Indo Global Journal of Pharmaceutical Sciences, 2012; 2(3): 262-278

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

Blooming Pharma Industry with Transdermal Drug Delivery System

Nikhi Sharma*, Bharat Parashar, Shalini Sharma, Uday Mahajan

Manav Bharti University, Solan, Himachal Pradesh, India

Address for Correspondance: nikhi6789@gmail.com

ABSTRACT: The human skin is a readily accessible surface for drug delivery.It is one of the most readily accessible organs of the human body. The potential of using the intact skin as the port of drug administration to the human body has been recognized for several decades, but skin is a very difficult barrier to the ingress of materials allowing only small quantities of a drug to penetrate over a period of time. During the past decade, the number of drugs formulated in the patches has hardly increased, and there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used. The present article reviews the selection of drug candidates suitable to be formulated as Transdermal system and the methods of evaluation are also stated.

KEYWORDS: Transdermal Drug Delivery System; Evaluation Parameters; Pharmaceutical Formulations.

INTRODUCTION

Transdermal drug delivery system (TDDS) is the dosage forms which deliver a therapeutically effective amount of drug across a patient's skin. It increases patient compliance and avoid first pass metabolism over injectables and oral routes[1]. TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It minimizes harmful side effects of a drug caused from temporary overdose[2]. Another advantage is convenience and a simple dosing, especially notable in patches that require only once weekly application which aid in patient adherence to drug therapy.

FDA approved the first Transdermal system Transderm-SCOP in 1979 for the prevention of nausea and vomiting associated with ravel, particularly by sea. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug; detectable excretion of the drug and its metabolites in the urine. The clinical response of the patient to the administered drug therapy is the other evidence[3].

Ingredients used for the preparation of TDDS[4]*:-*

1. *Drug*: It is in direct contact with release liner. Eg: Nicotine, Methotrexate and Estrogen.
2. *Liners*: These protect the patch during storage. Eg: polyester film.
3. *Adhesive*: These adheres the patch to the skin for systemic delivery of drug. Eg: Acrylates, Polyisobutylene, Silicones.
4. *Permeation enhancers*: Controls the Release of the drug. Eg: Terpenes, Terpenoids, Pyrrolidones. Solvents like alcohol. Surfactants like Sodium Lauryl sulfate, Pluronic F127, Pluronic F68.
5. *Backing layer*: Protect patch from outer environment. Eg: Cellulose derivatives, poly vinyl alcohol.

Advantages of transdermal drug delivery system

1. Easy elimination of drug delivery during toxicity.
2. Avoidance of first pass metabolism of drugs.
3. Reduced plasma concentration levels of drugs, with decreased side effects.
4. Reduction of fluctuations in plasma levels of drugs, Utilization of drug candidates with short half-life and low therapeutic index.
5. Reduction of dosing frequency an enhancement of patient compliance.
6. Transdermal medications deliver a steady infusion of a drug over an extended period of time. Adverse effects
7. It increases the therapeutic value of many drugs via avoiding specific problems associated with the drug like GI irritation, lower absorption, decomposition due to 'hepatic first pass' effect.
8. Due to above advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if e.g. the drug is given orally.
9. The simplified medication regimen leads to improved patient compliance and reduced inter and intra-patient variability.

Disadvantages of transdermal drug delivery system

1. The possibility of local irritation may develop at the site of application. Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.

2. The skin's low permeability may limit the number of drugs that can be delivered in this manner. Because the skin serves protective functions, it inhibits compounds from crossing it. Many drugs with a hydrophilic structure permeate the skin too slowly to be of therapeutic benefit. Drugs with a lipophillic character, however, are better suited for transdermal delivery.

Limitations for a drug substance to be incorporated into a transdermal delivery system is: -

1. Heavy drugs molecules (>500 Da) usually difficult to penetrate the stratum cornea.
2. Drugs with very low or high partition coefficient fail to reach blood circulation.
3. Drugs with high melting point can be given by this route due to their low solubility both in water and fat[5].
4. Many approaches have been attempted to deliver medicament across skin barrier and enhance the efficacy.

Enhancers for transdermal drug delivery system

1. Physical enhancers (ultrasound, iontophoresis, electroporation, magnetophoresis, microneedle)
2. Particulate systems (liposome, niosome, transfersome, microemulsion, solid lipid nanoparticle)
3. Chemical enhancers (sulphoxides, azones, glycols, alkanols, terpenes etc.)

Transdermal drug absorption depends on a several parameters [5] *including the following-*

1. Medicament application site
2. Thickness and integrity of the stratum cornea epidermidis.
3. Size of the molecule that is to be administered.
4. Permeability of the membrane for the transdermal drug delivery.
5. Hydration state of skin.

6. pH of the drug.
7. Drug metabolism by skin flora.
8. Lipid solubility.
9. Drug depot in skin.

ROUTES OF TRADITIONAL TRANSDERMAL DRUG PREPARATION [6-8]

Two main pathways by which drugs can cross the skin and reach the systemic circulation are

1. Transcellular pathway
2. Intercellular route
3. Follicular rout

1. Transcellular pathway-Here drug crosses the skin by directly passing through both the phospholipid membranes and the cytoplasm of the dead keratinocytes that constitute the stratum corneum. Although this is the path of shortest distance, the drugs encounter significant resistance to permeation. This is because the drugs must cross the lipophilic membrane of each cell, then the hydrophilic cellular contents containing keratin, and then the phospholipid bilayer of the cell one more time. This series of steps is repeated numerous times to traverse the full thickness of the stratum corneum.

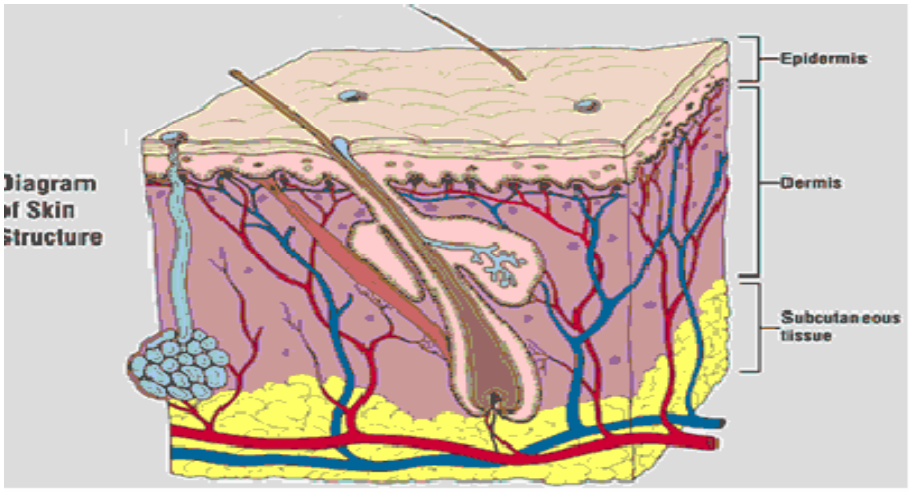

Figure- skin structure

2. Intercellular pathway-Drugs crossing the skin by this route must pass through the small spaces between the cells of the skin, making the route more tortuous. Although the thickness of the stratum corneum is about 20 μm, the actual diffusional path of most molecules crossing the skin is on the order of 400 μm. The 20-fold increase in the actual path of permeating molecules greatly reduces the rate of drug penetration.

3. Follicular route-Follicles penetrate through the stratum corneum, allowing more direct access to the dermal microcirculation. Hair follicles occupy only 1/1,000 of the entire skin surface area.

Ideal Properties of a Transdermal Drug Delivery System

Sr. no.	Properties	Comments
1	Shelf life	Up to 2 yrs
2	Particle size	$<40cm^2$
3	Dose frequency	Once in a day or once in week
4	Aesthetic appeal	Clear or white colour
5	Packaging	Easy removal of release liner & min. no. of steps required to apply
6	Skin reaction	Non irritating & non sensitizing
7	Release	Consistent pharmacokinetic & pharmacodynamic profile over time.

Basic components of T.D.DS

1. Polymer matrix / Drug reservoir
2. Drug
3. Permeation enhancers
4. Pressure sensitive adhesive (PSA)
5. Backing laminates
6. Release liner
7. Other excipients like plasticizers and solvents

1. Polymer matrix / Drug reservoir:

Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and PSAs. They should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be safe[9]. For example, Alza Corporation mainly concentrates on ethylene vinyl acetate (EVA) copolymers or microporous polypropylene and Searle Pharmacia concentrates on silicon rubber[10]. Company like Colorcon, UK uses HPMC for matrix preparation for propranolol transdermal delivery and Sigma uses ethylcellulose for isosorbide dinitrate matrix[11-12].

Polymers utilized for TDDS can be classified as:

1. Natural Polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan *etc*.
2. Synthetic Elastomers: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber *etc*.
3. Synthetic Polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc*.

The polymers like cross linked polyethylene glycol[13], eudragits[14], ethyl cellulose, polyvinylpyrrolidone[15] and hydroxypropylmethylcellulose[16] are used as matrix formers for TDDS. Other polymers like EVA[15], silicon rubber and polyurethane[17] are used as rate controlling membrane.

2. Drug: The transdermal route is appropriate for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches are suitable for drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non- compliance due to frequent dosing. It is imporatanat for TDDS that the drug should possess the right mix of physicochemical and biological properties for transdermal drug delivery[18-19]. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be non ionic, of low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1-3), a low melting point (less than 200°C) and are potent (dose in mg per day)[20]. Drugs like rivastigmine for Alzheimer's and Parkinson dementia, rotigotine for Parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS.

3. Permeation Enhancers: The chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate are called permeation enhancers[21]. These interact with structural components of stratum corneum *i.e.,* proteins or lipids and alter the protein and lipid packaging of stratum corneum and modifying chemically the barrier functions which increases permeability[22]. Over the last 20 years, a tremendous amount of work has been directed towards the search for specific chemicals, combination of chemicals, which can act as penetration enhancers.

4. Pressure sensitive adhesives: A PSA is a material which maintains an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue[22-23]. Silicones based adhesives and polyacrylates, polyisobutylene are mostly used in TDDSs[24]. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. For matrix systems with a peripheral adhesive, an incidental contact between the adhesive and the drug and penetration enhancer should not cause instability of the drug, penetration enhancer or the adhesive. In case of reservoir systems that include a face adhesive, the diffusing drug must not affect the adhesive. In case of drug-in-adhesive matrix systems, the selection will be based on the rate at which the drug and the penetration enhancer will diffuse through the adhesive. Ideally, PSA should be physic-chemically and biologically compatible and should not alter drug release[25].

5. Backing Laminate: The consideration of chemical resistance of the material is most important while designing a backing layer. Excipient compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusivity to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. Backing which exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate[26-27] are considered for backing. Examples of some backing materials are vinyl, polyethylene and polyester films is considered an excellent backing.

6. Release Liner: It is a protective liner that is removed and discharged immediately before the application of the patch to skin during application of patch. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a

base layer which may be non-occlusive (*e.g*. paper fabric) or occlusive (*e.g*. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Other materials used for TDDS release liner include polyester foil and metallized laminates[24,28].

7. Other excipients: Solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir[16,29]. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch[30-32].

TECHNIQUES FOR ENHANCING TDDS

A) Structure-based enhancement techniques
B) Electrically-based enhancement techniques
C) Velocity based enhancement techniques

A) STRUCTURE-BASED ENHANCEMENT TECHNIQUES

1. Transdermal Patches

A transdermal patch or skin adhesive patch is that device which is loaded with drug candidate and usually applied on the skin to transport a specific dose of medication across the skin and into the blood circulation[33]. Adhesives serves two functions: It is glue in nature that keeps the patch adhered to the skin, and it acts as the suspension that holds the drug. The problems associated with this is the concentration of the drug within the adhesive directly affects the "stickyness" of the adhesive so if the large quantities of drug is to be administered, either the size of the patch have to be increased or the patch needs to be reapplied again and again. Several pharmaceuticals usually combined with substances, like alcohol, within the patch to improve their penetration via skin in order to improve absorption.

Components of Transdermal Patches:-

1. Liner - Protects the patch during storage. The liner should be removed before its use.

2. Drug-Drug solution is in direct contact with release liner.

3. Adhesive- It serves to adhere the components of the patch together along with adhering the patch to the skin. E.g. - Acrylic, polyisobutylene (PIB), and silicone are the adhesives have many pharmaceutical applications. For applications in which the adhesive, the drug, and perhaps enhancers are compounded, the selection of a PSA is more complex (e.g., a matrix design).

4. Membrane- It controls the release of the drug from the reservoir and multi-layer patches.

5. Backing- The film protects the patch from the outer environment[34-35].

2. Microfabricated Microneedles

These are the devices which are having the features of both the hypodermic needle and transdermal patch that can deliver the drug that transports the drug effectively across the memberane. The systems consists of a drug reservoir and some projections (microneedles) extending from the reservoir, these helps in penetrating the stratum cornea and epidermis to deliver the drug.

Poke with patch approach- Involves piercing into the skin followed by application of the drug patch at the site of treatment.

Coat and poke approach- Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.

- *Biodegradable microneedles*- Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.
- *Hollow microneedles*- Involves injecting the drug through the needle with a hollow bore[36].

3. Macroflux These are devices having an area of around 8cm as well as 300 micro projections per cm^2 with the length of individual micro projection less than 200Î¼m. Three types of Macroflux have been designed. They include, Dry-Coated Macroflux system-this is used for short period delivery that consists micro projection array coated with medicament that adhered to a elastic polymer adhesive backing.

4. Metered-Dose Transdermal Spray (MDTS)

It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come non volatile in nature, which consists the completely dissolved medicament in solution . The use of MDTS reaches the sustained level and better permeation of the drug via skin. The MDTS has the following potential advantages:

- Improves delivery potential without skin irritation due to its non-occlusive nature.
- Increased acceptability.
- Dose flexibility
- Simple manufacture

B) ELECTRICALLY-BASED ENHANCEMENT TECHNIQUES

1. Iontophoresis: It involves passing of current (few milliamperes) to skin limited to a certain area using the electrode remains in contact with the formulation which is to be administered. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anesthesia[37,38].

2. Ultrasound: In this technique, there is a mixing of drug substance with a coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier.

3. Photomechanical Waves: Photomechanical waves significantly led to the stratum cornea highly permeable to drug substance through a possible permeabilisation mechanism due to development of transient channels.

4. Electroporation: It this method, short and high-voltage electrical pulses are applied to the skin thus the diffusion of drug is improved with the increasing permeability. The electrical pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea[37,39-41].

5. Electro-Osmosis: To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

C) VELOCITY BASED ENHANCEMENT TECHNIQUES:

1. Needle-Free Injections

- Intraject
- Implaject
- Jet Syringe
- Iject
- Mini-ject

2. Powderject Device

The solid drug particles are propelled across the skin with the aid of high-speed gas flow. This consists of a gas canister that allows helium gas at high pressure to enter a chamber at the end of which drug cassette containing powdered drug between two polycarbonate membranes. After release, the instantaneous rupturation of both membranes usually seen that results in the gas to expand quickly which forms a strong motion like a wave that travels down the nozzle. This takes place at the speed of 600-900 m/s.

D) OTHER ENHANCEMENT TECHNIQUES:

1. Transfersomes: This device penetrates the skin barrier along the skin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles.

2. Medicated Tattoos: Medical Tattoos is a modification of temporary tattoo which contains an active drug substance for trandermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms.

3. Skin Abrasion: This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substance. In general, one approach is adopted to create micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules is generally known as Microscissuining.

4. Controlled Heat Aided Drug Delivery (CHADD) System: It facilitates the transfer of drug substance to the blood circulation by applying heat to the skin that increases the temperature and ultimately led to increase in microcirculation and permeability in blood vessel. CHADD system consists of small unit that is used for heating purpose, placed on top of a conventional patch device. An oxidation reaction occurs within the unit which tends to form heat of limited intensity and duration.

5. Laser Radiation: This involves the exposure of the skin to the laser beam that results in the ablation of the stratum cornea without damaging the epidermis which remains in contact with it. Removal of the stratum cornea by this technique is considered to improve the delivery of lipophilic and hydrophilic drugs.

6. Magnetophoresis: The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength[42].

TYPES OF TRANSDERMAL PATHCES

1. Single layer drug in adhesives: Drug is in adhesive layer. It adheres various layers together and release drug to skin. The adhesive layer is surrounded by temporary liner and backing.

2. Multi-layer drug in adhesive: It is also similar to the single layer but it contains a immediate drug release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

3. Vapour patch: In this type of patch the role of adhesive layer not only serves to adhere various layers together but also serves as release vapour. The vapour patches are new to the market, commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

4. Reservoir system: In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

5. Matrix system

i. Drug-in-adhesive system

In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting (in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

ii. Matrix-dispersion system

In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

6. Microreservoir system[43]

In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents.

METHODS FOR PREPARATION of TDDS:

a. Asymmetric TPX membrane method[44]

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.

b. Circular Teflon mould method[45]

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-butylphthalate 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[46]

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 with inverted funnel to control solvent evaporation.

d. By using IPM membranes" method[47]

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[48]

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 used 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[49]

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 custam made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

g. Preparation of TDDS by using Proliposomes[50-51]

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 80-90rpm 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[52]

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 is 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.

EVALUATION PARAMETERS

1. Interaction studies[53-54]:

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 susuch as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.

2. Thickness of the patch[55]

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 [55]

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 [55]

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 [55]

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. Percentage Moisture uptake [55]

Films are weighed and kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs, the films are reweighed and the percentage moisture uptake is determined from the below mentioned formula.

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

7. Water vapour permeability (WVP) evaluation [54]

Water vapour permeability is usually 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/m^2 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 m^2.

8. Drug content [54]

A specified area of patch is dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

9. Uniformity of dosage unit test [55]

An accurately weighed portion of the patch is cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution is allowed to settle for about an hour, and the supernatant is suitably diluted to give the desired concentration with suitable solvent. The solution is filtered using 0.2m membrane filter and analyzed by suitable analytical technique (UV or HPLC) and the drug content per piece is calculated.

10. Polariscope examination [55]

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

11. Shear Adhesion test [55]

This test is performed for the measurement of the cohesive strength of an adhesive polymer which is influenced 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.

12. Peel Adhesion test [55]

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. Peel adhesion is the force required to remove an adhesive coating from a test substrate. Adhesive should provide adequate contact of the device with the skin and should not damage the skin on removal. Peel adhesion properties are affected by the molecular wt of the adhesive polymer, the type and amount of additives, and polymer composition. It is tested by measuring the force required to pull a single coated tape, applied to a substrate, at an 1800 angle. No residue on the substrate indicates 'adhesive failure' which is desirable for transdermal devices. Remnants on the substrate indicate 'cohesive failure' signifying a deficit of cohesive strength in the coating.

13. Thumb tack test

This test is for tack property determination of adhesives. The thumb is simply pressed on the adhesive and the relative tack property is detected.

14. Flatness test [56]

Three longitudinal strips are 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.

15. Percentage Elongation break test [57]

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

Elongation percentage = L1-L2 ×100 L2 .Where, L1is the final length of each strip and L2 is the initial length of each strip

16. Rolling ball tack test[58]

This test measures the softness of a polymer. 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.

17. Quick Stick (peel-tack) test [58]

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.

18. Probe Tack test [58]

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.

19. In vitro drug release studies [59]

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5- mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

20. In vitro skin permeation studies [59]

In vitro permeation study is carried out by using diffusion cell on full thickness abdominal skin of male Wistar rats of weights 200 to 250g. Hair from the abdominal region is removed carefully by using a electric clipper; the dermal side of the skin is 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 is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is replaced. Samples are 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 is deduced by dividing the flux by the initial drug load (mg cm^2).

21. Skin Irritation study [55]

Skin irritation and sensitization testing is performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm^2) of the rabbit is cleaned and the hairs are removed from the clean dorsal surface by shaving and cleaning the surface by using rectified spirit and the representative formulations is applied over the skin. The patch is removed after 24 hr and the skin is observed and classified into 5 grades on the basis of the severity of skin injury.

22. Stability studies[60]*:*

Stability studies are conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples were withdrawn at 0,30,60,90 and180 days. Drug content is analyzed.

CONCLUSION

Transdermal drug delivery systems has been used as safe and effective drug delivery system since 1981.Its potential role in controlled release is being globally exploited by the scientists with high rate of attainment. Drug with right mix of physical chemistry and pharmacology, is remarkably effective in transdermal delivery. Due to large advantages of the TDDS, many new researches are going on in the present day to incorporate newer drugs via the system. A transdermal patch has several basic components like drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers and solvents, which play a vital role in the release of drug via skin. Transdermal patches are divided into various types like matrix, reservoir, membrane matrix hybrid; micro reservoir type and drug in adhesive type transdermal patches and different methods are used to prepare these patches by using basic components of TDDS. These are after preparation of transdermal patches, evaluated for physicochemical studies, *in vitro* permeation studies, skin irritation studies, animal studies, human studies and stability studies. All prepared and evaluated transdermal patches must receive approval from FDA before sale. Future developments of TDDSs will likely focus on the increased control of therapeutic regimens and the continuing expansion of drugs available for use. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care.

REFERENCES

1. Loyd V. Allen Jr, Nicholas G. Popovich, Howard C. Ansel. Pharmaceutical dosage forms and drug delivery systems, 8th Edition., Wolter Kluwer Publishers,New Delhi, 2005 pp. 298-299
2. Aggarwal Geeta,Dhawansanju Development, Fabrication and Evaluation of Transdermal Drug Delivery System - A Review Pharm Res,2009
3. Kumar R, Philip A. Modified Transdermal Technologies: Breaking the Barriers of Drug Permeation via the Skin. Trop J Pharm Res. 2007, 6(1):633-644.
4. Kumar P, Sankar C, Mishra B. Delivery of macromolecules through skin. The Indian Pharmacist 2004,5(3): 7-17.
5. Kumar R, Philip A. Modified Transdermal Technologies: Breaking the Barriers of Drug Permeation via the Skin. Trop J Pharm Res. 2007, 6(1):633-644.
6. Jasti BR, Abraham W, Ghosh TK. Transdermal and Topical drug delivery systems. *In* : Ghosh TK, Jasti BR, editors. Theory and Practice of Contemporary Pharmaceutics. 1st ed. Florida: CRC Press; 2005. p. 423-53.
7. Franz TJ, Tojo K. Shah KR, Kydonieus A. Transdermal delivery. In: A Kydonieus, ed. Treatise on Controlled Drug Delivery. New York: Marcel Dekker, 1992:341-421.
8. Prochazka AV. New developments in smoking cessation. Chest. 2000; 117 (4 Suppl1):169-175.
9. Minghetti P, Cilurzo F, Casiragh A, Molla FA, Montanari L. Dermal patches for controlled release of miconazole: Influence of drug concentration on the technical characteristics, Drug Dev Ind Pharm 1999, 25, 679-684.
10. Guyot M, Fawaz F. Design and in vitro evaluation of adhesive matrix for transdermal delivery of propranolol, Int J Pharm 2000, 204, 171-182.
11. Gabiga H, Cal K, Janicki S. Effect of penetration enhancers on isosorbide dinitrate penetration through rat skin from a transdermal therapeutic system, Int J Pharm 2000, 199, 1-6.
12. Minghetti P, Cilurzo F, Casiragh A, Molla FA, Montanari L. Dermal patches for controlled release of miconazole: Influence of drug concentration on the technical characteristics, Drug Dev Ind Pharm 1999, 25, 679-684.
13. Bromberg L. Cross linked polyethylene glycol networks as reservoirs for protein delivery, J Apply Poly Sci 1996, 59, 459-466.
14. Verma PRP, Iyer SS. Transdermal delivery of propranolol using mixed grades of eudragit: Design and in vitro and in vivo evaluation, Drug Dev Ind Pharm 2000, 26, 471-476
15. Ubaidulla U, Reddy MV, Ruckmani K, Ahmad FJ, Khar RK. Transdermal therapeutic system of carvedilol: Effect of hydrophilic and hydrophobic matrix on *in vitro* and *in vivo* characteristics, AAPS PharmSciTech 2007, 8(1), Article 2.
16. Gannu R, Vamshi Vishnu Y, Kishan V, Madhusudan Rao Y. Development of nitrendipine transdermal patches: In vitro and ex vivo characterization, Current Drug Delivery 2007, 4, 69-76.
17. Chung SJ. Future drug delivery research in South Korea, J Controlled Release 1999, 62, 73-79.
18. Chung SJ. Future drug delivery research in South Korea, J Controlled Release 1999, 62, 73-79.

19. Izumoto T, Aioi A, Uenoyana S, Kariyama K, Azuma M. Relationship between the transference of drug from a transdermal patch and physicochemical properties, Chem Pharm Bull (Tokyo) 1992, 40, 456-458.
20. Gordon RA, Peterson TA. Four myths about transdermal drug delivery, Drug Delivery Technology 2003, 3, 1-7.
21. Williams AC, Barry BW. Penetration enhancers, Advanced drug delivery reviews 2004, 56, 603-618.
22. Shin SC, Shin EY, Cho CY. Enhancing effects of fatty acids on piroxicam permeation through rat skins, Drug Dev Ind Pharm. 2000, 26, 563-566.
23. Pocius AV. Adhesives. In: Howe- Grants M, Ed. Kirk-Othmer Encyclopedia of Chemical Technology. New York, Wiley-Interscience. 1991; 445-466.
24. Walters KA. Transdermal drug delivery systems In: Swarbick K, Boylan JC, eds. Encyclopedia of pharmaceutical technology. New York, Marcel Dekker Inc. 1997; 253-293.
25. Franz TJ. Transdermal Delivery: Kydonieus A, ed. Treatise on controlled drug delivery: Fundamentals, optimization, applications. New York, Marcel Dekker Inc. 1991; 341-421.
26. Tan HS, Pfister WR. Pressure sensitive adhesives for transdermal drug delivery, Pharm Sci Technol Today 1999, 2, 60-69.
27. Pfister WR, Hsieh DS. Permeation enhancers compatible with transdermal drug delivery systems. Part I: Selection and formulation considerations, Med Device Technol 1990, 1, 48-55.
28. Godbey KJ. Improving patient comfort with nonocclusive transdermal backings, American Association of Pharmaceutical Scientists 1996, 1-2.
29. Foco A, Hadziabdic J, Becic F. Transdermal drug delivery systems, Med Arch 2004, 58, 230-234.
30. Khatun M, Ashraful Islam SM, Akter P, Abdul Quadir M, Selim Reza M. Controlled release of naproxen sodium from eudragit RS 100 transdermal film, Dhaka University J Pharm Sci 2004, 3(1-2).
31. Rao PR, Diwan PY. Permeability studies of cellulose acetate free films for transdermal use: Influence of plasticizers, Pharm Acta Helv 1997, 72, 47-51.
32. Gondaliya D, Pundarikakshudu K. Studies in formulation and pharmacotechnical evaluation of controlled release transdermal delivery system of bupropion, AAPS Pharm SciTech 2003, 4, Article3.
33. Helier J, Trescony PV. Controlled drug release by polymer dissolution II, Enzyme mediated delivery device. J. Pharm. Sci. 1979, 68: 919.
34. http://www.pharmainfo.net/jasmine-jose/transdermal-patches-innovative-technology
35. Hopp SM. Developing Custom Adhesive Systems for Transdermal Drug Delivery Products. Pharmaceutical Technology 2002, 30-36.
36. Yan-yu X, Yun- mei S, Zhi-Peng C and Qi-nerg P. Preparation of silymarin proliposomes; A new way to increase oral bioavailability of silymarin in beagle dogs. Int. pharm. 2006; 319: 162-168
37. Tipre ND &Vavia RP. Formulation Optimization and Stability Study of Transdermal Therapeutic System of Nicorandil. Informa Healthcare 2002, 7(3):325-332.
38. Calhoun A Darlene et al. Recent Advances in Neonatal Pharmacotherapy: Transdermal Therapy in Neonates. Ann. Pharmacother. 2006, 40 (4): 710-719.
39. http://www.theiaforum.org/april2004.htm
40. Sugar IP, Neumann E. Stochastic model for electric field-induced membrane pores. Electroporation. Biophys. Chem.1984, 19(3): 211. 25.
41. http://berkeley.edu/news/media/releases/2007/02/12_IRE.shtml
42. Loyd V. Allen Jr, Nicholas G. Popovich, Howard C. Ansel. Pharmaceutical dosage forms and drug delivery systems, 8th Edition., Wolter Kluwer Publishers,New Delhi, 2005 pp. 298-299.
43. William A.C and Barry B.W,"penetration enhancers ",Advance Drug delivery Rev.2004;56:603-618.
44. Baker W and Heller J. "Material Selection for Transdermal Delivery Systems", In Transdermal Drug Delivery: Developmental Issues and Research Initiatives, J.Hadgraft and R.H.Guys, Eds. Marcel Dekker, Inc.,New york 1989 pp. 293-311
45. Wiechers J. Use of chemical penetration enhancers in Transdermal drug delivery-possibilities and difficulties. Acta pharm. 1992 : 4: 123.
46. Yamamoto T, Katakabe k, Akiyoshi K, Kan K and Asano T. Topical application of glibenclamide lowers blood glucose levels in rats. Diabetes res. Clin. Pract. 1990; 8: 19-22.
13. Al- Khamis K, Davis S.S and Hadgraft J. Microviscosity and drug release from topical gel formulations. Pharm. Res. 1986; 3: 214-217.
47. Anon. Transdermal delivery systems-general drug release standards. Pharmacopeial Forum, 1980; 14: 3860-3865.
48. Mayorga P, Puisieux F and Couarraze G.Formulation study of a Transdermal delivery system of primaquine. Int. J. pharm. 1996; 132: 71-79.
49. Deo M.R, Sant V.P,Parekh S.R, Khopade A.J and Banakar U.V. Proliposome-based Transdermal delivery of levonorgestrel. Jour. Biomat. Appl. 1997; 12: 77-88.
50. Yan-yu X, Yun- mei S, Zhi-Peng C and Qi-nerg P. Preparation of silymarin proliposomes; A new way to increase oral bioavailability of silymarin in beagle dogs. Int. pharm. 2006; 319: 162-168.
51. Crawford R.R and Esmerian O.K. Effect of plasticizers on some physical properties of cellulose acetate phthalate films. J. Pharm. Sci. 1997;60: 312- 314.
52. Crawford R.R and Esmerian O.K. Effect of plasticizers on some physical properties of cellulose acetate phthalate films. J. Pharm. Sci. 1997;60: 312- 314.
53. Shaila L, Pandey S and Udupa N. Design and evaluation of matrix type membrane controlled Transdermal drug delivery system of nicotin suitable for use in smoking cessation. Indian Journ. Pharm. Sci. 2006;68: 179-18
54. Aarti N, Louk A.R.M.P, Russsel.O.P and Richard H.G. Mechanism of oleic acid induced skin permeation enhancement *in vivo* in humans. Jour. control. Release 1995; 37: 299-306.

55. Wade A and Weller P.J. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical Publishing Association 1994; 362-366.
56. Lec S.T, Yac S.H, Kim S.W and Berner B. One way membrane for Transdermal drug delivery systems / system optimization. Int. J Pharm. 1991; 77: 231 - 237.
57. Vyas S.P and Khar R.K. Targetted and controlled Drug Delivery Novel carrier system1st Ed., CBS Publishers and distributors, New Delhi, 2002; 411-447.
58. Singh J, Tripathi K.T and SakiaT.R. Effect of penetration enhancers on the *invitro* transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. Drug Dev. Ind. Pharm. 1993; 19: 1623-1628.
59. Singh J, Tripathi K.T and SakiaT.R. Effect of penetration enhancers on the *invitro* transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. Drug Dev. Ind. Pharm. 1993; 19: 1623-1628.

Indo Global Journal of Pharmaceutical Sciences(ISSN 2249 1023 ; CODEN-IGJPAI) indexed and abstracted in EMBASE(Elsevier), SCIRUS(Elsevier), Chemical Abstract Services(CAS), American Chemical Society(ACS), Index Copernicus, EBSCO, DOAJ, Google Scholar and many more. For further details, visit http://iglobaljournal.com