucosal administration, and intravenous injection. Among them, the transdermal drug delivery system (TDDS) represents an attractive approach.

TDDS has become one of the most widely investigated routes of noninvasive drug delivery into the body through the skin, unlike conventionally used direct administration routes that make use of needle-based

injections. TDDS has significantly influenced the delivery of various therapeutic agents, especially in pain management, hormonal therapy, and treatment of diseases of the cardiovascular and central nervous systems [6,7,8,9]. TDDS does not involve passage through the gastrointestinal tract; therefore, there is no loss due to first-pass metabolism, and drugs can be delivered without interference from pH, enzymes, and intestinal bacteria. In addition, TDDS can be used to control drug release according to usage restrictions, thereby contributing to the high persistence of this method. Most importantly, because TDDS is a noninvasive administration method and involves minimal pain and burden on the patient, drugs can be safely and conveniently administered to children or the elderly [10,11,12]. Transdermal drug delivery systems are typically delivered drugs in the form of patches or semisolids that distribute the drug for systemic side effects at a fixed or regulated rate.

## II. REQUIRED

- Drugs that perform comprehensive first-pass metabolism may be developed as a transdermal drug delivery system.
- Drugs that are volatile in the gastrointestinal setting are being developed as a transdermal drug delivery system.
- If the medication has significant adverse effects, if intervention is taken locally.

The purpose of any drug delivery system is to ensure that the therapeutic quantity of the drug is adequately processed in the body and that the optimal dosage of the drug is retained. Drugs are administered through different routes, such as oral, maternal, nasal, transdermal, rectal, intravaginal, ocular, etc. (Bhanja et.al.2012) Among them. The oral route is more popular and widespread, although this drug delivery system might have some disadvantages, such as first-pass metabolism, drug degradation in the gastrointestinal system due to pH, enzyme, etc. The most popular methods of delivery systems being oral and topical form, also with bulk of drug products normally administered orally. (Anselmo et.al.2014) The transdermal preparation pathway is always known to be one of the probable routes, this path offers many advantages, such as improving patient compliance in long-term treatment, bypassing the first-pass metabolism, ensuring medication distribution, maintaining a stable and prolonged plasma drug level, minimizing heterogeneity in pre and inpatient. (Han et.al 2015) Moreover, it is possible to delay or avoid treatment if appropriate. However, the highly ordered composition of the stratum corneum makes it an efficient drug authorizing inhibitor that must be changed, if improperly penetrated medications are to be administered. The number of drug molecules appropriate for transdermal delivery is increased with drugs that improve chemical penetration. The type of transdermal patch dose is user-friendly, comfortable, and painless, typically enhancing patients' compliance. Physical strategies (iontophoresis, electroporation, sonophoresis, or microneedle) or the need for additives for structural stimulation, along with organic solvent, emulsifiers, adipose cells & esters, are two main approaches to raising the transdermal transit rate. Transdermal patches were planned to keep the substance from spreading from the surface of the pad. The most popular routes of drug distribution are parenteral or intranasal pathways. The primary mode of administration macromolecules via injection (Anselmo et.al.2014; Han et.al.2015) which is not without restriction, like the Invasive design of pain-provoking injections and lower patient acceptance/compliance, in addition to the necessity for administration by a qualified administrator. (Schoellhammer et.al.2014). Rationally, the traditional route of drug delivery has certain inherent

drawbacks that can be theoretically solved via new drug delivery technologies, including the transdermal drug delivery technique (Kermode et.al.2007) Transdermal Scope, which was developed in 1980, was the first transdermal drug delivery device to produce scopolamine avoidance of motion sickness. A transdermal interface is a machine moderated by membranes. A micro porous film of polypropylene is the membrane here device. Drug reservoir is a medical medication solution in a combination of mineral oil and polysialic acid.

## III. SKIN STRUCTURE

Skin is the most effective or readily accessible part of the human body. The alternative name of skin is integumentary system structure having the largest body organ, approximately 16 percent of the overall adult body weight required from 1.5 to 2 m in area. It occupies about 1.73 m<sup>2</sup> for average adults and receives one-third of the blood flowing through the body at any given time. The skin is the dynamic organ that enables substances to migrate through and across the skin. The skin's permeation (chemicals, toxicants, and drugs) is much slower than most body biological membranes. Drugs with low biological half-life as well as a clinical effect of less than 10 mg per day are best materials for transdermal drug delivery. However, skin inflammation or interaction dermatitis that may be exacerbated by the drug, as such as the requirement for excipient and permeation enhancers, may be a drawback of transdermal drug delivery. Often the boundary structure of the skin varies. (Semalty et.al.2007) Microscopically, the skin consists of two primary layers: the epidermis and the dermis (0.1 and 1mm in thickness). The appendageal arrangement included structural features of the skin: the hair follicles, nails, and sweat glands. The stratum corneum is a brick wall, with fully separated coenocytes forming the bricks enclosed in the intercellular lipids. On average, the stratum corneum consists of around 20 cell layers with a thickness of 0.5µm in thickness. ( Ramteke et.al.2012) Skin is the main route of transdermal substance or preparation administration formed by three layers of epidermis, dermis, hypodermis, or subcutaneous membrane. (Ramteke et.al.2012) The skin acts as a physical, chemical & microbial barrier to transdermal transport. It is separated into three layers, the subcutaneous tissue, the dermis and the epidermis. The outermost bilayer of the skin, referred to as the stratum corneum, is normally the main shield for movement across the body. However, the skin allows lipophilic low - molecular - weight medications to be absorbed passively amounts that could be adequate to induce systemic or local impact. (Semalty et.al 2007)

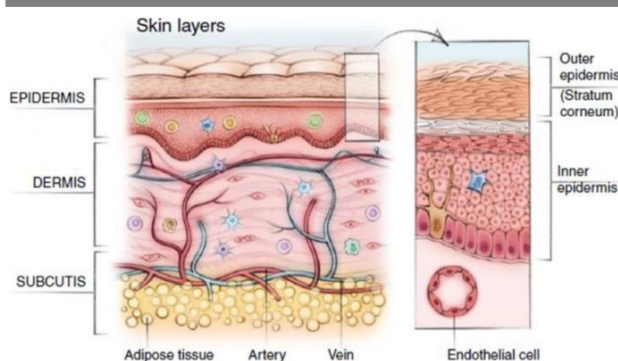


Figure 1: Anatomy of the Skin

### Epidermis

An outer layer seems to be an essential tissue barrier consisting of stratified epithelium and proliferating super basal keratinocytes with basal differentiation. The thickness of the palm of the hands and soles of the foot varies by around 0.8 mm. It consists of multi-layered epithelial cell regions and the epidermal is often denoted as the viable epidermis the stratum corneum's lower layers. The epidermis cellular content consists predominantly of keratinocytes.

### Dermis

The dermis is the second most essential skin layer consisting of collagen and elastin or protein fibers and can provide the skin with strength and durability. The dermis resides between the epidermis and the subcutaneous layer. The dermis is a network of nerves, blood, and lymph vessels closely related across the basement membrane to the epidermis. In the dermis layer, muscles, macrophages, and lymphatic channels are also present.

### Hypodermis

The subcutaneous layer is also identified as the layer located on the bottom of the adipose and bonding tissue. It serves as a supportive cushion for the outer skin. It is the layer of contacts, such as muscle or bone, between the skin and the body's underlying tissues. Therefore, defense from better reasoning, heat, including structural or structural able for heat transfer or neuronal impulses of the skin is the primary function of the hypodermis. Along with fibroblasts and other large cells, the hypodermis comprises macrophages and fat neurons that constitute about 50 % of fat mass.

## IV. TRANSDERMAL DRUG DELIVERY SYSTEM FORMULATION

### Basic Components:

- Polymer matrix
- Drugs
- Permeation Enhancers
- Pressure Adhesives Sensitive
- Backing Laminates
- Release Liner
- Other things, such as plasticizers and solvents

### Polymer matrix:

Polymers are also the heart of TDDS and regulate the release of drugs from the system. The polymer matrix can be primed by dispersing the drug in a liquid or solid-state. The polymer is essential to the Intramuscular Drug Delivery device. Based on a biodegradable polymer, natural or synthetic -state, the polymer matrix could be, prepared by dispersing the drug. The polymer used for the targeted delivery of injectable drugs must have good stability and consistency with the drug and other system elements and provide them efficient drug release in the secure positioning device. The polymers used for transdermal drug delivery systems are as follows

**Synthetic elastomers:** such as polybutadiene, polyisobutylene, silicone rubber, Butyl rubber, hydrin rubber, and so on.

**Synthetic polymers:** Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, and so on.

**Natural polymer:** cellulose derivatives, waxes, gum, glycol 17 polyethylene, eudragits18, etc.

### Drugs

The medicine should be selected with due caution to build a Transdermal Drug Delivery System successfully. A pharmacological and toxicological characteristic of medication is essential for further thought. The selection of transdermal delivery drugs depends on the drug's optimal physicochemical properties and biological properties for transdermal delivery. (Kaur et.al.2012)

### Physicochemical Characteristics:

- Medicine will have to be less than about 1000 Daltons in molecular weight.
- A drug must have the ability with both lipophilic and hydrophilic levels.
- The characteristics of separation were not conducive to the efficient delivery of medications while in the skin.
- A drug may have a medium melting point.

### Products in Biology:

- With a typical dosage of around a few mg/day, the medication must be potent.
- The half-life of the drug ( $t_{1/2}$ ) is meant to be short.
- The drug does not cause allergic or cutaneous inflammation.
- Acceptable candidates for transdermal delivery are drugs that diminish but are discarded by renal first-pass in the gastrointestinal system.
- It under transdermal distribution close to zero drug release, tolerance of achieving optimum drug must not establish.

### Permeation Enhancers

Such compounds were important for enhancing the permeability of the stratum corneum by connecting with the functional portion of the stratum corneum. Improve stratum corneum permeation to achieve the optimum drug. Such compounds helped raise a stratum skin surface's conductivity to reach high therapeutic

levels of the substance. They change the stratum corneum's protein and lipid packing, thus chemically changing the inhibitory roles to improve permeability. Dimethyl sulfoxide, propylene, etc. are other examples. (Karande et.al. 2005)

**Pressure Adhesives Sensitive**

The transdermal drug delivery system of the drug mechanism is tightly affixed towards the skin by a pressure-sensitive adhesive (PSA). It must meet with no almost as much application of skin friction, be vigorously or indefinitely fatigued & apply a tight gripping pressure. Also, it can be separated from a flat surface without leaving the required residue. The adhesive must be skin-friendly and should be removable without leaving physical trauma or residue, creating minimal pain or sensation. Moreover, sample amounts must be able to dissolve them. (Walters et.al 1997)

**Backing Laminate**

The supporting material needs to be flexible. The polyolefin, polyester, and elastomers materials widely used are transparent, manufacturing output stained or metabolizable materials, including limited polyethylene cope with skin motions more effectively and have more excellent adhesion than materials like polyester that are less compliant. (Patel et.al. 2010)

**Release Liner**

A release liner consists of a base layer that can be no- occlusive and a silicon and or Teflon release coating layer. Polyester foil and metalized laminate are other fabrics used for TDDS release liners. (Ubaidulla et.al.2010)

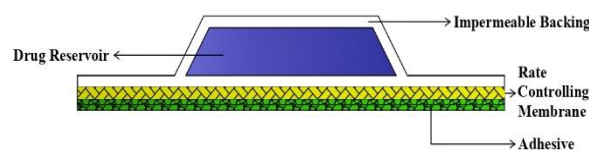
**Additional Excipients:**

Different solvents are used to prepare the drugstore, like chloroform, methanol, acetone, isopropanol, or dichloromethane. (Khatun et.al. 2004)

**V. DEVELOPING TECHNOLOGY FOR TRANSDERMAL DRUG DELIVERY SYSTEM**

**1. Regulated TDDS –Polymer Membrane Permeation - Controlled**

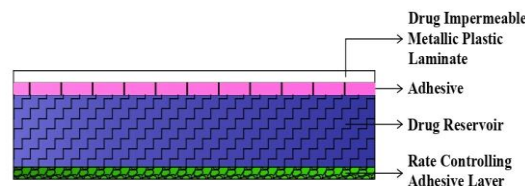
There is an embedded drug reservoir in the impermeable matrix and a rate-controlled backup sheet into the system. The substance is emitted only through rate-controlled membranes, which Might be flexible or nonporous microscopic. A substance may be a mixture, flow, or liquid with the drug's reservoir compartment or distributed Hypo allergic polymer additive in a solid matrix phase, a thin film of medication, may be added to an outer surface of the polymer membrane. The amount of drug production is being created while changing the composition of such a drug delivery system. The polymer layout, coefficient of permeability, and the thickness of the membrane regulated by the rate. (Dipen et.al.2010).



**Figure 2: TDDS-Controlled Polymer Membrane Permeation**

**2. Regulated Adhesive Diffusion Controlled TDDS**

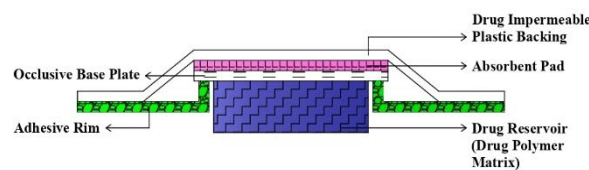
The reservoir of a drug is created by spreading the drug into an elastic substance instead of extending or impermeable supporting surface via solvent evaporation or melting to disperse. The drug delivery surface of a prescribed medication silicone additive is being procured by a non-drug fluid surface that influences the constant thickness to create the adhesive diffusion that controls the delivery mechanism of the drug. (Dipen et.al 2010)



**Figure 3: Regulated TDDS Adhesive Diffusion Controlled**

**3. Matrix Diffusion Controlled TDDS**

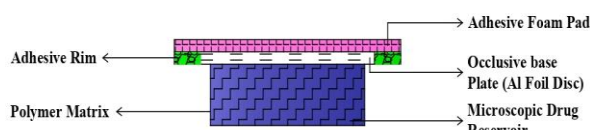
In a simulation hydrophilic or lipophilic of polymers, a pure compound substance is distributed. The above silicone disk, which includes drugs, is then fixed in a pocket made of a drug impermeable backing sheet on an exclusive base plate. It spreads around the perimeter to create a strip of the adhesive rim rather than applying that additive to both the reservoir's medication surface. (Dipen et.al.2010)



**Figure4: Matrix Diffusion Controlled TDDS**

**4. Micro reservoir Controlled TDDS**

It is a mixture of a reservoir and a matrix dispersion device. It is a product inside an organic compound with a water-based polymer solution uniformly inside a hydrophilic matrix to shape a mixture of both the reservoir or substrate diffusion framework. The volatile thermal distribution of a miniature area of a protective film quickly passes through the solvent in situ, a therapeutic ring mounted throughout the middle but covered by either an in situ membrane via an adhesive rim. (Dipen et.al.2010)



**Figure 5: Microreservoir controlled TDDS**

### **Variables Affecting Transdermal Drug Delivery Mechanism:**

- Not all medical drugs are sufficient for transdermal distribution. The physiological or mechanical characteristics of a product, along with its permeation coefficients or depression continuous (PKA) particle size bioavailability, its existence of a carrier system, skin status are those factors that play a role in percutaneous absorption.
- A significant element is opioid concentration. Generally, with an increase in doses, the volume for substance venous ingested every element to specific heat improves over time.
- The wider field of application for more drugs is ingested.
- The substance can infiltrate with such a particle size between 100 to 800 or ample membrane or sustained-release lipid, causing the skin to have aqueous solubility.
- It is assumed that a drug's optimal molecular weight for transdermal drug delivery is 400 or less.
- Skin hydration typically facilitates TDDs functions as a film with occlusive moist where the venous penetration, which does not flow, raises the skin's hydration.
- When adding the TDDS on a forum with such a horny fine coating, percutaneous absorption tends to be more significant that was more than a thickened layer.
- Much matter how long this same medication development could even remain fairly in skin contact, a much more significant amount of the drug's permeability. (Jain.et.al.2007)

### **Analysis of In-Vivo Transdermal Distribution of Medications:**

Analysis should be performed by the use of the transdermal drug delivery system,

- Animals Models
- Human studies
- Biophysical Designs

#### **Animal Models**

The animal in vivo models is chosen because human research takes ample time and energy. Mouse, rodent, guinea pig, bunny, Mouse without fur, rat without hair, dog, pig, pig, donkey, squeaker, monkey, monkey rhesus, chimpanzee, etc. Other animals used for in vivo research include: Similar tests have been performed. The experiments include the best predictor of the system's behavior being studied to determine the animal models are in humans. (Arunachalam et.al.2010)

#### **Human studies**

The final stage of transdermal system creation includes the pharmacokinetic and pharmacodynamic

selection. In vivo, human subject assessment can include relevant detail with limited subject exposure within a reasonable period. The marking of human models for in vivo assessment of emissions after topical application of the drug involves calculating percutaneous absorption using an indirect radioactivity measurement process. <sup>14</sup>C is widely used for assessing absorption by radiolabeling. Various refinements have been made to this system; these are described (Aggarwal et.al.2009).

#### **1. Technique of the Reservoir**

This approach includes the analysis of a straightforward, low risk of skin-to-skin (radiolabel) compound, followed by tape stripping of the stratum corneum and the compound substance is examined mostly in stated that the "stratum, this is possible from measure a predicted volume of the drug entered for such a long period from this study (Mitrogotri et.al.1996).

#### **2. Technique of Mass Equilibrium**

This approach requires the application site protected by a special chamber, replacing the chamber with a new one given interval of time. The platform is subject to these timely washouts. Radio labelling procedures are used and research is carried out on the cells, washes and faces, and patient's urine. This approach's advantages include maintaining a large-scale equilibrium between the dosage and emission levels applied, so doing this with the substrate rinse measurements for forecast water solubility to predict percutaneous absorption.

#### **Biophysical Designs**

The literature has defined models focused on the equation of steady-state mass equilibrium, the Second rule in fiction for both the method, alternatives to stratum corneum or functional epithelium, and also regular activation energy. It can be inferred that many strategies have been put forward for in vivo assessment of transdermal structures that need more space for refining. Skin blockage with age, skin metabolism, in vivo functioning to improve penetration, etc. (Arunachalam et.al.2010)

#### **Transdermal Patch Applications**

- The transdermal patch best seller nicotine in controlled doses to better discourage cigarette smoking is the bestselling transdermal patch in the United States.( jain et.al.2002)
- They are providing round-the-clock relief with extreme pain. Fentanyl (marketed as Duragesic) and Buprenorphine are often prescribed as patches for the two prescription medications (marketed as BuTrans).
- To relieve menopausal complications as well as postmenopausal osteoporosis, estrogens patches are often administered. Some hormone transmission transdermal patches contain contraception patches (marketed as Ortho EVRA or EVRA).
- For sublingual capsules, nitroglycerin patches are also used; modifications are recommended for angina therapy. (chien et.al.1992)

- Clonidine is used in transdermal patch form as an antihypertensive drug. For selegiline, a transdermal form of an antidepressant, MAOI: the first transdermal production department.

- The Attention Deficit Hyperactivity Disorder transdermal transmission agent (ADHD). (jain et.al.1997)

**Properties of The Transdermal Drugs Delivery Mechanism Are:**

- Optimum coefficient of partition
- Two-year shelf life
- High drug freezing point <200° c
- The scale of patch <40cm square
- PH should be between 5-99 of the saturated solution

**Items for Transdermal Industry**

There has been a significant upward trend in demand for transdermal drugs, which is expected and begin to growing kinds of products only for. (Mitragotri et.al.2001). The transdermal drug delivery system offers real clinical benefits to patients around the world. As many as 35 transdermal drug delivery systems. Items were already permitted to sell in the US, including 16 major compounds were allowed in this worldwide application for vesicular drug delivery system goods. (Mitragotri et.al.1996)

**VI. ADVANCEMENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM**

The adhesive technology drug has been preferred passive transdermal delivery method. Two fields of formulation analysis based on adhesives and excipients. Adhesive study focused on customising the adhesive to enhance skin adhesion over the wear cycle, enhancing medication durability or solubility, minimising latency time and growing delivery speeds. Over the past 10 to 15 years, a rich study area has focused on developing transdermal technologies that improve the skin barrier (primarily through Alteration) of the skin. Usage of mechanical energy to improve opioid use. The application of mechanical energy to improve the movement of drugs (Stratum corneum) or an increase in drug molecule energy. Transdermal "accessible' strategies Identify iontophoresis (Using electromagnetic field and low voltage move Skin activated medicines), electrification (that utilizes) small vibrates in electricity produce Sonophoresis (using short-wavelength ultrasound power for both the persistent ionic glands through your skin) interrupt A nuclear radiation as well as the stratum cornea. (Mitragotri et.al.2001)

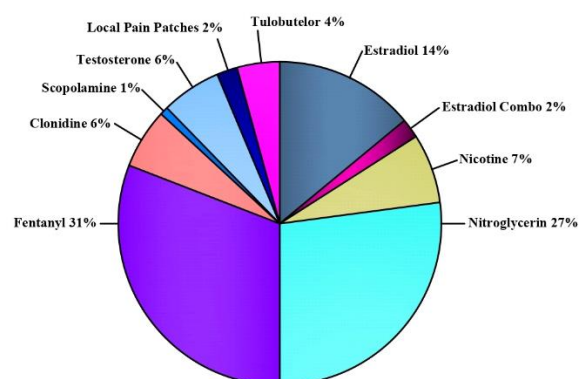


Figure 6: Sales of Global TDDS Products by Segment

**VII. ADVANTAGES OF THE TRANSDERMAL DRUG DELIVERY**

- In patients who are polymedicated, transdermal drug delivery can be beneficial.
- Oral dosing and parenteral administration have a continuous drug release rate to prevent peaks and valleys associated with transdermal drug delivery and retain drug concentration levels for a prolonged time.
- Reducing heterogeneity in intra and inter-patient with more straightforward treatment.
- The more significant advantage is increased compliance in unconscious, indigested, or constipated patients.
- Elimination of systemic metabolism leads to a reduction in the volume of drugs given, leading to a decrease in outcomes and is thus better in patients who are hepato-compromised.
- Fruitful, mainly where sustained therapy is necessary, for example in the treatment of chronic pain. Hormone substitution and reduction in treatment for smoking.
- At any time the drug input is removed by removing the transdermal system can be eliminated. (Arunachalam et.al.2010)

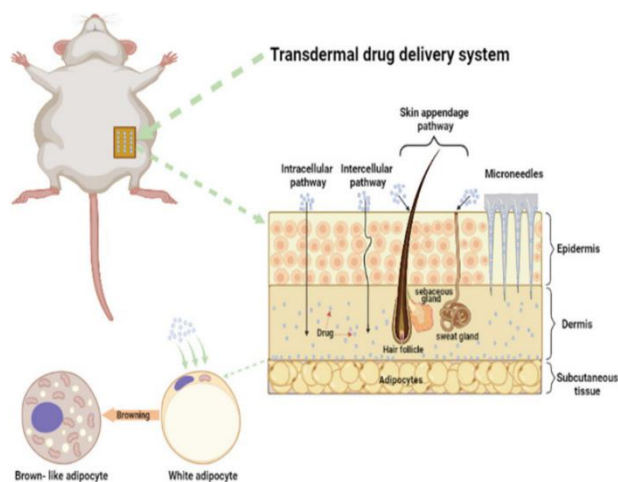
**Limitations for Transdermal Drug Delivery System Selection:-**

- Via this path, various types of drugs should not be administered; the medication must include specific suitable Physico-chemical properties.
- Not yet ideal for drugs with elevated plasma levels.
- Not yet appropriate for medicine that cause inflammation of the skin and get in communication. Skin irritation, well not acceptable large molecular strength products.
- Not yet appropriate for medications that are metabolized through the passage
- For a significant range of drugs.
- The transdermal route should not be used, since the skin is a powerful drug penetration buffer. It can only be given at a reduced dose.

**TDDS: Uses as Anti-Obesity agents**

People generally have a low level of awareness of obesity, and they think that there is no need for drug treatment or understand the side effects of drugs, resulting in resistance to long-term medication. Therefore, the development of external anti-obesity drugs with low side effects may have more extensive research and application prospects. TDDS has the advantages of low dose, high bioavailability, low side effects, and easy application, so it is very suitable for delivering anti-obesity drugs. The high targeting of TDDS also seems to show great potential for the reduction of local subcutaneous/ In order to improve the role of agents in anti-obesity and avoid the adverse effects caused by defects in the drug delivery system, some scholars began to study the transdermal delivery of anti-obesity agents.

TDDS for managing obesity is illustrated in Figure 7 CL316243, a  $\beta_3$ -adrenoceptor agonist, has been shown to promote the browning of adipocytes in obese mice. FDA has approved Mirabegron, a  $\beta_3$ -adrenoceptor agonist for the treatment of overactive bladder. However, systemic use of the drug can lead to an increase in heart rate and blood pressure. Thyroid hormone T3 can promote fat browning and increase thermogenesis. Human and animal experiments have shown that T3 or T4 can lead to weight loss. The reason why thyroid hormone has not been approved as an anti-obesity drug is that long-term systemic use of T3 can lead to hyperthyroidism and cardiovascular disease. Peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) is not only the main gene regulating fatty acid storage and glucose metabolism, but also one of the main transcriptional regulators of BAT production. ROSI is a kind of PPAR $\gamma$  activator, which can enhance the sensitivity of skeletal muscle, liver, and AT to insulin, and it has been used to treat diabetics. Recent studies have shown that it also has the effect of browning. However, taking ROSI also has a potential risk of cardiovascular disease

**Figure 7: Management of Obesity with TDDS****VIII. CONCLUSION**

The current review article may conclude that with improved bioavailability, the transdermal patch can prolong medication release by several hours and prevent the first-pass effect. This article aimed to provide useful knowledge on transdermal drugs. Supply networks. Transdermal drug delivery mechanisms are being used as secure and convenient medicines. Drug delivery systems have been in place since 1981. Several medications were being developed in the form of TDDS, like Hormonal treatment, a huge selection of analgesics, heart disease medications, GI avoidance, and first-time metabolism. TDDS is a plausible practical implementation as the next phase of the drug delivery system although, thanks to its great benefits, several trials were currently ongoing to introduce newer medications into the system. Future advances in TDDS are expected to concentrate on improved regulation of clinical therapies as well as the ongoing extension of medications and treatments to be used. As the next generation of drug delivery technologies: TDDS is a reasonable practical implementation.

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