An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

TRANSDERMAL DRUG DELIVERY SYSTEM- AN OVERVIEW

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ARTICLE INFO

Key words:

TDDS
Preparation
Evaluation
methods

ABSTRACT

Transdermal drug delivery is the application of drug on the skin surface so that it can permeate through the skin and reaches the systemic circulation. Transdermal route have a number of advantages over conventional drug delivery routes such as avoidance of first pass effect, enhanced bioavailability, patient compliance, steady state plasma drug level, painless delivery of drugs, ease of application and easy removal of patch in case of toxicity. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Today about two third of drugs (available in market) are taken orally, but these are not as effective as required. To improve upon the features the transdermal drug delivery system was emerged. Amongst all techniques which were used for release drugs in a controlled way into the human body, transdermal drug delivery system (TDDS) is widely recognized as one of the most reliable, appealing as well as effective technique. Over the last two decades, transdermal drug delivery had become an appealing and patience acceptance technology as it is minimize and avoids the limitations allied with conventional as well as parenteral route of drug administration such as peak and valley phenomenon i.e. exhibit fluctuation in plasma drug concentration level, pain and inconvenience of injections; and the limited controlled release options of both.

1. INTRODUCTION:

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient.[1]

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To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific), spatial and temporal placement within the body thereby reducing both the size and number of doses. New drug delivery system are also essential for the delivery of novel, genetically engineered pharmaceuticals (i.e. peptides, proteins) to their site of action, without incurring significant immunogenecity or biological inactivation.[3] Drugs can be delivered across the skin to have an effect on the tissues adjacent to the site of application (topical delivery) or to have an effect after distribution through the circulatory system (systemic delivery). While there are many advantages to delivering drugs through the skin the barrier properties of the skin provide a significant challenge. By understanding the mechanisms by which compounds cross the skin it will be possible to devise means for improving drug delivery.

Classification Of TDDS [2,4]

TDDS generally fall into the following sub categories

1. Polymer membrane permeation – controlled
2. Polymer matrix diffusion controlled
3. Drug reservoir gradient controlled
4. Micro reservoir dissolution controlled
   a) Liquid filled laminate structure
   b) Peripheral adhesive laminate structure
   c) Solid state laminate structure

In terms of the drug release mechanism, TDDS is divided into 6 categories

1. Solution in matrix
2. Suspension in controlled matrix
3. Suspension in porous matrix
4. Solution upstream of membrane
5. Suspension upstream of membrane
6. Laminated membrane down stream

TDDS in skin targeting [1,3,8]

The transdermal drug delivery systems are used to target the drugs for purposes, described under

1. Surface of skin: Surface of skin is targeted for locally acting substances like disinfectants, cosmetics, insect repellent etc. in which drug acts only on the surface of the skin and no penetration of drug or chemicals in the skin.

2. Skin layers itself: The delivery of drug substances within the skin layers is also known as topical delivery and skin layers are targeted when disease or infection is present in skin itself. E.g., microbial infection, inflammation of skin and neoplasias etc.

3. Systemic Circulation: It is considered as an alternative to oral and other conventional delivery routes for systemic delivery of drugs. The drug has to be permeated through the various skin layers to the blood circulation for its systemic effect.

Advantages of TDDS [4,5,6,7]

Transdermal drug delivery systems offer several important advantages over more traditional approaches, including:

1. longer duration of action resulting in a reduction in dosing frequency
2. Increased convenience to administer drugs which would otherwise require frequent dosing
3. improved bioavailability
4. more uniform plasma levels
5. Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.
6. Self administration is possible with these systems.
7. The drug input can be terminated at any point of time by removing transdermal patch.

Disadvantages of TDDS [4,5,6,7]

1. The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.
2. Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin's impermeability.
3. Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
4. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
5. The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

Limitations [3,5,10,11,12]

1. The drug moiety must poessess some physicochemical properties for penetration through
   skin and if dose of drug is large i.e. more than 10-25mg/day transdermal delivery is very difficult.daily dose of drug preffered less than 5mg/day.
2. Local irritation at the site of administration such as itching ,erythema and local edema may be caused by drug or the excipients used in the formulations.
3. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
4. Some patients develop contact dermatitis at the site of application due to system components.
5. The barrier function of the skin changes from one site to another ,from person to person and with age.
6. Poor skin permeability limits the number of drugs that can be delivered in this manner.
7. A high drug level cannot achieve by this system.
8. Transdermal drug delivery is unable to deliver ionic drugs.
9. Transdermal drug delivery system is restricted to potent drug.
10. It cannot deliver drugs in a pulsatile fashion.

11. Tolerance inducing drugs or those (e.g., hormones) requiring chronopharmacological management is not suitable candidates.
12. Required significant lag time.
13. Drug molecule having large molecular size (>1000 Dalton) cannot developed for transdermal deliver.

Pathways of drug absorption by skin [1,9,13,14]

The drug can be absorbed by various pathways through the skin depending on the physicochemical properties of the drug. Both lipophilic and hydrophilic drugs are absorbed from different routes. The upper stratum corneum of the skin opposes the absorption of drug but presence of various absorption routes facilitates the entry of drug and transport of drug to the systemic circulation.

Various drug absorption routes are as follows:

a) Transfollicular route

Transfollicular route is the shortest pathway that drug has to follow to reach the systemic circulation that provides a large area for diffusion of drugs. Skin has various sweatglands, oil glands, hair follicles and pores opening to the outer surface of the skin via their ducts. These ducts offer a continuous channel across the stratum corneum for drug transport but various factors like secretion from glands, content and amount of secretion etc., affect the transport of drugs through this route. Howeve this route occupies only 0.1% of total skin surface and therefore contributes a little.

b) Transcellular route

Drug delivering through this route passes from corneocytes which has highly hydrated keratin creating hydrophilic pathway. Corneocytes are surrounded by lipids connecting these cells. So a drug requires a number of partitioning and diffusion steps. It is the most widely used route by various types of drugs. In transcellular route drug passes through the matrix (cytoplasm) of cells. This route is suitable for hydrophilic drugs. The drug passes through the corneocytes of stratum corneum. The highly hydrated keratin provide aqueous pathway to the hydrophilic drugs. A number of partitioning and diffusion steps are needed to pass the drug through the cell matrix.

c) Intercellular route

As name indicates in intercellular pathway the drug diffuses through the continuous lipid matrix present between the cells. The barrier property of this route is due tortuous structure formed by corneocytes and the drug has to pass through the alternating lipid and aqueous domain by partitioning into the lipid bilayer and diffusing to the inner side. It has been found that water has to travel 50 times more by this route so; it is suitable mainly for uncharged lipophilic drugs.

Factors affecting transdermal permeability [1,18]

Various factors are involved in controlling and rendering permeability of drugs through the skin. These factors may be drug related or skin physiology related. Not only a single reason is responsible in affecting the permeation of drugs but a number of factors are involved which are mutually dependent on each other and are classified below:[16]

1) Physiochemical properties of drug
2) Formulation characteristics
3) Skin physiology and pathology

1) Physicochemical properties of drug

The various physicochemical properties of drug which can alter the absorption and diffusion of drug through the skin are:

a. Size of drug molecules and molecular weight

Size of drug molecules varies inversely to the penetration through the skin. Drug molecules larger than 500 dalton creates problem in percutaneous transport. Greater the molecular weight smaller is the absorption. So size of drug molecules should not be so high that it creates
problem in absorption.

b. Partition coefficient and solubility

Drugs are either lipophilc or hydrophilic in nature. The partition co-efficient determine the solubility or diffusion of drug in lipids and aqueous systems. Drugs possessing both lipid and water solubility are suitable for percutaneous absorption as skin is made of lipid bilayer so drug should have some lipid solubility for absorption but at same time it should have some hydrophilicity to diffuse inside the skin in aqueous environment. Therefore, a drug candidate should have optimum partition co-efficient. The partition coefficient of a drug can be altered by changing the solvent system or by chemical modification in the structure of the drug candidate without affecting its pharmacological activity of the drug.

c. Drug concentration

The absorption of drugs through the skin is governed by passive diffusion. Drug moves according to concentration gradient i.e. from high concentration to low concentration. So the concentration of drug in the formulation applied over the skin determines the diffusion rate across the skin. Higher the concentration more will be the permeation.[17]

d. pH conditions

Most of the drugs are either acidic or basic in nature. So the pH of the drug molecule determines its ionization at skin surface. Unionized drugs or species have better absorption than ions or ionic species, so pH plays an important role in determining extent of penetration of drug. Transport of ionizable species in aqueous environment is pH dependent.

2) Formulation characteristics [15,18]

The various formulation characteristics can also alter the permeation of drug molecule through the skin. These are as follows:

a. Release rate of the drug

The release of drug from the formulation is influenced by the affinity of the carrier for the drug in formulation and physiochemical properties of drug like solubility of drug in solvent and interfacial partitioning of drug from formulation to skin determines the release rate of the drug.

b. Ingredients of formulation

Various excipients and polymers present in the formulation can affect either release of drug or permeation of drug through the skin by altering the physicochemical properties of drug or skin physiology.

c. Presence of permeation enhancers

Permeation enhancers of different categories are used to increase the permeation of drug through the skin. These alter the integrity of the skin (physicochemical and physiological modification) temporarily and open the skin pores for absorption. Permeation enhancer may be chemical substance which act chemically or physical permeation enhancer which physically interact with the skin integrity.

3) Physiological and pathological condition of the skin [20]

The physiological and pathological conditions of the skin alter and affect the permeation of drug candidate through the skin by changing the properties of the skin.

a. Hydration of skin

Hydration of the skin causes the swelling of stratum corneum of the skin and provides some fluidity to the skin. Hydration also increases the permeant solubility and partitioning from vehicle to the membrane. So the permeation of drug molecules occurs easily through the hydrated skin.

b. Skin temperature

On increasing the temperature of the skin the percutaneous absorption of the drug increases due to fluidization of lipids and vasodilation of the blood vessels which are in contact with the skin so increase in blood flow to the skin increases the absorption through the skin.

c. Skin age

It is assumed that skin of young and elderly are more permeable than middle aged persons. In premature infants stratum corneum is absent and children are more susceptible to toxic effects of drugs through the skin.

d. Blood flow

Changes in peripheral circulation do not affect transdermal absorption butan increase in blood flow increase the concentration gradient across the skin and reduces the total time of residence of the drug molecules in the dermis by continuously removing it.[21,22]

e. Pathology of the skin

Disease of the skin and any injury to the skin causes the rupturing of the lipid layers of the stratum corneum which alters the skin penetration of drugs. Pathogens cause the disruption of skin layers by digesting them and can create pores in the skin so the integrity of the skin changes in both pathological conditions and in injury.

f. Regional Site of skin

The skin differs in anatomical features such as thickness of stratum corneum, number of hair follicles and number of sweat glands per unit surface area. This difference may exist from site to site, person to person and species to species. So in all cases percutaneous absorption differs from one another.[23]

g. Skin flora and enzymes

Various metabolizing enzymes and metabolizing microbes are present in the skin which metabolizes the drugs passing through the skin. Only a few drug candidates are there which reaches in active form in the circulation otherwise drugs are metabolized to various extents in the skin. E.g., 95% of the testosterone absorbed gets metabolized in the skin

Kinetics of drug absorption [1, 24, 25]

The main mechanism by which the drug is absorbed through the skin is passive diffusion of drug through the skin. It means drug is absorbed according to the concentration gradient as high concentration of drug is present on the skin as compared to inside of the skin so drug molecules diffuses from reservoir to systemic circulation through the skin. The rate of drug absorption by passive diffusion is controlled by fick's law of diffusion.

The rate of permeation is dQ/dt is given by:

$$dQ/dt = Ps (Cd - Cr) \longrightarrow 1$$

Where Cd is the concentration of the in donor phase i.e., on the skin surface and Cr is the concentration of the drug in receptor phase i.e., inside the skin in systemic circulation.

Pr is the overall permeability constant and is given by following equation:

$$Pr = (KsDss/ hs) \longrightarrow (2)$$

Where Ks is partition coefficient of the drug, Dss is apparent diffusivity of the drug and hs is thickness of the skin.

So, permeability constant Ps may be considered as constant since Ks and Dss and hs (from equation 2) are constant under certain given set of conditions. So a constant rate of diffusion is achieved if

$Cd > Cr$.

So rate of diffusion dQ/dt in equation 1 can reduce to:

$$dQ/dt = Ps. Cd \longrightarrow (3)$$

To maintain the permeation rate (dQ/dt) constant, Cd value should remain constant throughout the permeation process across the skin. To maintain Cd constant the drug release rate (Rr) should be always greater than absorption

rate (Ra) i.e.,(Rr) > (Ra).
So the concentration of drug on skin surface is always greater than saturation solubility of the drug in the skin (C^e_s) i.e.,Cd > C^e_s and a maximum skin permeation rate
(dQ/dt)m is obtained:
(dQ/dt)m = Ps. C^e_s ⟶ (4)

Basic Components of Transdermal Drug Delivery Systems [5, 10,12]
1. Polymer matrix or matrices.
2. The drug
3. Permeation enhancers
4. Other excipients

1. Polymer Matrix
The Polymer controls the release of the drug from the device. Possible useful polymers for transdermal devices are:
a) Natural Polymers:
e.g. Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.
b) Synthetic Elastomers:
e.g. Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.
c) Synthetic Polymers:
e.g. Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidine, Polymethylmethacrylate, Epoxy etc. [31]

2. Drug
For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.
Physicochemical properties [26]
1. The drug should have a molecular weight less than approximately 1000 daltons.
2. The drug should have affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
3. The drug should have low melting point.
Along with these properties the drug should be potent, having short half life and be non irritating.

3. Permeation Enhancers
These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant.
These may conveniently be classified under the following main headings:
Solvents These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids.
Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide; pyrrolidones – 2 pyrrolidone, N-methyl, 2-purrolidone; laurocapram (Azone), miscellaneous solvents – propylene glycol, glycerol, silicone fluids, isopropyl palmitate. [27]
Surfactants
These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs.The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.
Anionic Surfactants: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl sulphoxide etc.
Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.
Bile Salts: e.g. Sodium ms taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.
Biary system: These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways .e.g. Propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid.
Miscellaneous chemicals
These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents.
Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-o-methyl-ß-cyclodextrin and soyabean casein

4. Other Excipients
Plasticizers: Palsticizers have also been used in many formulations ranging from 5 to 20% (w/w, dry basis). Along with the brittleness and ductility of the film, it is also responsible for adhesiveness of the film with other surfaces or membranes and improvement in strength of film. Some of its examples are glycerol or sorbitol, at 15%,w/w, dry basis, phosphate, phthalate esters, fatty acid esters and glycol derivatives such as PEG 200, and PEG 400.

Various methods for preparation TDDS: [5]
a. Asymmetric TPX membrane method:
A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive. [(Asymmetric TPX membrane preparation): These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°c to form a polymer solution.
The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardner knife. After that the casting film is

evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs.[28]

b. Circular teflon mould method:

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular teflon mould. The moulds are to be placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation.

c. Mercury substrate method:

In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10- 15 minutes to produce a homogenous dispersion and poured in to a leveled mercury surface, covered withinverted funnel to control solvent evaporation.

d. By using "IPM membranes" method:

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

e. By using "EVAC membranes" method:

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is us+ed for the preparation of gel. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

f. Aluminium backed adhesive film method:

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custammade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

g. Preparation of TDDS by using Proliposomes:

The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°c temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

h. By using free film method:

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

Advances in Transdermal Drug Delivery: [2,3,4,10]

The continuous advancement in the science and technology is making the TDDS as the preferred and most convenient route for most of the drugs. The transdermal delivery is categorized into 3 generations according the advancements in TDDS

First generation

It includes traditional patches having simple design. These include simple reservoir patches or matrix adhesive systems. These are composed of simple backing layer, rate controlling membrane, laminate and adhesive system.

Second generation

The second generation patches are having addition of permeation enhancers with simple patch. These permeation enhancers increase the drug delivery rate and amount of small lipophilic drug molecules through the skin. The permeation enhancer causes the irritation, damage or disruption of the skin to reverse its barrier property. Second generation patches includes chemical permeation enhancers, solvents, gentle heat and physical damage as the mean of permeation enhancement.

Third generation

The third generation patches are developed to permeate large hydrophilic drug molecules. Hormonal delivery through the skin patch become possible only by using latest techniques such as Iontophoresis, Sonophoresis, electrophoresis, Magnetophoresis and microneedle technique etc. These permeation enhancers forcefully allow the drug molecules to pass across the skin or physically damage the skin.

Recent Technology Used in TDDS

Iontophoresis:

This method involves the application of a low level electric current either directly to the skin or indirectly via the dosage form in order to enhance permeation of a topically applied therapeutic agent. Increased drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms: Electro-repulsion(for charged solutes), electro-osmosis (for uncharged solutes) and electro-pertubation (for both charged and uncharged). Several iontophoretic systems are currently under commercial development including the Phoresor device developed by Iomed Inc. and the Vyteris and E-TRANS devices developed by Alza Corp.

Electroporation:

This method involves the application of high voltage pulses to the skin which has been suggested to induce the formation of transient pores. High voltages (100 V) and short treatment durations (milli seconds) are most frequently employed. Other electrical parameters that affect permeation rate include pulse properties such as waveform, rate and number. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with molecular weights greater than 7000 Daltons.

Microneedle-based Devices:

The very first microneedle systems, described in 1976, consisted of a drug reservoir and a plurality of projections (microneedles 50 to 100 mm long) extending from the reservoir, which penetrated the stratum corneum and epidermis to deliver the drug. The ALZA Corp. has recently commercialized a microneedle technology named Macroflux which can either be used in combination with a drug reservoir or by dry coating the drug on the micro projection array24, the latter being better for intracutaneous immunization.

Abrasion:

The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. Some of these devices are based on techniques employed by dermatologists for superficial skin resurfacing (e.g. microdermabrasion) which are used in the treatment of acne, scars, hyperpigmentaion and other skin blemishes.

Needle-less Injection:

This is reported to involve a pain-free method of administering drugs to the skin.

Over the years, there have been numerous examples of both liquid (Ped-O-Jet, Iject, Biojector2000, Medi-jector and Intraject) and powder (PMED device formerly known as Powderject injector) systems. The latter device has been reported to successfully deliver testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin. of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre-treatment and is frequently referred to as sonophoresis or phonophoresis. The SonoPrep device (Sontra Medical Corp.) uses low frequency ultrasound (55 kHz) for an average duration of 15 seconds to enhance skin permeability. This battery-operated, handheld device consists of a control unit, ultrasonic horn with control panel, a disposable coupling medium cartridge, and a return electrode

Laser Radiation

This method involves direct and controlled exposure of a laser to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs.

Approaches in the development of transdermal therapeutic system:[3]

Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies are as follows:

Adhesive dispersion type system:

The system consists of drug-impermeable backing membrane, the drug reservoir which is prepared by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting or hot melting onto a flat sheet of drug-impermeable backing to form a thin drug reservoir layer. On top of this, a layer of rate-controlling adhesive polymer(non-medicated) of constant thickness is spread to produce an adhesive diffusion-controlled drug delivery system with

detachable release liner which in an ideal situation is removed and the patch is applied to the skin for a required period of time.

Membrane permeation controlled system:

In this system the drug reservoir is totally embedded in a compartment molded between a drug-impermeable backing laminate and a rate controlling polymeric membrane The drug molecules are permitted to release across the rate controlling membrane simply by diffusion process through the pores. In the reservoir compartments, the drug solids are dispersed homogenously in a solid polymeric matrix (e.g. polyisobutylene) suspended in the unleachable viscous liquid medium (e.g. silicon fluid) to form a gel-like suspension, or dissolved in a releasable solvent (e.g. alkyl alcohol) to form a gel like in solution. The rate controlling membrane, can be either a microporous or non-porous polymeric membrane e.g. ethylene–vinyl acetate copolymer, having specific drug permeability. On the top surface of the polymeric membrane a thin layer of drug compatible adhesive polymer, e.g., silicone adhesives, can be applied, to provide intimate contact of the transdermal system with the skin surface. The release rate from this transdermal system can be tailored by varying the polymer composition, thickness of the rate controlling membrane, permeability coefficient and adhesive. Examples of this system are TransdermScop (Scopolamine- 3 days protection) of motion sickness and Transderm Nitro (Nitroglycerine-for once a day) medication of angina pectoris.[10]

Matrix diffusion controlled system:

In this approach, the drug reservoirs are prepared by homogeneously dispersing drug particles in a hydrophilic or lipophilic polymer matrix or combination of both.. The resultant medicated polymer is then molded into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in polymer matrix can be accomplished by either homogenously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of the polymer chains or homogenously blending drug solids with a rubbery polymer at an elevated temperature and/or under vacuum. The polymer disc which contains drug reservoir is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing. The adhesive polymer is then spread to form a strip of rim along the medicated disc. This matrix type of transdermal system is best exampled by the nitroglycerin releasing transdermal therapeutic system. The advantage of matrix dispersion type transdermal system is the absence of the dose dumping since the polymer cannot rupture.

Microreservoir type controlled system:

This system is basically hybrid of reservoir and matrix dispersion type of drug delivery system. In this approach, drug reservoir is formed by suspending the drug in an aqueous solution of liquid polymer and then dispersing the drug suspension homogeneously in a lipophilic polymer

e.g. silicone elastomers by high energy dispersion technique by shear mechanical force to form thousands of unreachable, and microscopic spheres of drug reservoirs. This technology has been utilized in the development of Nitro disc. Release of a drug from a micro reservoir-type system can follow either a partition-control or a matrix diffusion-control depending upon the relative magnitude of solubility of the drug in the liquid compartment and in the polymer matrix.

EVALUATION PARAMETERS: [1, 5,30,31,32]

1. Interaction studies:

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.

2. Thickness of the patch:

The thickness of the drug-loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

3. Weight uniformity:

The prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

4. Folding endurance:

A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

5. Percentage Moisture content:

The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100.

6. Water vapour permeability (WVP) evaluation:

Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula

WVP=W/A

Where, WVP is expressed in gm/m2 per 24hrs, W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m2

7. Polariscope examination:

This test is to be performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.

8. Shear Adhesion test:

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can beinfluenced by the molecular weight, the degree of crosslinking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength

9. Peel Adhesion test:

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180º angle, and the force required for tape removed is measured.

10. Thumb tack test:

It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected

11. Flatness test:

Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

12. Percentage Elongation break test:

The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula.

Elongation percentage = L1-L2/ L2 ×100

Where, L1is the final length of each strip and L2 is the initial length of each strip

13. Rolling ball tack test:

This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive.

The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

14. Quick Stick (peel-tack) test:

In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

15. Probe Tack test:

In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.

16. *In vitro* skin permeation studies:

An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2).

17. Skin Irritation study:

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to

1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

Table no 1: List of Transdermal drugs that are approved by USFDA

Active ingredients	Type of delivery system	Name	Type of patch	uses
Testosterone	Transdermal patch extended release	Androderm	Reservoir type	Hypogonadism (testosterone deficiency)
Testosterone	Transdermal gel	Androgel	1% gel	Hypogonadism (testosterone deficiency)
Selegiline	Transdermal patch extended release	Emsam	Drug in adhesive	Major depressive disorder
Scopolamine	Transdermal patch extended release	Transderm Scop	Matrix reservoir containing drug	Motion sickness, Postoperative nausea and vomiting (prophylaxis).
Rivastigmine	Transdermal patch extended release	Exelon	Matrix reservoir containing drug	Dementia associated with Alzheimer's disease and Parkinson's
Oxybutynin chloride	Transdermal gel	Gelnique	10% gel	Bladder dysfunction
Oxybutynin	Transdermal patch extended release	Oxytrol	Adhesive matrix containing drug	Bladder muscle dysfunction
Nitroglycerin	Transdermal patch extended release	Nitro Dur	Drug in adhesive	Angina prophylaxis
Nicotine	Transdermal patch extended release	Nicoderm	Matrix type patch	Smoking cessation
Methylphenidate	Transdermal patch extended release	Daytrana	Adhesive type	Attention-deficit hyperactivity disorder
Granisetron	Transdermal patch extended release	Sancuso	Adhesive matrix containing drug	Chemotherapy-induced nausea and vomiting
Fentanyl	Transdermal patch extended release	Fentanyl transdermal system	Matrix type and reservoir	Chronic pain (opioid tolerant) that cannot be managed by any other
Ethinyl estradiol and norelgestromin	Transdermal patch extended release	Ortho Evra	Adhesive matrix containing drug	Contraception
Estradiol and norethindrone acetate	Transdermal patch extended release	Combipatch	Adhesive layer contains drugs	Menopausal symptoms
Estradiol and levonorgestrel	Transdermal patch extended release	Climara Pro	Drug in adhesive layer	Menopausal symptoms
Estradiol	Transdermal patch extended release	Alora	Adhesive matrix drug reservoir	Menopause, postmenopausal and osteoporosis
Clonidine	Transdermal patch extended release	Catapres TTS	Drug in reservoir and in adhesive formulation	Essential hypertension

Applications of TDDS: [3, 5, 15, 22,33,34]

- Nicotinetransdermal patch marketed as Nicodermis to help in smoking cessation. It is the highest selling patch in United State.
- Two opioid medicationsFentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans) used to provide round-the-clock relief for severe pain available in patch form.
- Estradiol patches available as Estraderm for treat menopausal symptoms as well as postmenopausal osteoporosis. It is also available in combination with levonorgestrel as Climara Pro for menopausal symptoms.

- Nitroglycerintramsdermal patches For the treatment of angina pectoris, prescribed in place of sublingual pills.
- Transdermal patch of clonidine available for treatment of hypertension.
- Transdermal patch of the selegiline(MAO inhibiter) became the first transdermal delivery agent for major depressive disorder.
- Transdermal delivery agent Methylphenidate for the Attention Deficit Hyperactivity Disorder (ADHD).

Marketed transdermal drugs :

The U.S. sales of advanced drug delivery systems were over $54.2 billion in 2004. In 2005 they reached $64.1 billion and will eventually grow to $74.4 billion by the end of 2006. Over 5 years, this market will continue to grow at an average annual growth rate (AAGR) of 15.6% to reach $153.5 billion by 2011.The largest sector of the market consists of sustained release/implants/transdermal drug delivery systems, with more than 50% of the total U.S. market in 2005.

- Through the forecast period this sector will gradually give way to targeted drug delivery systems, which should control almost 48% of the market in 2011.

CONCLUSION

The Transdermal drug delivery system has gained importance in recent years. The Transdermal route is an extremely attractive option for the drug with appropriate pharmacology and physical chemistry. The Transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood level for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and improved patient compliance.16 Recently ,it is becoming evident that the benefits of intravenous drug infusion can be closely duplicated , without its hazards by using the skin as a part of drug administration to provide continuous Transdermal drug infusion through intact skin.

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