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A BRIEF REVIEW ON THE TRANSDERMAL DRUG DELIVERY SYSTEM

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Abstract

Recently, the most widely used conventional dosage form such as tablets capsules, and injections but due to some cases we are preferable to choose the transdermal drug delivery system (TDDS) because conventional oral dosage forms undergo first-pass metabolism. Delivery of drugs through the skin has been always a challenging area for research due to barrier properties exhibited by the outermost layer the of skin stratum corneum. Nowadays different types of skin penetration enhancement techniques are used for increasing the penetration. These types of techniques also increase bioavailability. The patient has more preferable to choose this type of drug delivery system because it has more advantages than the conventional dosage form. This article discusses the anatomy and physiology of skin and its drug penetration capacity. Polymers used in transdermal drug delivery of different types of TDDS and marketed

Keywords: transdermal drug delivery, skin, polymers, technique

Introduction

Transdermal drug delivery systems (TDDS), also known as “patches,” are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin. To deliver a therapeutically effective agent through the human skin for systemic effects, the skin's comprehensive morphological, biophysical, and physicochemical properties are to be considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first-pass metabolism respectively.[1] Transdermal delivery provides controlled, constant administration of the drug, allows continuous drug input with short biological half-lives, and eliminates pulsed entry into the systemic circulation, which often causes undesirable side effects. Thus various forms of novel drug delivery systems such as transdermal drug delivery systems, controlled released systems, and transdermal drug delivery are limited to hepatic first-pass metabolism, enhancement of therapeutics efficiency, and maintenance of steady plasma level of drug. The first Transderm -SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel, particularly by sea. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine, and through the patient’s clinical response to the administered drug therapy.[2]

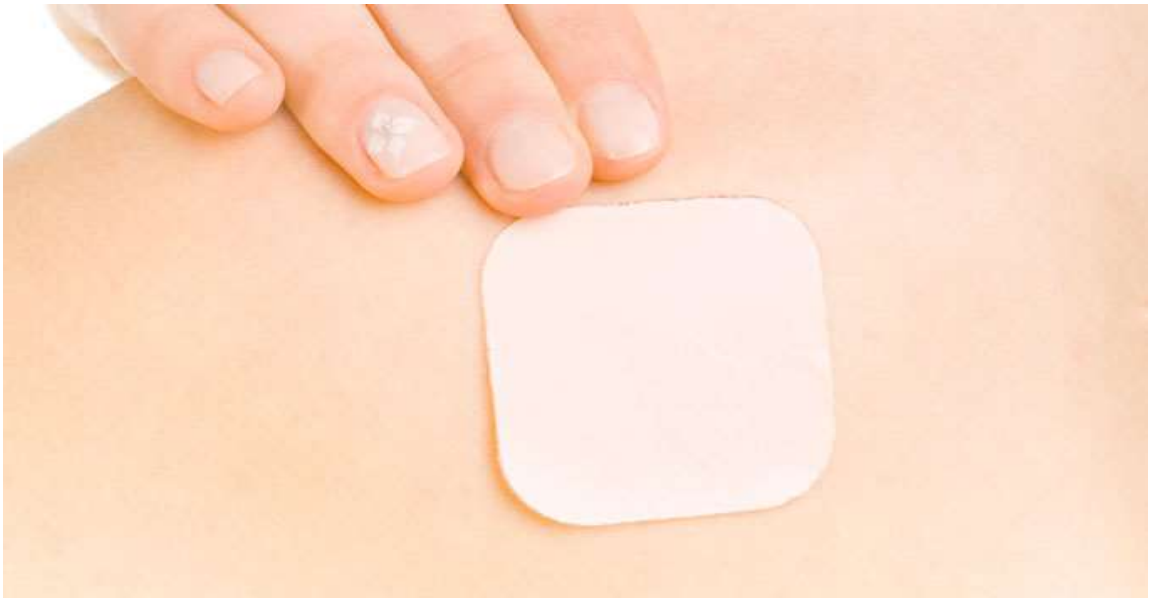

Figure no.1 Transdermal patch

Skin structure

Skin is the most effective or readily accessible part of the human body. The alternative name of the skin is the 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^2 for average adults and receives one-third of the blood flowing through the body at any given time. The skin dynamic organ 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 a low biological half-life and less than 10 mg clinical effect per day is the best material for transdermal drug delivery. However, skin inflammation or interaction dermatitis that may be exacerbated by the drug, 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.[3] Microscopically, they consist of two primary layers: the epidermis and dermis (0.1 and 1mm in thickness). The appendageal arrangement includes 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 0.5um in thickness.[4] Skin is the main route of transdermal substance or preparation administration formed by three epidermis, dermis hypodermis, or subcutaneous membrane layers. 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 in amounts that could be adequate to induce systemic or local impact.

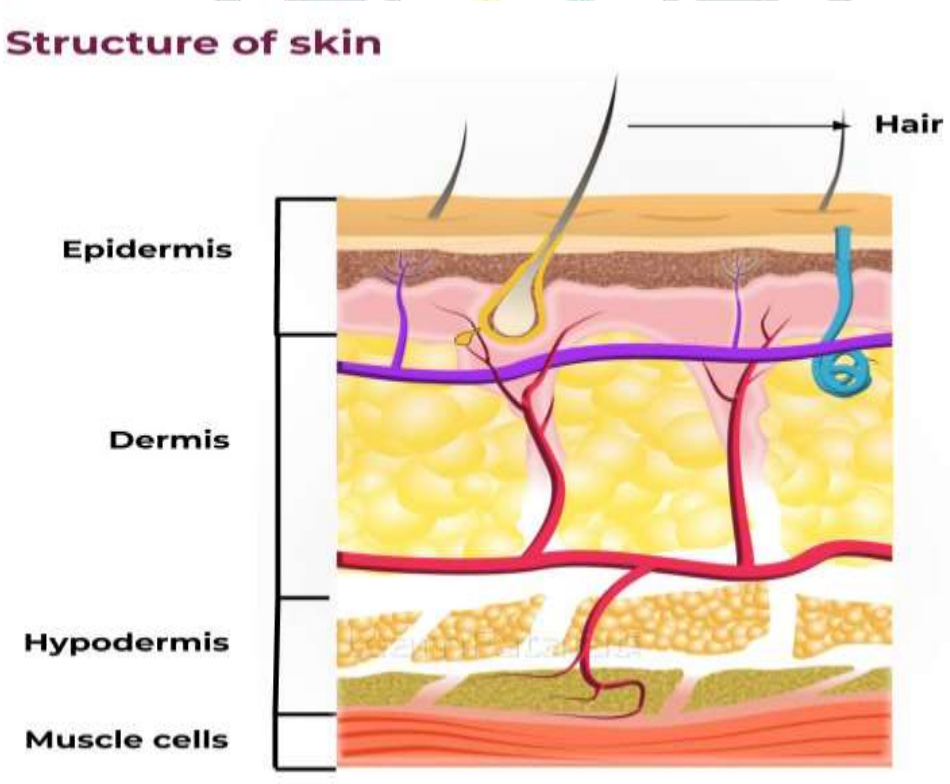

Figure no. 2 Structure of the skin

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 sows 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.

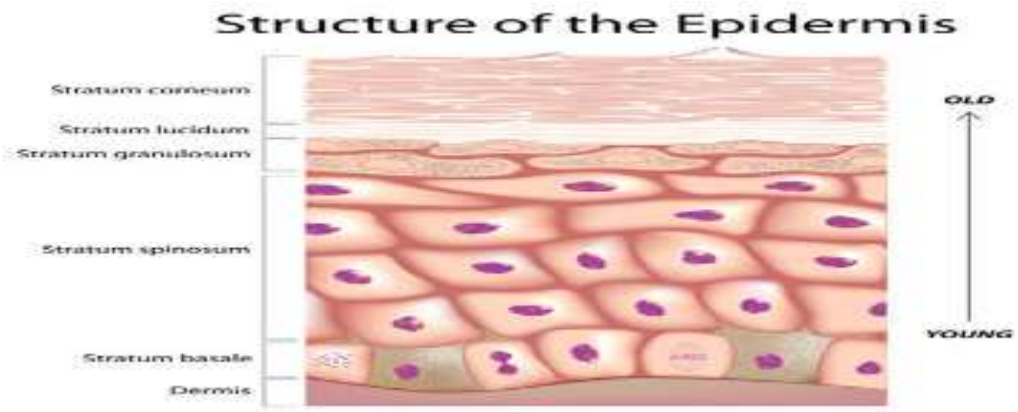

Figure no. 3 structure of the epidermis

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. Muscles, macrophages, and lymphatics channels are also present in the dermis layer.

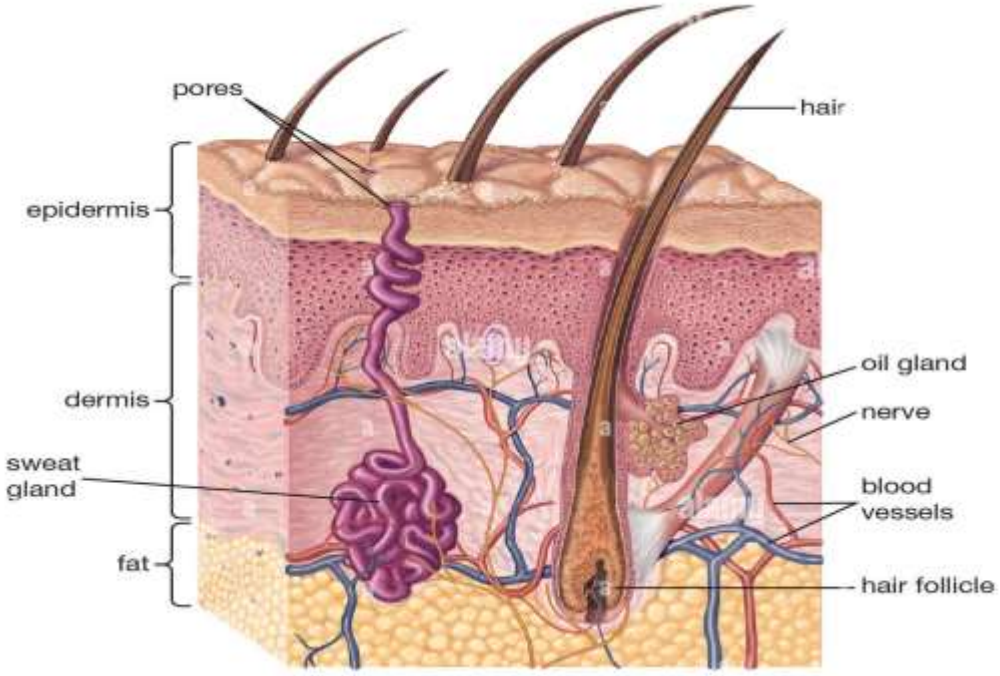

Figure no. 4 Structure of dermis

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 contact, such as muscles or bone, between the skin and the body's underlying tissues. Therefore, defense from better reasoning, and heat, including the structural or structural ability 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, constituting about 50% of fat mass [4].

Penetration of drug through the skin

In skin drug molecules penetrate directly to the stratum corneum, this is achieved mainly through three pathways such as hair follicles, sweat duct, and sebaceous gland. In stratum corneum having a lot of water acts as a plasticizer; they avoid the cracking of the stratum corneum. The drug contains any hydrophilic chemicals it diffuses or passes through the aqueous membrane similarly lipophilic chemicals diffuse through

the lipoid membrane [5]. This type of molecular transport of drugs through the barrier is determined by fluxes. At a given period, the number of molecules passing through a specific area of the cross-section known as flux is determined by using equation 1.

J= m/At

J= Flux,

M= Mass of the compound,

A= Area of cross-section,

t=time.

The molecules are migrating through the barrier; this migration happens because of external force applied to individual solute molecules [6]. Penetration of drug through the outer membrane of the stratum corneum obeys Fick's first law is state that flux is directly proportional to the concentration gradient. Fick's law is determined using equation 2.

dm /dt = -DS (dc/dx)

dm = change in mass of material, g,

dt = change in time, sec,

D = diffusion coefficient, cm^2 / sec,

S = barrier surface area, cm^2,

Dc = change in concentration of material, g/cm^3 [7,8].

ADVANTAGES OF TDDS:

- avoids first-pass metabolism It is systemic and systemic.
- It removes can be quickly terminated by removal of the patch from the skin.
- It provides ease of rapid identification of medication in emergency non-responsive patients, unconscious or comatose patients.
- It provides steady permeation of the drug across the skin, allowing consistent serum drug levels.
- It permits self-administration
- It has fewer side effects
- It increases the therapeutic value of many drugs by avoiding specific problems associated with the drug example GI irritation, lower absorption, and decomposition due to 'hepatic first pass' effects
- It is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary if, for example- the drug is given orally.
- It improved patient compliance and reduced inter and intra- patient variability
- It provides stable and controlled blood levels.
- Long duration of action ranging from a few hours to one week.
- These dosages are suitable for the administration of drug having….
    - Very short half-life, for Example- Nitroglycerine.
    - Narrow therapeutic window.
    - Poor oral availability [9,10].

DISADVANTAGES OF TDDS:

- It causes skin irritation and allergic response.
- Many drugs with hydrophilic structures that permeate the skin too slowly may not achieve therapeutic levels.
- Heavy drug molecules (>500 Daltons) are usually difficult to penetrate the stratum cornea.
- Drugs with very low or high partition coefficients fail to reach blood circulation.
- Drugs that are highly melting drugs can be given by this route due to their low solubility in water and fat.
- Many approaches have been attempted to deliver medicament across the skin barrier and enhance efficacy.
- This route is unsuitable when
    - Drug dose is large.
    - Drug is skin-sensitizing and irritating.
    - Drug is metabolized in the skin.
    - Drug undergoes protein binding in the skin.
    - Drug is highly lipophilic or hydrophilic [9,10].

ENHANCEMENT STRATEGIES OF TDDS

Three strategies are used to enhance TDDS. They are chemical, physical, and biochemical enhancement. When a compound is blind or interacts with stratum corneum containing lipoidal membrane there by an increase in permeability is known as a chemical enhancement. Biochemical enhancement directly increases the permeability of the stratum corneum lipid membrane and also indirectly affects skin permeability through changes in lipid metabolism. Physical enhancement increases drug delivery using some devices such as stripping, iontophoresis, electroporation, ultrasound, microneedles, and mechanical abrasion.

TECHNOLOGIES FOR THE DEVELOPMENT OF 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 in 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 thickness of the membrane are regulated by the rate [11].

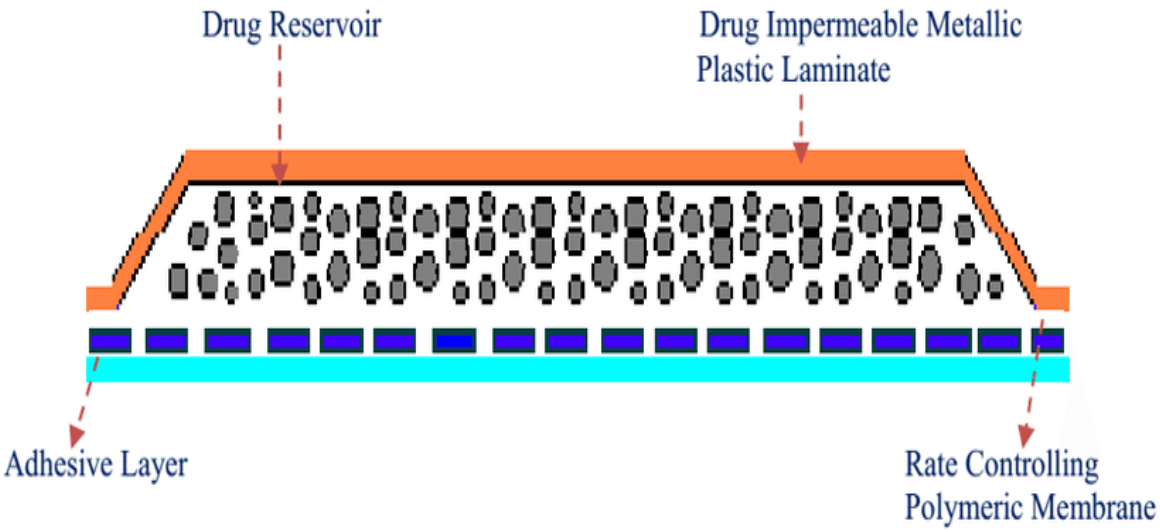

Figure no. 5 membrane controlled system

2. Regulated Adhesive dispersion/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

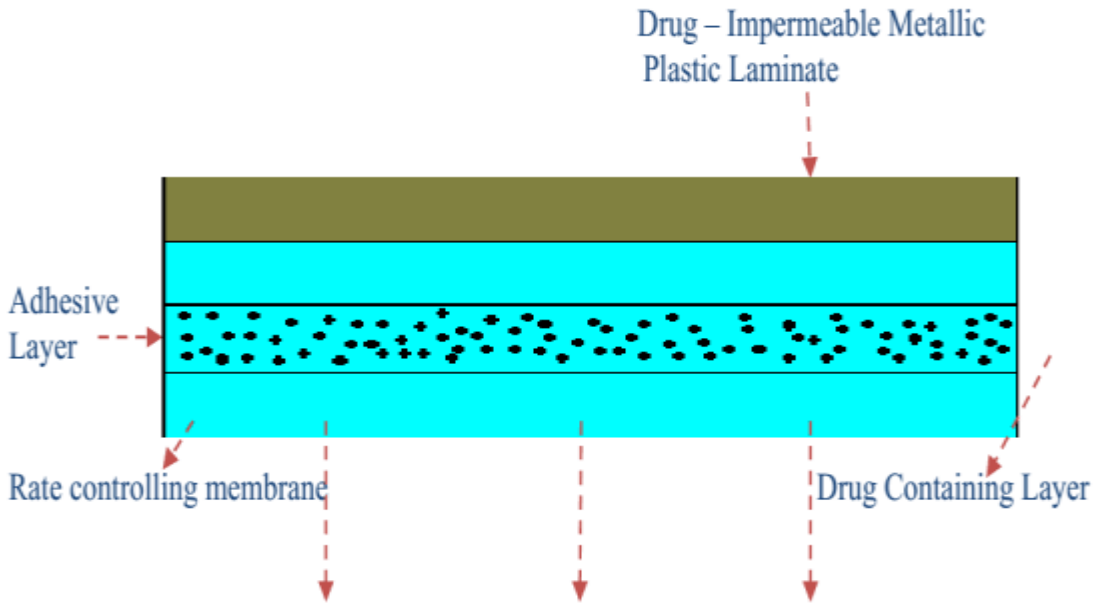

Figure no.6 Adhesive diffusion- controlled tdds

3. Matrix diffusion-controlled TDDS

A pure compound substance is distributed in a simulation of hydrophilic or lipophilic polymers. 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

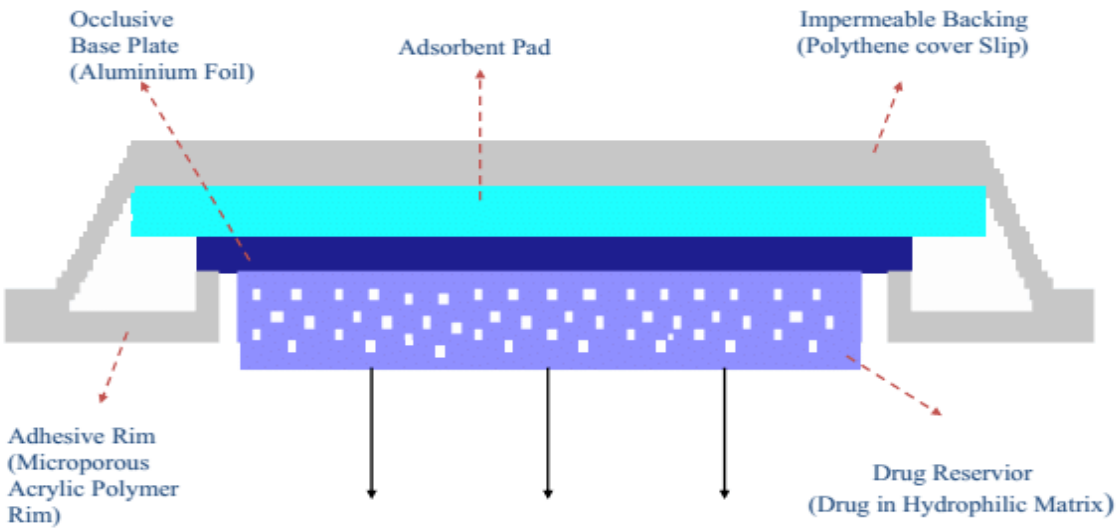

Figure no. 7 Matrix diffusion-controlled TDDS

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 and 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 [11].

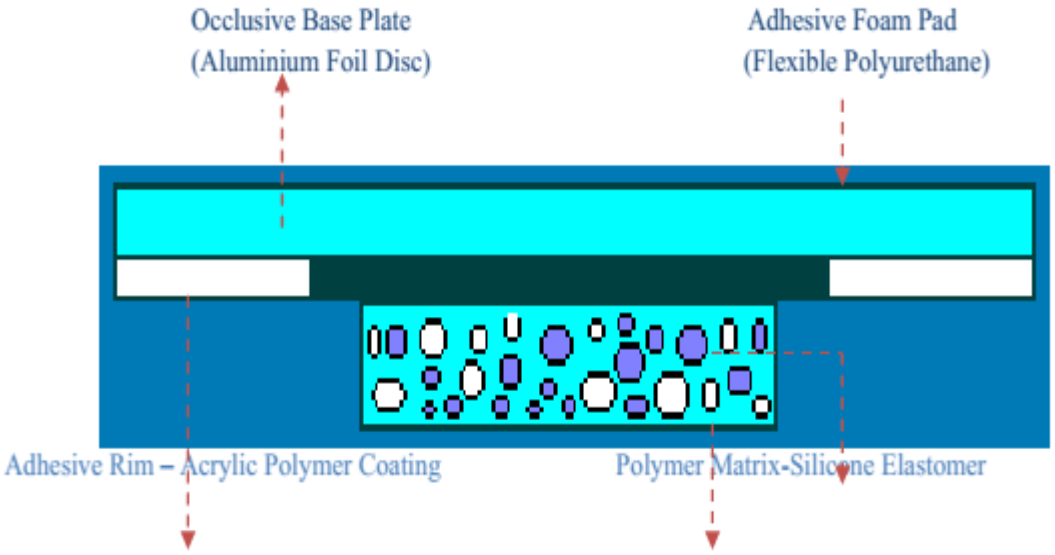

Figure no. 8 micro reservoir controlled TDDS

ENHANCEMENT OF TRANSDERMAL DELIVERY BY EQUIPMENT BY (ACTIVE DELIVERY)

External stimuli, such as electrical, mechanical, or physical stimuli, are known to enhance the skin permeability of drugs and biomolecules, as compared to the delivery of drugs by topical application on the skin [12]. TDDS supplement by appropriate equipment is termed active transdermal delivery, which is known to deliver drugs quickly and reliably into the skin. In addition, this mode of enhanced TDDS can accelerate the therapeutic efficacy of delivered drugs.

method

- Iontophoresis
- Sonophoresis
- Electroporation
- Photomechanical waves
- Microneedle
- Thermal ablation

TDDS using chemical enhancers (passive delivery)

Chemical penetration enhancers (CPEs), which are also referred to as sorption promoters or accelerants have several advantages in transdermal drug delivery. These are painlessness, non-invasiveness, and the capacity to increase the transdermal flux in comparison with passive diffusion.

method

- vesicles
- polymeric nanoparticles
- nanoemulsion[13,14].

IDEAL CHARACTERISTICS OF TDDS:

- The pH of the solution should be between 5-9.
- For the therapeutic action of the drug, there is a need for an optimum partition coefficient.
- Drugs with low melting points (less than 200^0c) should use.
- Patch size should be less than 40 cm^2.
- Shelf life up to 2 years.
- low molecular weight (less than 500 Daltons)
- Lipophilicity (Log Ko/w: 1-3)
- Dose is less than 50 mg per day, and ideally less than 10 mg per day [15].

COMPONENTS OF TDDS

- Drug: The drug is in direct contact with the release liner.

  Ex: Nicotine, Methotrexate and Estrogen

- Liners: Protects the patch during storage.

  Ex: Polyester film.

- Adhesive: Serves to adhere the patch to the skin for systemic delivery of the drug.

  Ex: Acrylates, polyisobutylene, silicones.

- Permeation enhancers: Controls the release of the drug

  Ex: Terpenes, Terpenoids, Pyrrolidone. Solvents like alcohol, Ethanol, and Methanol. Surfactants like sodium Lauryl sulfate, Pluronic F127, and Pluronic F68.

- Backing layer: Protect the patch from the outer environment.

  Ex: Cellulose derivatives, polyvinyl alcohol, and polypropylene silicon rubber [16].

POLYMERS

Polymers are the backbone of TDDS. Polymers play a key role in the human body. Polymers are classified into three types: natural, semisynthetic, and synthetic. The selection of polymers is very important for the development of products. And also polymers have several ideal properties, which play a major role in this system. Ideal properties such as [17,18]:

- It should be chemically inert.
- It should be non-toxic.
- It doesn't decompose during storage.
- Diffusion of the drug is dependent on the chemical, and physical characteristics of the polymer and also depends on the molecular weight of the polymer.

The main uses of natural polymer are it is biodegradable, and has good cytocompatibility. Synthetic polymers are mainly used for different purposes such as film (polyethylene), rope and automotive (polypropylene), insulation and packaging (polystyrene), cable wire insulator (polyvinyl chloride), and aqueous soluble thickening agent (polyvinyl alcohol) [19,20]. Different types of polymers are used based on the type of actions. The polymers and drugs are arranged like a "sand witch" model in the TDDS. Polymers prevent drug leakage and provide a sustained release into the body. The polymers are selected depending on the pH of a particular region of the body. The polymers are swells and release the drug at only that region of pH In TDDS using different polymers given below: [21,22].

Table- 1 Types of polymers used in tdds

Types	Polymers
Matrix formers	Polyethylene glycol
	Ethyl cellulose and polyvinylpyrrolidone
	Hydroxy methylcellulose
	Organic gels
Rate-controlling	Silicon rubber
	Polyurethane
Pressure sensitive	Silicon
Adhesives	Polyacrylates
Thermoplastic hot	Compounded
Melt pressure-sensitive	Ethylene vinyl acetate copolymer
Adhesives	Paraffin wax
	Low-density polypropylene
	Styrene-butadiene copolymer
	Uncompounded
	Polyesters
	Polyamides
	Polyurethanes
Backing layer	Polyurethane
	PVC
	PE
	EVA

ROLE OF ADHESION IN DRUG DELIVERY

TDDS's main principle is that it selectively adheres to the skin and provides drug release. Drug delivery is varied in age and gender function. Because in this system drug release is through the skin and also younger and older patients have different skin natures. Younger skin is greater dehydrated while aged skin has less moisture content so younger skin has more elasticity than aged skin so carefully selecting the adhering is very important [23]. Here, drug absorption is based on the drug partition between TDDS and skin. Good permeation and action is depending on the proper adhesion covering the particular effective area, that area only provides greater action [24]. And also so many factors are affecting drug absorption such as the thickness of the skin, skin temperature, blood flow, no hair follicles, skin cleansing, sweat gland function, pH of skin Surface, and body temperature [25-26]. After the application of the patch, it warms the sin temperature swells the polymer, and sustained the release of the drug to the stratum corneum [27].

FACTOR AFFECTING DRUG PENETRATION

Two types of factors affect drug penetration such as biological and physiochemical factors these factors are listed below

Biological factors

- Skin age
- Skin condition
- Blood supply
- Skin metabolism
- Regional skin site.

Physiochemical factors

- Temperature and pH
- Skin hydration
- Diffusion coefficient
- Drug content
- Molecular size and shape
- Partition coefficient [28,29].

METHODS FOR CHARACTERIZING TDDS

The evaluation of delivery efficiency and effectiveness is a very important process in TDDS. There are various methods used for this, depending on the type and purpose of the drug to be delivered. However, the three most common methods involve diffusion cells, tape stripping, and microscopic and spectroscopic examination, [30,31] in which each method makes use of a distinct analysis method. As the drug applied to the

surface is absorbed, all these characterization methods are based on the principle of measuring the amount of the drug in each surface layer or storing an imaging material instead the drug to visually confirm the absorption behavior.

Diffusion cell method:

It involves the transfer by diffusion of the antimicrobial agent from the chromatogram (PC or TLC) to an agar plate previously inoculated with the microorganism tested. after some minutes or hours to allow diffusion, the chromatogram is removed and the agar plate is incubated.

Tape stripping methods:

tape stripping is a simple and efficient method for the assessment of the quality and efficacy of cosmetical and dermatological formulations. After topical application and penetration of formulations, the cell layers of the stratum corneum are successively removed from the same skin area using adhesive films.

Microscopic and spectroscopic methods:

The microscopy-based technique can also provide important information about the spatial distribution of the drug within different skin layers or shed light on the drug within different skin layers or the mechanism of penetration. The two most common modalities of microscopy are confocal laser scanning microscopy (CLSM) and two-photon fluorescence microscopy CLSM is a non-invasive method developed for fluorescence microscopy [32].

MARKETED TRANSDERMAL DRUG DELIVERY PRODUCT:

The transdermal drug delivery system market is projected to reach USD 7.1 billion by 2023, at a CAGR of 4.5%. the growth of this market is primarily driven by factors such as the increase in the prevalence of chronic diseases and technological advancements in transdermal drug delivery systems.

By application, the pain management segment is estimated to hold the largest share of the transdermal drug delivery systems market

Based on applications, the market is segmented into five categories pain management, central nervous system disorders, hormonal applications, cardiovascular diseases, and other applications (smoking cessation, motion sickness, and overacting bladder treatment). In 2018, the pain management segment is expected to account for the largest transdermal drug delivery systems market share. The large share of this segment can be attributed to the high burden of chronic pain worldwide and the growing availability of transdermal products for pain management.

Transdermal patches to dominate the transdermal drug delivery systems market during the forecast period

Based on type, the transdermal drug delivery systems market is segmented into transdermal semisolid. On the contrary, the transdermal patches segment is also expected to grow at a higher rate during the forecast period. This can be attributed to the benefits offered by transdermal patches such as reduced dosing frequency, improved bioavailability, reduced adverse events, and drug input termination at any point by the removal of the patch.

The home care settings segment is expected to grow at the fastest rate during the forecast period

Based on end users, the transdermal drug delivery systems market is segmented into home care settings and hospitals & clinics. The home care setting segment is expected to grow at a higher CAGR during the forecast period. The high growth in this segment can be attributed to the increase in self-administration of medication at home, rapid growth in the geriatric population across the globe, and the growing need for cost-effective drug administration.

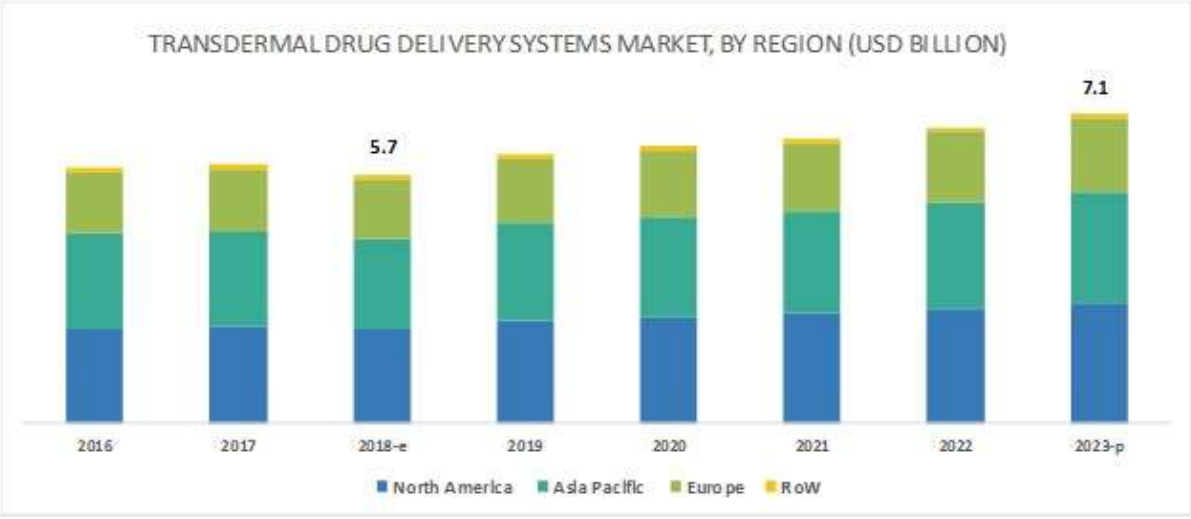

Figure No. 9 Transdermal drug delivery system market, by region

North America is expected to hold the largest market share during the forecast period

North America is one of the major revenue-generating regions in the transdermal drug delivery systems market. The TDDS market in the region is driven by the rising prevalence of targeted diseases (such as chronic pain, central nervous system disorders, and cardiovascular diseases) in the region, the increasing use of contraceptives, and the increasing number of research activities related to transdermal drug delivery systems.

Key market players

The key market players in the transdermal drug delivery systems market are Hisamitsu Pharmaceuticals (Japan), Mylan (US), UCB (Belgium), Novartis (Switzerland), and GlaxoSmithKline (UK). Boehringer Ingelheim (Germany), Johnson & Johnson (US), Endo International (Ireland), and Purdue Pharma (US).

Scope of the report

Report research categorizes the transdermal drug delivery systems market based on applications, type, end, user, and region.

Based on applications, the transdermal drug delivery systems market has been segmented as follows:

- Pain management
- Hormonal applications
- Central nervous system disorders
- Central nervous system disorders
- Cardiovascular diseases
- Other applications
    - Diabetes
    - Smoking cessation
    - Motion sickness
    - Overactive bladder

Based on type, the transdermal drug delivery systems market has been segmented as follows:

- Transdermal patches
- Transdermal semisolids

Based on end users, the transdermal drug delivery systems market has been segmented as follows:

- Home care settings
- Hospitals & clinics

Based on region, the transdermal drug delivery systems market has been segmented as follows:

- North America
    - US
    - Canada
        - Europe
            - Germany
            - France
            - UK
            - Rest of Europe (RoE)
        - Asia Pacific
        - Rest of the world

Recent developments

- In January 2018, Hisamitsu Pharmaceuticals (Japan) launched ALLESAGA TAPE in the Japanese market.
- In July 2018, UCB (Belgium) received the import drug license (IDL) for its transdermal rotigotine patch- NEUPRO from the China Food and Drug Administration (CFDA).
- In August 2018, Luye Pharma (China) signed an agreement with Bayer AG (Switzerland) to acquire the global rights to the Apleek contraceptive transdermal patch [33].

Conclusion: Transdermal patches have been available for more than 25 years, and they have a proven history of success in some promising technologies like iontophoresis, microneedles, ultrasound, etc. Transdermal drug delivery technology is becoming one of the fastest-growing sectors within the pharmaceutical industry. Despite some disadvantages, transdermal drug delivery offers many advantages capable of

improving patient health and quality of life. As we know the basic function of the skin is protected and hence it is difficult to target the skin for drug delivery because the skin has numerous layers but using novel techniques TDDS we have successfully penetrated the drug into the systemic circulation

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