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A NOVEL APPROACH TOWARDS TRANSDERMAL DRUG DELIVERY SYSTEM: A PRECISE REVIEW

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ABSTRACT

Transdermal drug delivery system (TDDS) is a novel approach for delivering drugs across the skin. Most of the drugs are administered orally and are found not to be as effective as expected. To surmount these problems, TDDS was emerged and eventually these are having many advantages over other conventional drug delivery system. The potential of using the intact skin as the route of drug administration to the human body has been recognized for several decades and used as a site of drug administration successfully for both local and systemic effects, however, stratum corneum of skin act as barrier to drug penetration. This is overcome by the use of penetration enhancing techniques which increases the penetration ability and bioavailability of drugs depending upon various factors. Different types of transdermal patches have been formulated and used for TDDS. Over the years, the number of patches formulation has not increased much and formulation procedure is almost same. Many methods have been used in enhancing TDDS to further increase the permeation, bioavailability and therapeutic efficacy of drug. This review article describes briefly about the advantages and disadvantages of TDDS, skin, transportation through the skin, factors affecting permeability, permeation enhancers. Classification, components, types and preparation of TDDS is also discussed. Evaluation methods and recent enhancement techniques are also discussed in this review article. The overall study of TDDS is covered in this review article and this may lead to get lot of interests and topic of research in researchers in future.

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INTRODUCTION

A drug delivery system is defined as a formulation or a device that introduces a therapeutic substance in the body which increases its drug effect producing ability and safety by controlling the rate, time and place of release of drugs inside the body [1]. The aim of any drug delivery system is to give proper drug amount to adequate site for proper therapeutic effect to maintain the functioning and metabolism of body [2]. The different types of drug delivery system based on their route of administration are oral, rectal, parenteral, transmucosal, transnasal, pulmonary, transdermal and intra-osseous infusion [1]. Most regular route of drug delivery is oral route for its advantages but it also has few disadvantages like drug degradation due to enzymes, pH in Gastrointestinal Tract, first pass metabolism. So, for better administration and proper therapeutic effect, a novel drug delivery system was developed [3, 4]. Transdermal Drug Delivery System (TDDS) are defined as the unique dosage form which when applied over skin, transfers the drug(s) at controlled rate to the systemic circulation through the skin [5-8]. TDDS can also be defined as the topically administered medication in the form of patches, when applied, delivers the drug at a predetermined rate through the skin into the systemic circulation [9, 10]. TDDS have many advantages over other conventional dosage forms and these are reduced side effects, sustained drug delivery, removal of first-pass metabolism [5, 11-13]. For effective TDDS, drug should enter beneath the skin to reach the targeted place [14, 15]. Transdermal patch is used for delivering the drug through the skin. Transdermal patch is an adhesive containing drug in high concentration. The patch is placed on to the skin and kept for a long period of time. Since, concentration of drug inside the patch is high and that of blood is low, the drug diffuses through the skin into the blood stream maintaining the constant concentration of blood flow [3, 16, 17]. The first Food and Drug Administration (FDA) approved transdermal drug was Transderm SCOP in 1979 for the prevention of nausea and vomiting associate with ravel [4, 9]. Currently available TDDS drugs are clonidine and nitroglycerin for cardiovascular diseases, scopolamine for motion sickness, oestradiol alone or in combination with levenorgestrel for hormone replacement, testosterone for hypogonadism and fentanyl for chronic pain [18, 19]. The main objective of TDDS is to avoid first pass metabolism and to avoid GI disorders/side effects and these can be easily removed from the body.

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY [3, 4, 16, 17, 21]

i. TDDS is a drug delivery system in which a device usually known as patch is adhered on the skin surface to deliver the drug into the systemic circulation through the skin at predefined concentration for therapeutic effects, which avoids additional limitations due to other dosage forms.
ii. It offers constant permeation of drugs through the skin giving constant serum drug level, the goal of therapy.
iii. It can be used as an alternate to oral drug delivery system for those patients, who find difficulty in taking drugs through oral route.
iv. It can be used as an alternative for nauseated or unconscious patients.
v. Patients having gastrointestinal problems can be given drugs through TDDS as there will be no direct contact between drug and stomach.
vi. Like intravenous infusion, it also gives constant plasma level.
vii. If toxicity develops from TDDS, patch can be removed easily.
viii. It is very convenience as application of drug is very easy.
ix. It eliminates first pass mechanism.
x. It reduces systemic drug interactions
xi. It offers long duration of action.
xii. Self administration can be done.

DRAWBACKS OF TRANSDERMAL DRUG DELIVERY SYSTEM [3, 4, 17, 20-30]

i. Many hydrophilic drugs cannot pass or very slowly permeates the skin. This will affect the therapeutic efficacy of the drug.
ii. Many problems like itching, edema, erythema etc. may be seen due to patches.

iii. The barrier function of the skin may change from person to person, or with ages or with different sites on same person.
iv. There may be some possibility of irritation at the site of drug administration.
v. Uneconomic system of drug delivery.
vi. It is not use in acute condition, only used in chronic conditions
vii. TDDS is not compatible with ionic drugs.
viii. Dumping of dose may occur.
ix. Drugs having affinity for both lipophilic and hydrophilic phases are used.
x. High drug level in blood cannot be attained.

SKIN [2, 31-34]

Skin is one of the sensitive and accessible part of the body. Various functions of skin are temperature regulation, protection, sensation and control of water output through sweating. Average adult skin comprises surface of approximately 2 sq. m. and receives one third of the circulating blood through the body. Skin was thought to be impermeable at early days of scientific study but later it has been found that skin is a complex organ which allows passage of chemicals and other substances across them. Skin is used as a site of administration of various dermatological preparations. By knowing the complexity and passage phenomenon of various chemical substances, it was promising to develop transdermal drug delivery system where skin becomes the site of administration of active drugs. After drug passes the skin, it generally reaches the systemic circulation. From systemic circulation, it directly reaches the target site to show its maximum therapeutic activity.

Skin is the several layered organ composed of many histological layers. An average human skin contains approximately 40-70 hair follicles and 200-250 sweat ducts on unit sq. cm. of skin surface area. Both hair follicles and sweat ducts collectively occupy only 0.1 % of total skin surface area. Human skins comprises of three distinct but interdependent tissues:

1. Epidermis
2. Dermis
3. Hypodermis

Epidermis:-

It is multilayered and varies in thickness depending on the number of layers of cell and cell size. The water permeability and diffusivity also varies with the different region of skin. It consists of outer stratum corneum and inner viable epidermis.

Stratum corneum:- It is also called as horny layer. When dry, it is 10µm thick but swells to several times when hydrated. It contains many layers of corneocytes, dead and keratinized cells. Stratum corneum is almost impermeable but flexible and act as the main barrier for drug penetration. It is a wall like structure with middle layer of proteins (keratinized cells) embedded within lipid bilayer.

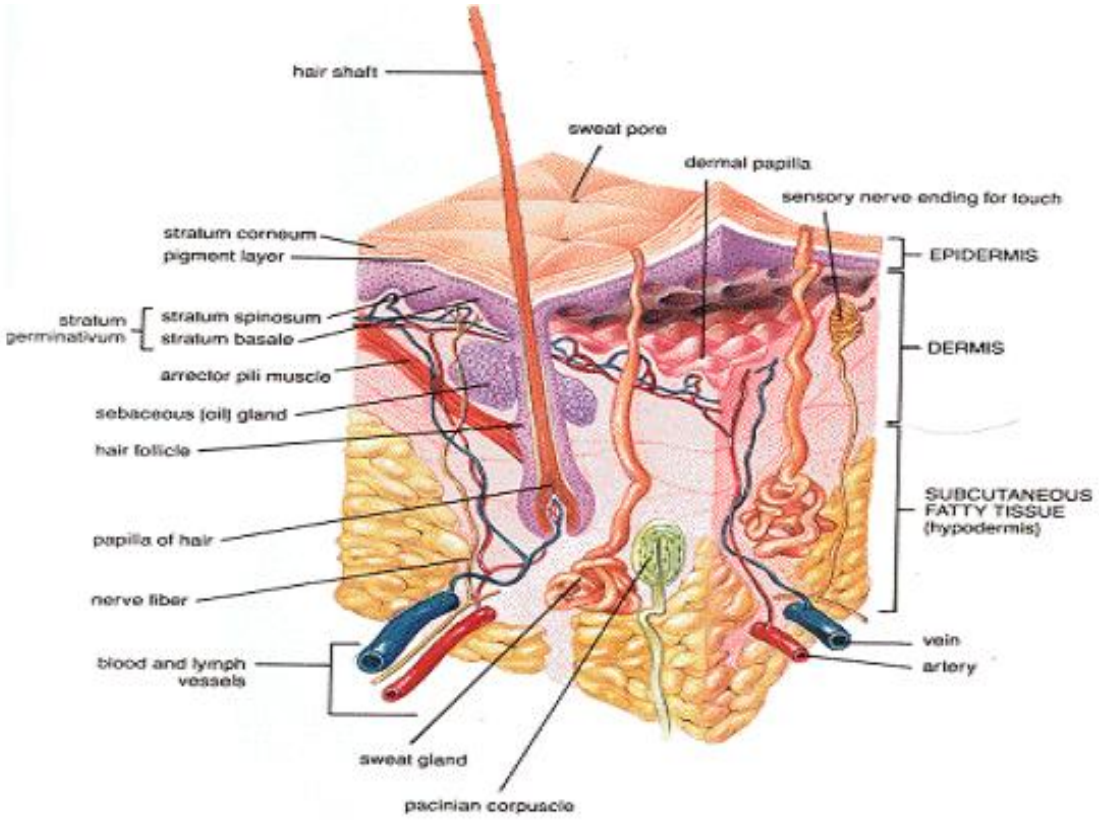


Figure 1: Structure of human skin

Viable epidermis:- It lies below the stratum corneum varies in thickness as per the position in the body. It contains different layers of stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. Basal layer cells divides constantly by mitosis to renew the epidermis by removing the dead keratinized cells from the epidermis. Newly formed basal layer cells changes morphologically and histologically to take the place of stratum corneum.

Dermis:- It is the middle and largest layer of skin supporting epidermis. It is 3 to 5 mm thick and has blood vessel, lymph vessel and nerves in the matrix of connective tissue. The supply of blood maintains the dermal concentration of permeant very low creating a concentration difference around the epidermis. This concentration difference creates necessary concentration gradient for transdermal permeation. It also provide nutrients and oxygen to the skin and eliminating waste and toxic products.

Hypodermis:- It is also called subcutaneous fat tissue. It stores fat and give support to the dermis and epidermis. It has primary blood vessel and nerves and some special sensory organs. It provides mechanical protection, nutritional support and helps in temperature regulation.
For the delivery of drugs through TDDS, drug should pass through all the layers of the skin which is a complex process and affected by many factors.

TRANSPORT THROUGH THE SKIN [2, 32, 34-38]

For the transportation of drug through the skin, drug must pass the stratum corneum first followed by viable epidermis. Then it must pass through the dermis and capillary wall of blood and lymph vessel to reach the systemic circulation.

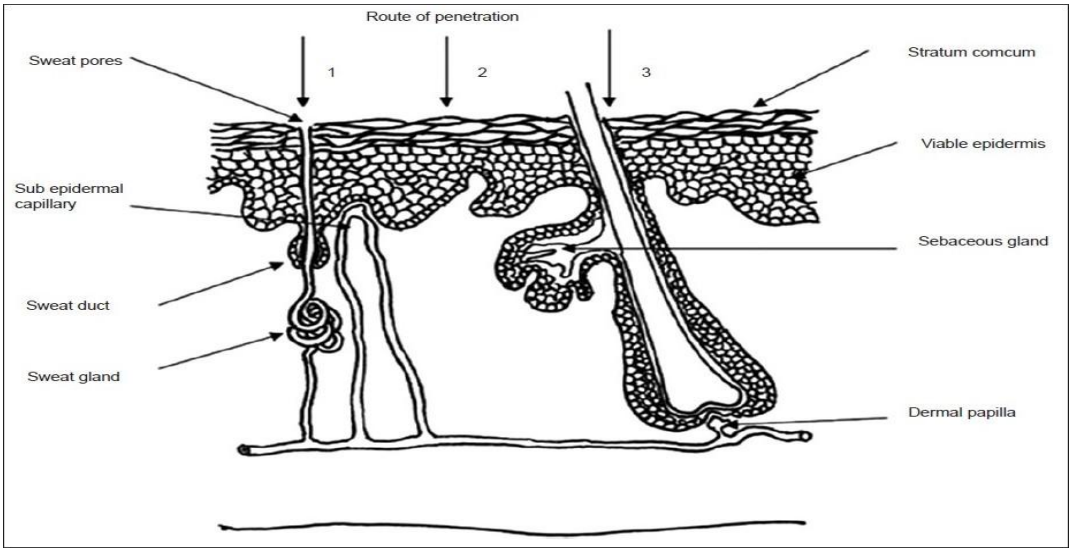


Figure 2: Simplified representation of skin showing routes of penetration: 1. through the sweat ducts; 2. Directly across the stratus corneous; 3. Via hair follicles

1. **Route of drug penetration through skin:-** There are three route of drug penetration through the skin. They are (a) through the hair follicle with associated sebaceous glands, (b) through sweat glands, or (c) across the stratum corneum.
2. Electron photo-microscopic studied shows that intracellular spaces in between the stratum corneum are filled with an amorphous material very reach in lipids. The diffusion volume of stratum corneum varies according to the condition inside the skin. In dry condition, its diffusion volume is as high as 5% while during hydrated condition, its diffusion volume is as low as 1%. The lipid structure between the cell and hydrated proteins within the corneocytes plays a very important role in the permeability of skin. Cell membrane does not have any great role in skin permeability. Two route of drug permeation are shown in figure 2 and 3.
3. Intracellular route: between the cells.
4. Trans cellular route: across the region of lipids. This route is the principal route for polar drugs.

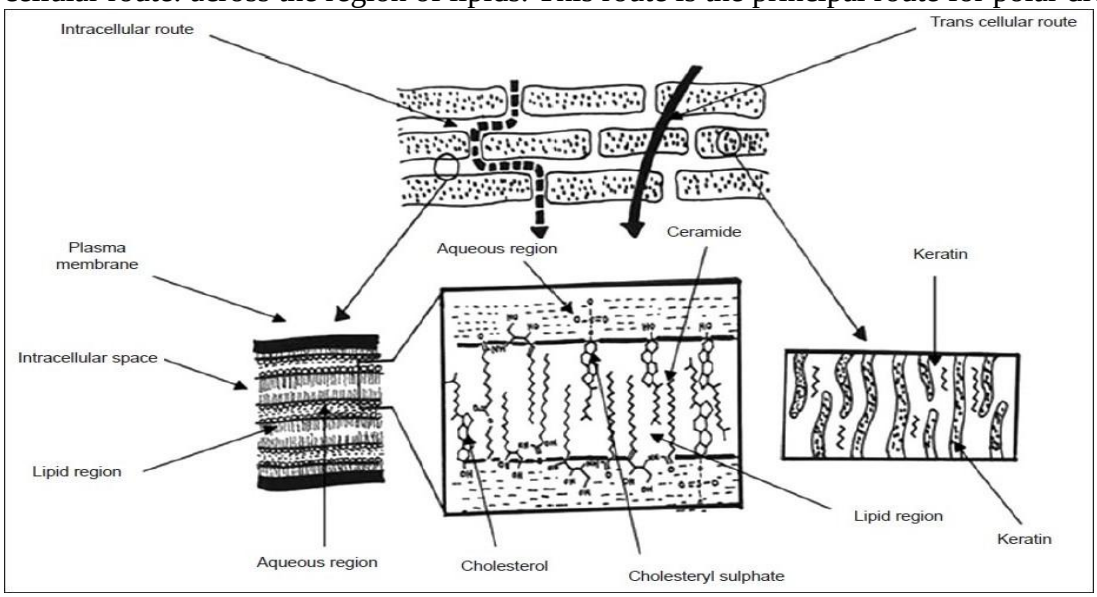


Figure 3: Diagrammatic representation of the stratum corneum and the intracellular and trans cellular routes of penetration

1. Epidermal barrier layer:-

Epidermis contains a layer of dead cells of stratum corneum which offer a great electrical resistance in the movement of drugs and other substances across the skin. Stratum corneum composed of flat keratinized cells. This cell are less denser so does not offer great resistance but the granular layer beneath this keratinized cell layer is very denser and provide almost impermeable resistance. These horny cells do not have nuclei and are inactive in nature.

Different electro microscopic studies and experiments shows that the penetration barrier composed of dead and dry keratin-phospholipid complex of entire stratum corneum cells. The composition of this stratum corneum barrier is cell membrane 5% (lipid & non-fibrous protein), cell contents 85% (lipid-20%, α-Protein-50%, β-Protien-20%, non fibrous protein-10%), Intracellular material 10% (lipid and non-fibrous protein). The resistance of the skin to the passage of water from the sum of the tissue resistance was calculated by Scheuplein and the equation is given as follows:

$$RS = RSC + RE + RD$$

Where, SC = Stratum Corneum
E = Epidermis
S = Skin
D = Dermis
R = Resistance

2. Epidermal diffusion:-

It is a passive process of movement of drug substances from the stratum corneum which is influenced by different factors. Epidermal diffusion is the first phase and clearance from the dermis is second. Clearance from the dermis is affected by different factors like the movements of intestinal fluid, flow of blood etc. The surface gets charged with penetrant after placing drug on the surface. The rate of drug penetration is stable and this stable state is proportional to the difference of concentration across the membrane. The ratio between the rate and concentration should be constant if the rate is equal to the concentration and is known as permeability constant. It gives the measure of permeability.

3. Percutaneous absorption:-

Penetration and permeation of substances into and across various layers of skin into systemic circulations. This process can be divided into three parts:

a. Penetration: entry of substances into a layer.
b. Permeation: movement of substances from one layer to another. Both layers are different in structure and function
c. Absorption: taking up of substances into systemic circulations.

PENETRATION ENHANCERS [9, 39, 40]

Penetration enhancers increases the penetration ability of permeant by breaking the stratum corneum structure. Breaking may be done by chemical which affects both extracellularly and intracellularly. Fluidization and randomization of intercellular lipids, protein denaturation may also cause disruption of stratum corneum. Enhancers of transdermal drug delivery system are physical enhancers, perticulate systems and chemical enhancers.

1. Physical enhancers:

Iontophoresis, electroporation, microneedle, magnetophoresis and ultra sound (also known as phonophoresis or sonophoresis) techniques are the physical enhancers of TDDS used for increasing the penetration of drugs.

2. Perticulate system:

liposomes, microemulsion, transfersome, niosomes and nanoparticles are the enhancers of TDDS.

3. Chemical enhancers:

sulphoxides, glycols, alkanols, terpenes, azones etc. are the chemical enhancers of TDDS.

FACTORS AFFECTING TRANSDERMAL PERMEABILITY [2, 38]

Passive diffusion is the main transport mechanism across skin. Factors affecting the permeability of skin can be grouped into three categories:

1. Physicochemical properties of the penetrant:
   i) Partition co-efficient: Both water and lipid soluble drugs are absorbed across the skin. Changing the penetrant changes the lipid/water partition co-efficient of the molecule.
   ii) pH condition: pH effects the rates of penetration of alkaline and acidic drugs. Ionizable species from aqeous solutions have very strong dependence on its transportation.
   iii) Drug concentration: Since transdermal drug transportation is mainly via passive diffusion. Therefore concentration of drug effects the permeability.

2. Physicochemical properties of the drug delivery system:
   i) The affinity of the vehicle for the drug molecules: It influences the release of drug from the medium and solubility determines its release.whether the drug is dissolved or suspended in the delivery system and its partition co-efficient from the delivery system are the factors on which the release of drugs depends.
   ii) Composition of drug delivery system: Rate of release of drug and permeability of stratum corneum are affected by the composition of drug delivery system.
   iii) Enhancement of transdermal permeation: Stratum corneum have very low permeability. Penetration enhancers can be used to increase the penetration and permeation ability of drugs across the skin.

3. Physicochemical and pathological conditions of the skin:
   i) Skin age: Infant and foetal skin is more permeable than the adult skin but permeability of water is same for both adult and children.
   ii) Lipid film: Lipid fim on skin formed from the excretion of sebaceous glands, sebum and epidermal cell containing emulsifying agents which provide a protection and felp in maintaining the barrier function of stratum corneum.
   iii) Skin hydration: More hydrated the stratum corneum, more will be the permeability of the skin.
   iv) Skin temperature: Rise in temperature increases the rate of skin permeation and subceutaneous absorption by increasing vasodilation of blood vesel.
   v) Cutaneous drug metaboilsm: Drug either reaches the systemic circulation in active form or inactive form. Some of the drugs passing through the skin layers get motabolised by the metabolic enzymes present inside the skin.
   vi) Species differences: mammalian skin shows differences in the anatomy from different species.
   vii) Pathological injury to the skin: permeability increases after skin getting injured. Injury causes disturbances in stratum corneum.

CLASSIFICATION OF TRANSDERMAL DRUG DELIVERY SYSTEM [41-43]

1. According to the transportation of drug molecule through the skin:
   a. Passive:
      i. Matrix
      ii. Reservoir
   b. Active:
      i. Iontophoresis
      ii. Electroporation
      iii. Sonophoresis
      iv. Heat or thermal energy
      v. Microneedles
2. Based on their technical sophistication:
   a. Rate pre programmed drug delivery system:

i. Polymer membrane permeation controlled drug delivery system
ii. Polymer matrix diffusion controlled drug delivery system
iii. Microreservoir partitioned controlled drug delivery system

b. Activation modulated drug delivery system:
i. Physical means:
- Hydrodynamic pressure controlled drug delivery system
- Vapour pressure activated drug delivery system
- Hydration activated drug delivery system

ii. Chemical means
iii. Biological means

c. Feadback regulated drug delivery system:
i. Bio-erosion regulated drug delivery system
ii. Bio-resposive drug delivery system

d. Carrier based drug delivery system:
i. Colloidal perticulates carrier system

COMPONENT OF TRANSDERMAL DRUG DELIVERY SYSTEM [2, 32, 44-54]

1. Drug:-

Drug should be selected with extreme care and precision for successful development of TDDS. Different properties on which the selection of drug for transdermal drug delivery system depends are dose, molecular weight, partition co-efficient, pH melting point, oral bioavailability, half life, therapeutic index, skin reaction, skin permeability co-efficient. Other characters are:

i) Drug should have affinity for both hydrophilic and lipophilic phases.
ii) Potent drug should be used.
iii) Drug should not produce any allergic reaction on the skin.
iv) Partition co-efficient of drug should be in between 1 to 4 (logP).
v) It should be non-sensitizing and non-irritating to the skin.
vi) It should have short self life.
vii) Therapeutic index should be low.
viii) Oral bioavailability should be low.
ix) Drug should be given at low dose, less than 20mg/day.
x) Molecular weight of drug should be less than 400 daltons as they can penetrate the stratum corneum.

Captopril, Indapamide, Clonidine, Propranolol hydrochloride, Carvedilol, Atenolol, Nicardipine hydrochloride, Metaprolol tartrate, Nitrendipine, Verapamil hydrochloride etc are the few examples of drugs which are suitable for transdermal drug delivery system.

2. Polymer matrix:-

It is the primary part of TDDS. It is called as the backbone of TDDS and regulate the release of drug in the skin. Criteria for the selection of polymer to be used in TDDS are:

i) Stable.
ii) Nontoxic.
iii) Easy to manufacture.
iv) Non-antagonistic to the host.
v) Cheap.
vi) Molecular weight and chemical functionality should be adecuate so that drug can diffuse easily.
vii) Should be compatible with the other components of TDDS.

Types of polymers used in TDDS are:

i) Natural polymers: Starch, rubber, gum, cellulose, waxes, proteins etc.
ii) Synthetic elastomers: Acrylonitrite, neoprene, nitrile, silicon rubber etc.
iii) Synthetic polymers: Polyvinyl chloride, polyethylene, polypropylene etc.

3. Permeation enhancers:-

They are also called as accelarant which increases the permeability of drugs across the skin. The flux of drug across the skin mat be written as

$$J = D\, dc/dx$$

Where, J = flux

D = diffusion co-efficient

C = Concentration of the diffusion species

X = Spatial coordinate

i) Solvents: Methanol, ethanol, propylene glycol, glycerol etc.

ii) Surfactants:

- Anionic: Sodium lauryl sulphate diacetyl sulphosuccinate.
- Nonionic: Pluronic F68, pluronic F127.
- Bile salts: Sodium deoxycholate, sodium taurocholate.

iii) Miscellaneous chemicals: Calcium thioglycolate, urea.

4. Other excipients:-

i) Adhesives: They are also called pressure sensetive adhesives (PSA). PSA adhere to the skin due to the interatomic and intermolecular forces between the surfaces.

- Should be non-irritant.
- Should be compatible with the drug.
- There should not be any affect on permeability.
- Can be removed easily.
- No residue should left after washing.

ii) Liner: It is used for the protection of transdermal patch during storage and is removed just before use. It is said to be a part of packing material more than a component of TDDS. It composed of base layer (paper fabric, polyvinylchloride) and release layer (teflon. Silicon).

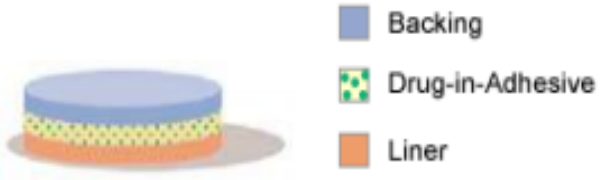
iii) Backing: it gives protection to the patch from environment. Examples are polyester films, polyurethylene etc.

TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM[4, 7, 10, 32, 33, 55-57]

There are four main type of transdermal patches(TDDS). They are:

1. Single-layer Drug-in-Adhesive:-

In this system, drug is placed in between the two layers of adhesives and both drug and adhesive forms a single layer. This single layer drug-in-adhesive is placed between layers of backing and liner. Adhesive plays a dual role of adhering to the skin along with being the formulation foundation containg all the excipients and drug in single layer. Simple diffusion controls the rate of drug release.



- Rate of drug release can be given by the following equation:

$$dQ/dT = \frac{Cr}{1/Pm + 1/Pa}$$

Where,

Cr = drug concentration in reservoir compartment

Pa = permeability co-efficient of adhesive layer

Pm = rate controlling membrane

- 'Pm' may be calculated as:

$$Pm = \frac{Km/r.\ Dm}{hm}$$

where,

Km = partition co-efficient for the interfacial partitioning of drug from the reservoir to membrane

Dm = diffusion co-efficient of rate controlling membrane

hm = thickness of the rate controlling membrane

- 'Pa' may be calculated as:

$$Pa = \frac{Ka/m.\ Da}{ha}$$

where,

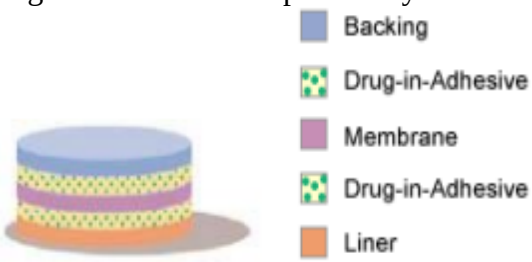
Ka = partition co-efficient for the interfacial partitioning of for the membrane to adheshive

Da = diffusion co-efficient of adhesive layer

ha = thickness of adhesive layer

2. Multi-layer Drug-in-Adhesive :-

It is similar to the single layer drug-in-adhesive but it contains more than one layer of drug-in-adhesive. Layers of drug-in-adhesive are seperated by membrane or backing film.



The rate of drug release is given by:

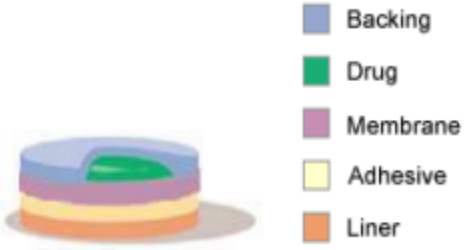
$$dQ/dt = \frac{Ka/r.\ Da}{ha} Cr$$

where,

Ka/r = partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.

3. Drug Reservoir-in-Adhesive:-

In this system, drug is not connected to the adhesive and is seperated by a layer of semi permeable membrane. Reservoir is placed in between the adhesive. Drug is situated in the form of solution or suspension.backing and liner forms the outer layer of this system.



The rate of drug release is given by;

$$dQ/dt = \frac{Ka/r.\ Da}{ha\ (t)}\ A\ (ha)$$

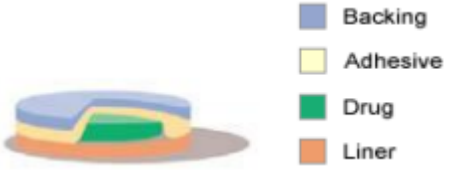
where,

t = time

Thickness of adhesive layer increases with increase in time resulting in drug loading level.

4. Drug Matrix-in-Adhesive :-

In this system, a semisolid matrix containing drug in solution or suspension form is incorporated in contact with liner. Adhesive is placed over the matrix which in turn in contact with backing.



The rate of drug release is given by:

$$\frac{dQ}{dt} = \frac{AC_P\ D_P^{1/2}}{2t}$$

Where,

A = initial drug loading dose dispersed in the polymer matrix

Cp = solubility of the drug in the polymer

Dp = diffusivity of the drug in the polymer

Here, Cp = Cr, since only drug is released from the polymer.

PREPARATION OF TRANSDERMAL DRUG DELIVERY SYSTEM [58-66]

1. Asymmetric TPX membrane method :-

Heat soluble polyester film (type 1009, 3m, concave 1cm diameter) is used as backing membrane. Concave membrane is consealed by TPX {poly(4-methyl-1-pentene)} membrane which in turn sealed with adhesive. TPX membrane is formulated by dissolving TPX in the mixture of solvent and nonsolvent additives at 60°C which forms polymer solution, kept at 40°C for 1 day., cast on a glass plate(predetermined thickness) and evaporated at 50°C for 30 sec. glass plate placed in coagulation bath(25°C). after 10 mins, membrane removed and air dried.

2. Circular teflin mould method :-

Organic solvent containing polymers is seperated into two half and in one part, drug(calculated) is added and in other part, enhancers are added. Both half are added and Di-N-butylphthalate(plastisizer) is added. Stirred for 12 hours and placed in teflon mouldand evaporated for 1 day. Dried film produced is kept for 1day at around 25°C in a dessicator containing silica gel.

3. Murcury substrate method :-

Drug in polymersolution with plastisizer is stirred for 10-15 mins to produce dispersion. Dispersion is placed in murcury surface covered with inverted funnel.

4. By using “IPM membranes” method :-

In water-propylene glycol mixture containing carbomer 940 polymer, drug is dispersed and stirred (12 hours). Nutralized and added triethanolamine to make viscous. Solution gel is formed if neccesary using buffer pH 7.4. gel is pored in the IPM membrane.

5. By using "EVAC membranes" method :-
   Drug is dissolved in propylene glycol(gel formation), carbopol resin is added and solution is nutralized by 5% w/w NaOH. Drug in gel form is placed on sheet of backing layer and rate controlling membranes{ethylene vinyl acetate copolymer (EVAC)} is placed over geland edges are heated to seal.

6. Aluminium backed adhesive film method :-
   System producing unstable metrices are formulated by this method. Drug dissolved in solvent(chloroform) and adhesive added to it. Custammade aluminium lined with aluminium foil is used and ends withdrawn with cork blocks.

7. Preparation of TDDS by using proliposomes :-
   Proliposomes can be prepared by keeping 5mg mannitol in 100ml round bottom flask at 60-70°C, rotated(80-90 rpm) and dried(30 mins).after drying, temperature of water bath is kept to 20-30°C. drug and lecithin(0.1:2.0) mixed in organic solvent and 0.5ml aliquot of organic solution added to flask at 37°C. Second aliquots(0.5ml) is added after drying. After last loading, flask is connected to lyophilizer. Then proliposomes placed in dessicator for a night and passed trhough the 100 mesh sieve apparture, stored in glass bottle at freeze temperature.

8. By using free film method :-
   Free film of cellulose acetate and 2% w/w polymer solution is prepared. Polymer solution(5ml) is introduced in a glass ring placed over mercury surface in glass petridish. Inverted funnel is plaed over petridish to control evaporation rate.after complete evaporation, film formation is observed and seperated when dry. Film is kept between wax paper in desiccator.

EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM [9, 44, 51, 58, 66 -72]

1. Physicochemical evaluation:-
   i) Interaction studies: These studies detects any chemical and physical interaction between drug and excipients which may affect the bioavailability and stability of drug. Studies are done in FT-IR, thermal analysis, UV and chromatographic techniques.
   ii) Thickness of the patch: Thickness is measured by digital micrometer at different position of patch and their average is taken. Standard deviation are also measured. Dial gauge, screw gauge are also used.
   iii) Weight uniformity: Patch is dried for 4 hours at 60°C. small pieces of patch having same area are obtained weighed using digital balance. Standard deviation is also calculated.
   iv) Folding andurance: Patch is folded repeatedly at specific place until breaking. The number of times it is being folded is the folding andurance value.
   v) Percentage moisture content: Patch is weighed and kept in desiccator containg fused calicium chloride for 1 day at room temperature and weighed again.
   Percentage moisture content = {(initial weight – final weight)/final weight}X 100
   vi) Percentage moisture uptake: Patch is weighed and kept in desiccator containg saturated potassium chloride solution for 1 day at room temperature and weighed again.
   Percentage moisture uptake = {(final weight – initial weight)/final weight} X 100
   vii) Water vapour permeability(WVP) evaluation: foam dresing method is used.
   WVP = W/A, where W= amount of vapour permeated(gm/24 hours), A= surface area exposed(m2).
   viii) Drug content: Patch is dissolved in a solvent and filtered. Drug content is analyzed using UV and HPLC technique.
   ix) Peel adhesion test: Tape is placed on a stainless steel plate and tape is pulled at 180°. Force required to remove tape is calculated.

x) Thumb tack test: Thumb is to be pressed on the tape and its tack property is determined.
xi) Rolling ball tack test: Stainless steel ball(7/16 inch diameter) is released from upward track which rolls over the adhesive. Distance traveled by ball on adhesive is the measure of tack(inch).
xii) Quick stick test: The force required to break te bond between adhesive and substate by pulling tape from substate at 90° at a speed of 12inches/mins is measured.
xiii) Prove tack test: The prove is made in contact with adhesive and bond formation takes place. The force required to remove prove from adhesive is the tack value.

2. *In vitro* evaluation:-
   i) *In vitro* drug release studies: Franz diffusion cell is used. Skin is placed on O ring and phosphate buffer(7.4 pH) is introduced in reservoir. Patch is placed over skin and diffusion medium in reservoir is stirred. At time interval, old fluid is replaced by same new fluid in reservoir.
   ii) *In vitro* skin permeation studies: Rat skin is placed in between the compartments of diffution cell having temperature around 32°C. Sampling is done at intervals and samples are filtered and analyzed using spectrophotometer and HPLC.
3. *In vivo* evaluation:-
   In vivo studies can be done using:
   i) Animal models: Mouse, hairless dog, hairless rat, hairless rhesus monkey, rabbit ets. Hairless animals are preffered over hairy animals.
   ii) Human models: clinical trials are done on human and groups of humans. It comprises phase I, II, III and IV and each having its perticular observation and significance.
   iii) Skin irritaion study: Skin of rabbit or gunia pig is removed and cleaned using rectified spirit. Patch is mounted over the skin and removed after 1 day and observed. Patch is classified according to injury.
   iv) Stability studies: Samples is stored at around 40°C for 6 months and withdrown after every 1 month to analyze.

OUTLINE OF RECENT TECHNIQUES IN ENHANCING TRANSDERMAL DRUG DELIVERY SYSTEM [73-80]

1. Structure-based enhancement techniques:
   i) Transdermal patches: It is a device which is applied over the skin for drug delivery across the skin into the systemic circulation.
   ii) Microfabricated microneedles: It contains patch along with a hypodermic needle for effective drug transportatio through the skin into systemic circulation.
   iii) Macroflux: device having an area of 8 cm and having 300 micro projection per cm2. Each microprojection is less than 200Î¼ m.
   iv) Metered-dose transdermal spray: A liquid preparation(solution) having drugs which is applied over the skin topically for drug transfer.
2. Electrically-based enhancment techniques:
   i) Iontophoresis: Current passed through the skin using electrode. Electrode is conected to the formulation.
   ii) Ultrasound: Drug mixed with creams or gels which produces ultrasound energy transfer across the skin.
   iii) Photomechanical waves: This waves increases the permeability of stratum corneum and increases drug transfer.
   iv) Electroporation: High-voltage electrical pulses are applied in the skin which increases diffustion of drugs.
   v) Electro-osmosis: A voltage difference is applied to porous membrane resulting in fluid flow with no concentration gradients.
3. Velocity-based enhancement techniques:
   i) Needle free injections: Intraject, jet syringe, iject, implaject and mini-ject.
   ii) Powderject device: Drugs are introduced into the skin with the help of air flow usually helium gas.
4. Other enhancement techniques:

i) Transfersomes: this device enter the skin along with skin moisture gradient and creates a drug store house in the systemic circulation.
ii) Medicated tatoos: Modification of temporary tatoo containing drugs for delivery through skin.
iii) Skin abrasion: Upper layer of skin is removed for better transport of drug.
iv) Controlled heat aided drug delivery(CHADD) system: heat is applied to the skin resulting in increased microcirculation and permeabilty in blood vessel.
v) Laser radiation: Skin is exposed to laser beam resulting in removal of stratum corneum and increased drug permeability.
vi) Magnetophoresis: Magnetic field also increases the permeability of drug.

MARKETED PRODUCTS OF TRANSDERMAL DRUG DELIVERY SYSTEM [81]

Transdermal drugs approved by US FDA are as follows:

Year of approval	Marketing company	Product name	Drug	Indication
1979	Novartis Consumer Health	Transdern-Scop	Scopalamine	Motion sickness
1981	Novartis	Transderm-Nitro	Nitroglycerin	Angina pectoris
1984	Boehringer Ingelheim	Catapress-TTS	Clonidine	Hypertension
1986	Novartis	Estraderm	Estradiol	Menopausal symptoms
1990	Janssen Pharmaceutica	Duragesic	Fentanyl	Chronic pain
1991	GlaxoSmithKline, Novartis Consumer Health, Elan	Nicoderm Habitrol, ProStep	Nicotine	Smoking cessation
1993	Alza	Testoderm	Testosterone	Testosterone deficiency
1995	Iomed	Iontocaine	Lidocaine/epinephrine	Local dermal analgesia
1998	Novartis	Combipatch	Estradiol/norethidrone	Menopausal symptoms
1999	Endo Pharmaceuticals	Lidoderm	Lidocaine	Post-herpetic neuralgia pain
2001	Ortho-McNeil Pharmaceutical	Ortho Evra	Ethinyl estradiol/norelgestromin	Contraception
2003	Bayer Healthcare Pharmaceuticals	Climara Pro	Estradiol/levonorgestrel	Menopausal symptoms
2003	Watson Pharma	Oxytrol	Oxybutynin	Overactive bladder
2004	Echo Therapeutics	SonoPrep	Lidocaine (ultrasound)	Local dermal anesthesia
2005	Endo Pharmaceuticals	Synera	Lidocaine/tetracaine	Local dermal analgesia
2006	Alza	Ionsys	Fentanyl HCl	Acute postoperative pain
2006	Shire	Daytrana	Methylphenidate	Attention deficit hyperactivity disorder
2006	Bristol-Myers Squibb	Emsam	Selegiline	Major depressive disorder
2007	Novartis	Exelon	Rivastigmine	Dementia
2007	Schwarz Pharma	Neupro	Rotigotine	Parkinson's disease

CONCLUSION [33]

Various works have been done related to transdermal drug delivery system. Transdermal drug delivery system is very useful for local and topical action of drugs. Because of its advantages and permeation enhancers which significantly increasing the number of drugs of transdermal drug delivery system and getting lot of interest and topic of research in researchers. This system of drug delivery is the next generation of drug delivery system which would increase the therapeutic effect of drugs. But these days researchers are inventing new devices and new drugs that can be administered via this system, the use of TDDS is growing rapidly in the recent days.

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