AN OVERALL REVIEW OF THE TRANSDERMAL DRUG DELIVERY SYSTEM

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Abstract: **Transdermal drug delivery system is one of the systems under the category of controlled drug delivery. It has number of advantages like prolonged therapeutic effects, reduces side effects, improved bioavailability. The stratum corneum is rate limiting barrier in permeation of molecules. The drugs get penetrate through three routes appendageal, transcellular and intercellular. While delivering drugs numerous factors with effect the action. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin often, this also promotes healing to an injured area of the body. Transdermal patch can be divided into various systems like reservoir system, matrix system and micro reservoir system. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile and, sometimes improved efficacy over other dosage forms. A transdermal drug delivery system(TDDS) represents the most attractive method among these because of its low rejection rate, excellent ease of administration and superb convenience and persistence among patients. A wide variety of pharmaceutical are now available in transdermal patch form. Advanced physical technique is used for enhancing delivery of drugs such as structure-based, electrically-based, velocity based, and several other miscellaneous physical techniques for enhancing permeation of drugs.**

***Keywords*: Transdermal; healing; matrix system; therapeutic effects; intramuscular; reduces side effects.**

1. Introduction

During the last few years development of existing drug molecules has been renewed in terms of efficacy, safety and also improves patients 'compliance [1]. TDDS is terms as self-contained dosage form which is also defines as patches [2, 3]. The main aim of TDDS is to deliver the effective amount of drug to patient skin at predetermined rate [3]. TDDS is one of the most methods for skin application. Transdermal provides controlled administration of drug and also continuous input of drugs with short biological half-life [3].The advantage is limitation of hepatic first pass metabolism and therapeutic efficacy [1]. It is multidisciplinary activity with fundamental feasibility study starting from selection of drug molecules to sufficient drug flux in ex-vivo and in-vivo models that meet all strategies and the patient, the manufacturer and most important economy [4]. The first transdermal transderm SCOP was approved by FDA in 1979 for prevention of nausea and vomiting. The patches are designed in such a way it releases the active ingredient at zero rate [5].

1.1. Skin

The skin is the largest human body organ which covers a surface area of 2 sq.m[6].However, the drugs available in transdermal drug product is limited. It is one of the most readily accessible organs of human body [7].

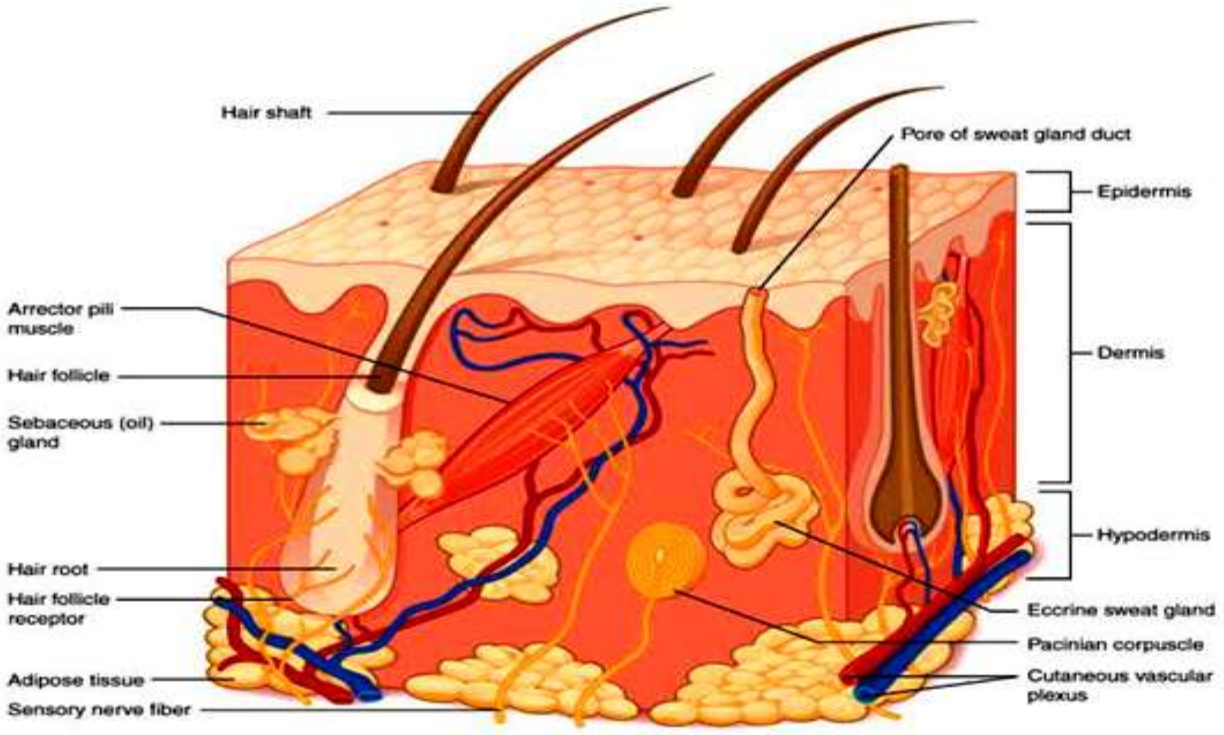


Figure 1: Structure of skin

1.2. ANATOMY OF SKIN

The structure of human skin is divided into

A. Epidermis
B. Dermis
C. Hypodermis

A. Epidermis

Non-viable and viable Epidermis both combines to makes up the Epidermis here staratum Corneum is called as non-viable Epidermis layer below it called as viable Epidermis [8]. Epidermis is self self renewing, stratified squamous epithelium covering the entire outer surface of body [9]. The stratum corneum is made up of number of sublayers with 50-100µm thick held together by tonofibrils[10]. Blood capillaries and nerve fibres passed through the dermis and subcutaneous fat layer [11]. The keratinocytes which make up 95% of total cells present in Epidermis [12]. The Epidermis had the following sublayers.

a. Stratum basale
b. Staratum spinosum
c. Stratum lucidum
d. Stratum granulosum

a. Stratum basale. (Basal cell layer)

It is the deepest sublayer of the epidermis and consist of single layer of basale cells, in this layer keratinocytes are produced. Stratum basale acts as a boundary to the epidermis, and it holds 8% of water with ageing this layer becomes thinner and losses the ability to retain water.Melanocytes are also present in this layer.

b. Stratum spinosum. (Prickle cell layer)

The basal call layer that lies with 10-20 layers and make their shape somewhat flatter they called as prickle cells with thickness of sublayer from 50-150µm.

c. Stratum lucidum. (Clear cell layer)

During turnover these cells become flatter and densely packed and found in soles and palms [13].

d. **Stratum granulosum. (Granular cell layer)**

Stratum granulosum consist of 2-4 layers with thickness 3mm. In this process cells becomes flatter and in sublayer keratinisation of keratinocytes begins and the organelles like mitochondria and nuclei resolve and cells filled with keratin fibres contain less moisture compared with prickle cells and basale layers.

B. Dermis

It composed of a matrix of connective tissues which contains nerves, blood vessels, and lymph vessels. It is the layer of the skin just beneath the Epidermis with thickness 3-5mm. The essential functions in regulation of body temperature are cutaneous blood supply. While removing toxins and waste products it's providing nutrients and oxygen to the skin. They provide sink conditions for molecules in penetrating the skin barrier of capillaries within 0.2mm of skin surface. The dermal concentration of permeate very low and concentration different across the Epidermis provides essential driving force for transdermal permeation. It's providing minimal barrier for the delivery of most polar drugs and significant to delivering highly lipophilic molecules [14].

C. Hypodermis

The thickness of this layer is 4-9mm on average. [13] Its supporting the dermis and epidermis of hypodermis or subcutaneous fat tissues. It acts as fats storage area and helps in regulating temperature, mechanical protection and nutritional support and carries blood vessels and nerve to skin. The drug has to penetrate through all three layers and reach in systemic circulation for transdermal drug delivery [15].

1.3. ADVANTAGES AND DISADVANTAGES OF TDDS

The various advantages and disadvantages of transdermal drug delivery system are listed below.

Advantages

- Patches are painless and easy to apply.
- No interaction of drug with the enzyme, food and GI flora.
- Suitable for old people who has difficulty in swallowing.
- Self administration is possible.
- Avoids first pass metabolism.
- Alternative for oral route.
- Minimize undesirable side effects.
- Intra and Inter patient's variations.
- Great advantage in patients who are unconscious.
- They are non-invasive.
- Termination of therapy is easy at any point.
- Avoids gastrointestinal drug absorption difficulties covered by drug interaction with food,drink and oral administration of drug.
- They have extended therapy with single application over other dosage form requiring frequent dose administration.
- Provide utilisation of drug with short biological half-life.
- Easy to use with low medical costs.

Disadvantages

- Skin irritation and sensitisation.
- No ionic drug delivery.
- High cost.
- No rapid/pulsatile release of drug.
- Molecular size restrictions (more than 500 dalton are not suitable for TDDS).
- Cannot achieve high drug level in blood plasma.
- Sometimes cause's allergic reactions.
- Administration of large dose is difficult.
- Drug with low or high partition coefficient may fail to reach systemic circulation.

2.0. FACTORS AFFECTING TRANSDERMAL PERMEATION

Biological factors [15, 16]

a. Skin condition

The skin itself acts as a barrier many agents like acids alkali penetrates through the skin. Methanol chloroform is the solvents that remove lipids fraction by making tiny shunts on skin.

b. Skin age

It is seen that skin of adult and young ones are more susceptible compare to old ones. Some acids like steroids, boric acid and hexachlorophene have several side effects on children.

c. Blood supply

Any kind of change in blood circulation affects the transdermal absorption.

d. Regional skin site

This factor effects the penetration. Nature of skin, thickness and density of skin layers vary from site to site this effects significantly penetration.

e. Species differences

Skin thickness keratinisation of skin vary from species to species so,it's effects the penetration.

2.1 Physicochemical factors [15]

a. Skin hydration

Generally, when skin absorbs water, it swells it softens the skin, and the ability to pass through the skin increases for the drug.

b. Temperature and pH

The penetration rate varies as temperature varies. If the temperature is less penetration is also less. Weak acids and weak bases dissociate depending upon pH and pka values. Temperature and pH is the important factor for the skin penetration.

c. Drug concentration

Flow of drug is proportional to concentration gradient across the barrier concentration gradient will be more when the concentration of drug will be more across the barrier.

c. Molecular size and shape

Small particles will penetrate easily than large particles.

3.0. Drug substance

For developing the transdermal drug delivery system drug should be carried out with great care. Following are the desirable properties for transdermal delivery [17].

Physicochemical properties

The molecular size of the drugs should be less than 1000daltons more than 1000 daltons drugs are suitable for TDDS.

- The drug should have both lipophilic and hydrophilic phase
- The drugs should be of low melting point.
- Apart from these properties the drug should be potent.
- The drug should have short half-life.
- It should be non-irritating.

Biological properties [1,18]

i. Drug should be potent.
ii. Should be stable.
iii. Dose is less than 50mg day on treatment it can reduce to 10 mg per day.
iv. The drug should be readily metabolised in the skin.
v. The drug should not interact with subcutaneous tissue.
vi. It should be non-irritant.
vii. It should not stimulate an immune reaction to the skin
viii.

4.0. PERMEATION ENHANCERS

Permeation enhancer are also known as accelerants,sorption promoter [19]or penetration enhancer [20]. They are the compound which promote skin permeability by altering skin the skin as Barrier of desiredpenetrate [21,22]. As the major route of drug is through the intracellular channel's lipid section is viable in first step of absorption

Ideal properties of permeation enhancer:

- Controlled and reversible action.
- Should not cause loss of body fluids electrolytes.
- Polymer should be of stable.
- Polymer should be nontoxic.
- Polymer should be easily manufactured.
- Polymer and its de-aggration product must be nontoxic or non-antagonistic.
- Polymer should be inexpensive.

Classifications of absorption enhancers

Table 1: Types of absorption enhancers

CLASSIFICATION	EXAMPLES	MECHANISM
Surfactants	**Anionic:** sodium lauryl sulphate **Cationic**: cetylpyridinium chloride,cetyltrimethyl ammonium bromide **Nonionic**: poloxamer, Brij,Span, Myrj Tween **Bile salts**: Sodium glycodeoxycholate, Sodiumglycocholate , sodium taurodeoxycholate, Sodium taurocholate, Azone	Perturbation of intercellular lipids, protein domain integrity
Fatty acids	Oleic acid, caprylic acid, Lauric acid, Propylene glycol methyloleate,phosphatidylcholine	Increase fluidity of phospholipids domain
Cyclodetrin	ά,β,δ, cyclodextrin,methylated,β-cyclodextrins	Inclusion of membrane compounds
Chelators	EDTA,Citric acis,Sodium salicylate,Methoxy salicylates.	Interfere with ca^{2+} Polycrylates
Positively charged polymers	Chitosan, Trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface
Cationic compounds	Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface

Other excipients

Many solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition, with those plasticisers such as dibutylpthalate, propylene glycol is also added to provide plasticity to patches. [22]

Pressure sensitive adhesive

A pressure sensitive adhesive (PSA) is a type of material used in maintaining intimate contact between skin surface and transdermal system. It should be adhered with not more than applied finger pressure, permanently tachy, exert strong holding force. It should be easily removable without leaving residue [4].e.g. Polyacrylamates, polyacrylates, polyisobutylene. The adhesive should be selected by examining various factors like patch design and drug formulation. It should be Physicochemical and biologically compatible. It should not be positioned on the face or device and extending peripherally. [23]

Backing laminates

They must have optimal elasticity, flexibility and tensile strength and should have low moisture vapour transmission rate. [24] While designing the backing layer the excipients and chemical resistance should be compatible because the prolonged contact between backing layer penetration enhancer through the layer. [4] E.g. aluminium vapour coated layer, a plastic film and heat real layer. [24]

Release linear

During the storage condition the release linear prevents loss of drug and contamination [24]. However linear is in close contact with the delivery system it complies with specific requirements regarding chemical inertness and permeation to the drug and water.

4.1. PERMEATION THROUGH SKIN [25]

The permeation through the skin occurs by the following routes

1. Transfollicular (shunt pathway absorption)
2. Transepidermal absorption
3. Clearance by local circulation

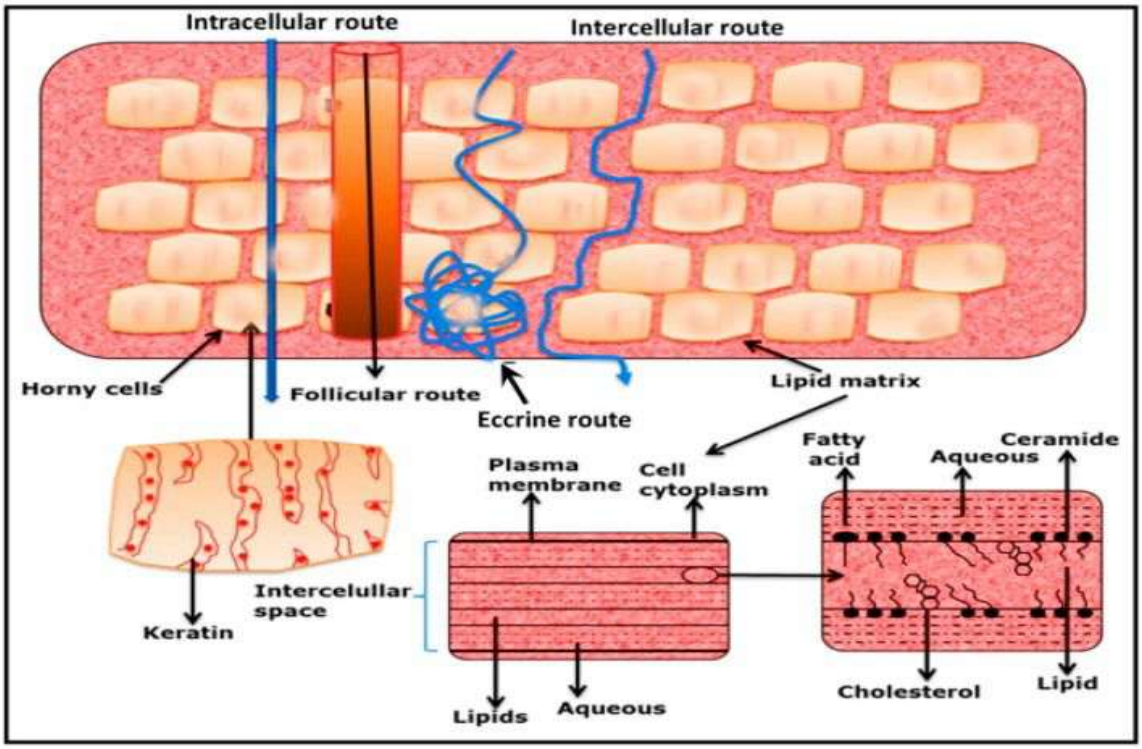


Figure 2: Possible drug penetration routes across human skin

1. Transepidermal absorption

- Stratum corneum is the main resistance for absorption through this route
- Permeation involves partitioning of the drug into stratum corneum
- Permeation through skin depends upon the o/w distribution tendencies of the drug
- Lipophilic drug concentrate in and diffuse with relative ease
- Permeation through the dermis is through the interlocking channels of ground substance.

2. Transfollicular absoption

- The skin appendages (sebaceous and ecrine glands) are considered as shunts for passing the stratum corneum.
- Follicular route is important for permeation because the opening of the follicular pore is relatively large and sebum aids in the diffusion of the penetrant.
- Partitioning into the sebum followed by the diffusion to the depths of epidermis is the mechanism.

3. Clearance by local circulation

- The earliest point of entry of drugs into the systemic circulation is within the papillary plexus in the upper epidermis.
- The process is thus regarded as end point.

4.2. FACTORS AFFECTING PERMEATION THROUGH SKIN

- Age has an effect on permeation of drugs through the skin.
- Blood flow (dermal clearance of molecules transversing the tissues) tends to decrease with the age and could reduce transdermal flux.

The other factors that affect the permeation of drug through skin are:

- The stratum corneum thickness.
- Presence of hair follicles.
- Injury or traumato the skin.
- Hydration of the skin.
- Effect of humidity and temperatures.
- Chemical exposure.
- Chronic use of certain drugs.

5.0. Pharmaceutical dosage forms [26]

Classification of pharmaceutical dosage forms according to its physical properties

Dosage forms:

a.Homogenous mixture.

b.Dispersion systems-one phase (dispersed phase) is distributed throughout another phase (continuous phase,dispersion medium).

c. According to size of dispersed particles a molecular colloidal and coarse dispersion can be distinguished.

d. May require shaking before administration.

5.1. According to overall physical properties of dosage forms both homogenous and dispersion medium one can distinguish

1. Gaseous dosage forms
2. Liquid dosage forms
3. Semisolid dosage forms
4. Solid dosage form

1. Gases: medicinal gases /inhalation / volatile anaesthetic (vaporised before administration by inhalation) ex.inhalers

Aero dispersions of solid particles (eg inhalation anti asthmatic)or liquid particles Ex. Sprays

2. Liquids:

Solutions: one homogeneous mixture is prepared one or more solutes in a solvent

Emulsions: a dispersion medium consist of two immiscible liquids like oil in water emulsion or water in oil emulsion

Cloudy appearance

Suspension: a dispersion medium where solid particles are dispersed in liquid phase.

Not intended for systemic administration.

3. Semi solid dosage forms

Un shaped (without any physical shape)

Gels: a semi solid system in which a liquid phase is considered within 3D cross linked matrix. Ex PLO (Pluronic lecithin organogel)

Creams: semisolid emulsion system (o/w or w/o) containing more than 10% of water

O/w creams are more comfortable and cosmetically acceptable because of less greasy and water washable nature where w/o are release better lipophilic API,moisturising, ex. cold creams

Ointments: semi sold dosage forms with the oleaginous water soluble and emulsifying base

Oleaginous (hydrocarbon) base: petrolatum (Vaseline white yellow) ex.nitroglycerine ointment

Shaped

Suppositories (for rectal administration)

- It has different shapes
- Melting / dissolving at body temperature
- Oleaginous (cacao butter) oraqueous(PEG's, gelatine)

Pessaries (for vaginal administration)

- It is used as vaginal suppositories
- Similar as above PEG's or gelatin is used as base

4. Solid dosage forms

The solid dosage forms used in transdermal drug delivery system are unshaped i.e they don't have any specific physical shape The dosage is in form of powders for external/internal use

Shaped

Tablets
Capsules
Transdermal patches

5.2. Pharmaceutical dosage forms according to route of administration

Dosage forms: For systemic administration

a) Sublingual and buccal
b) Rectal
c) Parenteral
d) Transdermal
e) Inhalation

For local administration

- Topical (on the skin or mucosa)
- Into/onto

a. The eye, nose and ear
b. For oral cavity
c. Vaginal, rectum
d. The bronchi
e. The skin

5.3. Pharmaceutical dosage forms for systemic administration.

Generations of dosage forms

1. First generation-conventional (unmodified) release of API
2. Second generation-controlled release of API
3. Third generation-targeted distribution of drug delivery system

Conventional V/S controlled release dosage forms

1. First generation of transdermal delivery system

The first generation of transdermal delivery system is responsible for transdermal patches that have been use so far in clinical use. Significant advances in patch technology and public acceptance have recent surge in first generation. First generation must be low molecular weight lipophilic and efficacious at low doses. Drug absorption and distribution is based only on physicochemical properties of API. Disintegration of dosage form and dissolution of API is spontaneous process. The transdermal delivery should be more attractive than oral delivery due to low oral bioavailability [27- 29]

2. Second generation of transdermal delivery system.

The release of API is under control of drug delivery system. It's recognising that skin permeability enhancement is needed. The ideal enhancer should increase skin permeability by disturbing stratum corneum structure. However, enhancement methods like conventional chemical enhancer, iontophoresis and non – avitational ultrasound as developed and struggled with the balance between achieving increased delivery across the stratum corneum protecting the tissues from damage. As a result, second generation has advanced clinical practise but has little impact on delivery of macromolecules.

3. Third generation of transdermal delivery system.

3rd generation TDDS aim to severely disrupt the stratumcorneum to allow large molecules to pass into the circulation. While iontophoresis can be used to deliver small molecules such as fentanyl, it can also be used to deliver much larger molecules aswell. Its targets stratum corneum this enables stronger disruption of corneum barrier thereby strong drug delivery system while protecting deeper tissues. In this way chemical enhancer electroporation cavitational ultrasound microdermabrasions have been shown to deliver macromolecules including proteins and vaccines across the skin in human and clinical trials.

6.0 MARKETED TRANSDERMAL DRUG DELIVERY PRODUCTS [30]

Table 2 : Marketed transdermal drug delivery products

Product name	Drug	Manufacturer	Indications
Androdrem	Testosterone	Thera/Tech/GlaxoSmithKline	Hypogonadism(makes)
Nitro-dur	Nitroglycerine	Key pharmaceuticals	Angina Pectoris
Nitrodisc	Nitroglycerine	Roberts's pharmaceuticals	Angina Pectoris
Minitran	Nitroglycerine	3M pharmaceuticals	Angina Pectoris
Deponit	Nitroglycerine	Schwarz-Pharma	Angina Pectoris
Climaderm	Estradiol	Ethical Holding/Wyeth-Ayerest	Postmenstrualsyndrome
Climara	Estradiol	3M Pharmaceutical/berlex labs	Postmenstrualsyndrome
Estraderm	Estradiol	Alza/Norvatis	Postmenstrualsyndrome
Fematrix	Estrogen	Ethical Holding/Solvay healthcare	Postmenstrualsyndrome
Fempatch	Estradiol	Parke-Davis	Postmenstrualsyndrome
Alora	Estradiol	TheraTech/Proctol and gamble	Postmenstrualsyndrome
Prostep	Nicotine	Elan corp/Lederle labs	Smoking cessation
Nicoderm	Nicotine	Also/GlaxoSmithKline	Smoking cessation
Habitraol	Nicotine	Novartis	Smoking cessation
Nuvelle TS	Estrogen/progesterone	EthicalHolding/Schering	Hormone replacement therapy
Combipatch	Estradiol/Norethindrone	Noven,Inc/Aventis	Hormone replacement therapy
Ortho-Evra	Norelgestromin/estradiol	Ortho-McNeil Pharmaceuticals	Birth control
Duragesic	Fentanyl	Alza/Janssen Pharmaceutic	A moderate/severe pain
Catapres-TSS	Clonidine	Alza/Boehinger Ingelheim	Hypertension

7.0 RECENT INNOVATIONS IN TRANSDERMAL DRUG DELIVERY SYSTEM

Iontophoresis

It involves permeation of ionised drug molecule under the influence of electrical current. Here the cationic drug is placed under anode and cationic under the cathode [31]. It is responsible for the movement of ions across the membrane with the small externally applied potential difference. This technique is used in in Vivo transport of ionic and non-ionic drugs by the application of electrochemical potential gradient [32]. Polarity, valency and mobility of the drug molecules will affect the iontophoresis the efficacy will get effect by this factor [33]. Iontophoresis is the electronic means of reminding to the patient to changes the dosage if needed [34,35].

Electroporation

High voltage in the form of direct current [100 volts] are applied on the skin for a very short period of time [milliseconds] which indies formation of transient pores. These pores allow the usage of macromolecules from the outside of the cell to the intracellular space via combination of diffusion and electrophoresis [31]. This is very safe and painless procedure. It's having disadvantages like small delivery loads sometimes death heating damage.

Sonophoresis

The technique is used to increase the skin permeation using ultrasonic energy (20 KHz to 20MHz). The drug is mixed with solvents placed on the skin Beneath the probes after applying coupling to skin. Waves are generated by applying AC electrical signal to form the crystal then the crystal undergoes rhythmic deformation to produce ultrasonic vibrations [31]. The desired range of ultrasound frequencies generated by device can improve transdermal drug delivery [36,37] low frequencies are more effective [38]. The accurate mechanism for this technique is still incomplete the problems with this device are availability, treatment cycles for delivery and undesirable side effects.

Microneedle

The first micro needle was discovered in the year 1976. Recently ALZA Corp has commercialised technology name Macro-flux. Macro-flux has advantage that it can be used either in combination with other drug reservoir or drug coating [39]. The drug is distributed through the needle it is most popular and Novel type of transdermal drug delivery system [40]. The needle could be of different types such as solid micro needle and micro needle patches with different mechanism of action [40,41,42,43,44]. For the Manufacturing of dissolving/hydrogel microneedle this method is mainly used [45].

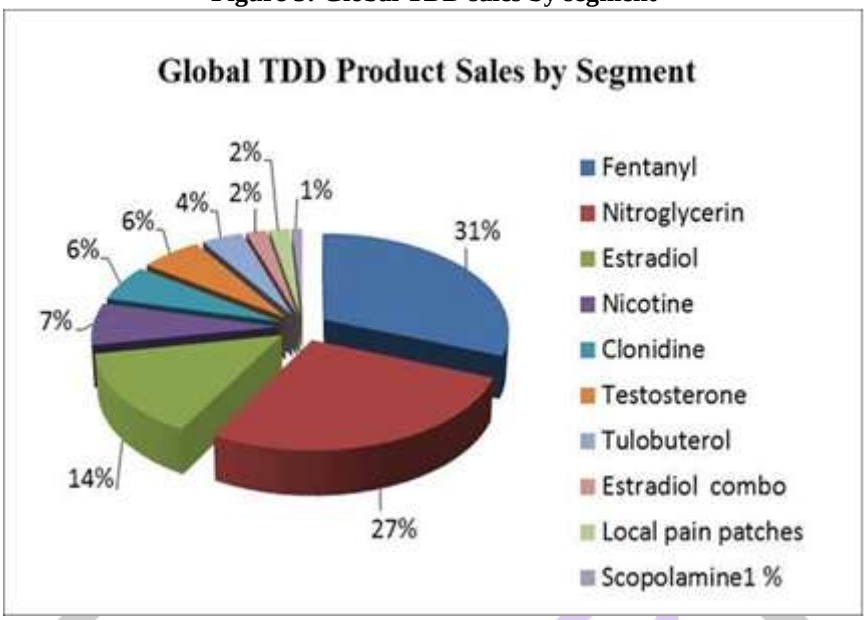
Abrasion

It involves the removal of upper layer of skin to ensure the permeation of applied medicaments. Some of the devices are used by dermatologist ex. Microdermabrasion treatment of acne's, scar other skin marks.

8.0 STATISTICAL USAGE OF TDDS

The usage of transdermal drug delivery system across in India and across the global has been increased due to its safe,efficacious and superb convinience, low rejection rate. It is the most attractive method. Due to its controlled release of drugs, it is widely used.
1.The below is the graphical representation of Global TDD Product sales by segment.
In this we have the highest percentage of Fentanyl i.e 31% followed by nitroglycerin (27%),Estradiol(14%),Nicotine (7%), Clonidine (6%),Testosterone (6%),Tulobuterol (4%), Estradiol combo (2%)Local pain patches (2%) and the scopolamine has the least percentage i.e 1%.

Figure 3: Global TDD sales by segment



CONCLUSION:

In recent years, the transdermal medication delivery technique has grown in popularity. Because of its pharmacology and physical chemistry, the transdermal route is the best alternative. There are various advantages to transdermal medication administration. Reduced dose, low rejection rate, and simple to administer Because of the numerous benefits and well-known manufacturing of transdermal drug delivery, additional research is being conducted to formulate more pharmaceuticals. This field has a better understanding of skin physiology and anatomy. A better understanding of biological interactions is required to optimize this system. As the next generation of medication delivery, TDDS has a practical application.

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