IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, January 2023
Impact Factor: 7.301

Review on Transdermal Drug Delivery System

Prof. Shirish B. Nagansurkar, Dr. Sanjay K. Bais, Mr. Pradip Daji Shembade
Fabtech College of Pharmacy, Sangola, Solapur, Maharashtra, India

Abstract: *Transdermal drug delivery system is an essential part of novel drug distribution system. The topically administered medications in the form of patches which when applied to the skin deliver the drug .For operative TDDS the drug are easily able to penetrate the skin and easily reach the target site. TDDS avoids the first pass metabolism, less frequency of administration, reduction gastrointestinal side effects. Adverse effects are minimized due to steady and optimum blood concentration. It has greater bioavailability and efficacy of drug. The human skin is multi-layered organ composed of many histological layers. Skin is the largest organ in the body. Its major functions are protection of major or vital internal organs for the external influences, temperature regulations, control of water output and sensation. Polymer should be chemically non-reactive, should not decompose on storage, should be non-toxic, cost should not be high. E.g. - cellulose derivatives, zein, gelatin etc. Backing films play a vital role in the transdermal patch and the role of the film is to protect the active layer. Transdermal patches can be evaluated by interaction studies thickness, weight uniformity, drug content, in vitro study,moisture content, swelling index basic component of TDDS.*

Keywords: TDDS, Peel adhesion, Shear strength

I. INTRODUCTION

Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth or by oral route. Patients often forget to take their medicine and also they get tired of swallowing pills. Additionally bypassing the gastrointestinal tract would obviate the GI irritation that frequently occurs & avoid partial first pass inactivation by the liver. Further, steady absorption of drug over hours or days is usually preferable to blood level spikes and troughs produced by oral dosage forms.

These advantages are offered by the currently marketed transdermal products. Transdermal drug delivery is defined as self-contained, discrete dosage forms which when applied to intact skin delivers the drug through the skin at controlled rate to the systemic circulation1. TDDS established itself as an integral part of novel drug delivery system. The transdermal patches uses a polymer membrane to control the rate at which the drug contained in the reservoir within the patch can pass through the skin and into the blood stream.

FDA approved the first transdermal patches product in 1981. TDDS are currently available containing scopolamine (Hyoscine) for motion sickness, clonidine & nitroglycerine for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation, oestradiol (alone or in combination with levonorgestrol or norethisterone) for hormone replacement and testosterone for hypogonadism. There are several product in late stage development that will further expand TDD usage into new therapeutic area including Parkinson's disease, attention deficit and hyperactivity disorder and female sexual dysfunction. Over the last two decades more than 35 transdermal patches have been approved, generating sales of $3.2 billion in 2002 to $4.5 billion in 2008 3. More recently such dosage forms have been developed and or modified in order to enhance the driving force of diffusion (thermodynamic activity) and or increase the permeability of skin. These approaches include permeability enhancer, prodrug, liposome and other vesicles.

Today four drug have been successfully incorporated into TDDS for clinical use (scopolamine, nitroglycerine, clonidine & estradiol) which established the dermal route for systemic drug delivery[1]

II. ANATOMY AND PHYSIOLOGY OF SKIN

Human skin comprises of three distinct but mutually dependent tissues: The stratified, vascular, cellular called as "epidermis" Underlying dermis of connective tissues, Hypodermis.

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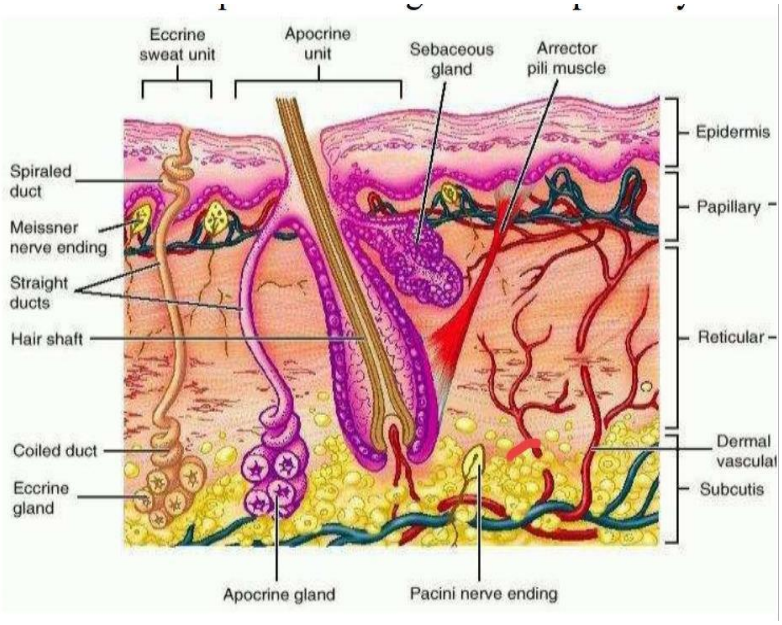
2.1 Epidermis

The multilayered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum. This is the outermost layer of skin also called as horny layer. It is approximately 10 mm thickwhen dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. Thearchitecture of horny layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein "bricks" embedded in lipid "mortar." The lipids are arranged in multiple bilayers.



There is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bilayer form. Viable epidermis is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. In the basal layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

2.2 Dermis

Dermis is 3 to 5 mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. Thecutaneous blood supply has essential function inregulation of body temperature. It also providesnutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeate very low and the resulting concentration difference across the epidermis provides essential concentration gradient for transdermal permeation.

2.3 Hypodermis

The hypodermis or subcutaneous fat tissu supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanically protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, drug has to penetratethrough all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.[2]

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2.3 Ideal Characteristics of TDDS:

1. The skin has pH of 4.2 to 5.6, solutions which have this pH range are used to avoid damage to the skin.
2. For the therapeutic action of the drug, there is a need of optimum partition coefficient.
3. The drug should have a low melting point (less than 2000C) should use.
4. Patch size should be less than 40 cm2
5. Shelf life upto 2 yrs.
6. The half-life t½ of the drug should be short;
7. The drug should be non-irritating and non-allergic;
8. The drug should be potent with a daily dose of the order of a few mg/day;
9. The drug should have a molecular weight less than approximately 1000 Daltons;
10. The drug should have affinity for both-lipophilic and hydrophilic phases. Extreme partitioning characteristic are not conducive to successful drug delivery via the skin;
11. However for a number of drugs, there may also be significant transdermal absorption at pH values at which the unionized form of the drug is predominant.

2.4 Conditions in which Transdermal patches are used:

Transdermal patch is used when:

When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.

Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia.

It can be used in combination with other enhancement strategies to produce synergistic effects.[3]

2.5 Evaluation of Transdermal Patches

physicochemical evaluation

In vitro evaluation

In vivo evaluation

2.6 Physicochemical Evaluation

- **Thickness:** The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.
- **Uniformity of Weight:** Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.
- **Drug Content Determination**: An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.
- **Content Uniformity Test:** 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.
- **Moisture Content:** The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

  % Moisture content = Initial weight – Final

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- **Moisture Uptake:** Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.

  % moisture uptake = Final weight – Initial weight X 100
- **Flatness:** A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

  constriction = I1 – I2 X 100

  I2 = Final length of each strip

  I1 = Initial length of each strip
- **Folding Endurance:** Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.
- **Tensile Strength:** To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation.

  Tensile strength= F/a.b (1+L/l)

  F is the force required to break; a is width of film;

  b is thickness of film; L is length of film; l is elongation of film at break point.
- **Tack properties:** It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer.
- **Thumb tack test:** The force required to remove thumb from adhesive is a measure of tack.
- **Rolling ball test:** This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.
- **Quick stick (Peel tack) test:** The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90? at the speed of 12 inch/min.
- **Probe tack test:** Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

In vitro release studies:

- **The Paddle over Disc:** (USP apparatus 5/ PhEur 2.9.4.1) This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C.
- **The Cylinder modified USP Basket:** (USP apparatus 6 / PhEur 2.9.4.3) This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32 ±5°C.
- **The reciprocating disc:** (USP apparatus 7) In this method patches attached to holders areoscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction cell method (PhEur 2.9.4.2) may be used.[4]

Components of transdermal drug delivery system

- Drug
- Matrix
- Reservoir

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- Semi-permeable membrane
- Adhesive
- Backing layer
- Release liner
- Solvents, penetration enhancers
- Plasticizers

Drug: The drug, of which transdermal system will be designed, should possess some physicochemical characteristics. Drug should have relatively low molecular weight , medium level lipophilic character and water solubility . Also, the drug should be a potent compound, which is effective at a low dose.

Matrix: In the formulation of matrix type transdermal systems, the drug is dispersed or dissolved in a polymer matrix . This matrix with polymer structure controls the release rate of the drug, synthetic and semisynthetic polymers (e.g. cellulose derivatives) are used as the polymer.

Reservoir: In this type of transdermal patches, a semi-permeable membrane controlling the drug release rate is used. The drug presents in a reservoir as liquid or solid.

Semipermeable (release) membrane: It takes place in reservoir type transdermal systems and multi-layer adhesive systems. Ethylene-vinyl acetate copolymer, silicones, high-density polyethylene, polyester elastomers, cellulose nitrate and cellulose acetate are used as amembrane. These membranes control the release rate of drugs.

Adhesive: Adhesive should enable the transdermal system to easily adhere to the skin and should not be irritant/allergen for skin. Generally, pressure-sensitive adhesives are used in transdermal systems.

Backing layer: It protects the system from external effects during administration and ensures the integrity of the system in the storage period. For this purpose, the materials impermeable for drug molecule are used as backing layer. The backing layer must be inert and not compatible with the drug and other substances used in the formulation. Generally, ethylene vinyl acetate, polyethylene, polypropylene, polyvinylidene chloride and polyurethane are used as backing layer.

Release liner: This is the part which protects the formulation from theexternal environment and which is removed before the system adheres tothe skin. Ethylene vinyl acetate, aluminum foil or paper can be used. Ideally, it should be easily peeled from the adhesive layer and should not damage the structure of adhesive layer. Also, silicone, fluorosilicone, perfluorocarbon polymers can be used.

Solvents, penetration enhancers: Various solvents are used to solve or disperse the polymer and adhesive or drug used in the preparation of the transdermal systems. Among those, chloroform, methanol, acetone, isopropanol, and dichloromethane are used frequently. Also, various penetration enhancer substances are added to the formulations to increase permeation from the skin of the drug.

Plasticizers: Plasticizers are generally non-volatile organic liquids or solids with low melting temperature and when added to polymers, they cause changes in definite physical and mechanical characteristics of the material.[5]

III. MATERIAL AND METHOD FOR TDD

3.1 Polymer

Polymer backbone of TDDS, which control the release of the drug. Polymer should be chemically non-reactive, should not decompose on storage, should be nontoxic, cost should not be high. E.g.- cellulose derivatives, zein, gelatin, shellac, waxes, gums, Polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, Polyvinyl

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alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate

3.2 Backing Films

Backing films play a vital role in the transdermal patch and also while using the system. The role of the film is to protect the active layer and safeguard the stability of the system, and to affect skin permeation and tolerance, depending on occlusion or breathability. In order to avoid any type of incompatibility the release liner must be fully inert to the ingredients. It must also be flexible, comfortable and must have good affinity with the adhesive and excellent printability. The most common release liners are polypropylene, polyesters, PVC and nylon.

3.3 Release Liners

An anti-adherent coating will be covering the release liners. The role of the release liner is to protect the system when it is in the package, it will be removed just before the application of TDDS to the skin. Release liners play an important role in the stability, safety and affectivity of the patch. Care should be taken to choose the release liners. An incorrect release liner will not permit the easy release of the patch, and can interfere with the active(s) or other components, thereby reducing its shelf life. The most common films used as release liners are paper-based, plastic film-based and composite films. The two major classes of coating are silicones and fluro-polymers.Pressure Sensitive Adhesives

3.4 Pressure Sensitive Adhesives

For both types of TDDS, pressure-sensitive adhesives (PSAs) play an important role, by serving as the matrix that carries the active like additives and permeation enhancers and the means for making the patch stick to the skin. There are three categories in PSAs: rubber-based, acrylic in the form of acrylic solutions, emulsion polymers or hot melts, and silicon PSAs. For each category there are several sub-categories that give the required flexibility to the patch.

3.5 Penetration Enhancers

These are the completely different chemical substances that belong to the same family by characteristics. They increase the permeation rate by several times of the active ingredient through the skin. This enhances the feasibility of a system, because most of the actives do not enter the skin in the required dosage through a relatively small area. Sometimes a combination of these ingredients is needed to create the correct enhancing effect. These are the agents which promote the skin permeability by altering the skin as a barrier to the flux of desired penetrate [6]

3.6 TDDS Adhesive Analysis

There are several methods used to predict the performance of patch adhesives in-vivo. For example, the adhesion performance of a patch is evaluated using an FDA score chart in which the patient selects a score based on the amount of the patch which adhered to the skin during the usage period. There are also tests that evaluate the peel adhesion of the patch by applying different rates of peeling to a patch that is placed on the skin. These studies have determined that the slower the patch is removed, the more adhesive is also removed. The tack strength can be evaluated similarly by using quick-stick tests and generating stress-strain curves after the patch is removed. In-vitro tests are also attempted in which the patch is applied to different plates with a similar surface energy to that of skin, such as stainless steel (40 dyne/cm) or poly(tetrafluoroethylene) (PTFE) . There are also several organizations that release specifications on transdermal delivery system performance. The American Society for Testing and Materials (ASTM) has specific requirements for testing relating to the adhesive properties of the transdermal patches. The Pressure Sensitive Tape Council also has similar specs that are relevant due to the use of the pressure sensitive adhesive. The peel adhesion is assessed using ASTM D330 and PSTC 101, which evaluates the force required to remove adhesive from a rigid substrate. Static shear, the ability of tape/adhesive to resist the application of static forces parallel to the backing, is tested using ASTM D3654 and PSTC 107. ASTM D979 evaluates the probe tack of a patch, by testing the force necessary to remove adhesive from an inverted probe . PSTC 4 evaluates release force, by testing the force required to remove an adhesive strip from the release liner. PSTC 6 evaluates rolling ball tack, by testing the ability of adhesive to

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bond with the surface of another material under brief contact with extremely low pressure . PSTC 16 evaluates the loop tack, by testing the force necessary to remove a loop of adhesive from a substrate[7]

IV. DRUG DELIVERY ROUTES ACROSS HUMAN SKIN

When a molecule reaches intact skin, it contacts with the cellular debris, normal flora of microorganisms, sebum and other materials.

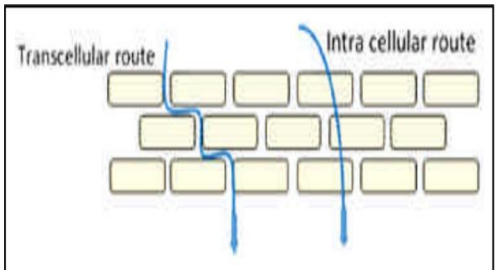

Figure: Routes of drug delivery

The molecule then can penetrate by three pathways:

- Sweat ducts
- Hair follicles
- Sebaceous glands (collectively called the shunt or appendageal route)

a. Intra cellular: between the cells and
b. Trans cellular: across lipid rich region.[8]

Applications of Transdermal Patches

- The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
- Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans).
- Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).
- Nitroglycerin patches are sometimes prescribed for the treatment of angina pectoris.
- The anti-hypertensive drug Clonidine is available in transdermal patch form.
- Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.

V. TYPES OF TRANSDERMAL PATCHES

5.1 Single Layer Drug -In- Adhesive

The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film.

5.2 Multi Layer Drug In Adhesive

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.

5.3 Drug Reservoir-in-Adhesive

The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive

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component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.

5.4 Drug Matrix-in-Adhesive

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.

5.5 Basic Components of Transdermal Patch

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates

5.6 Release liner and other excipients like plasticizers and solvents.

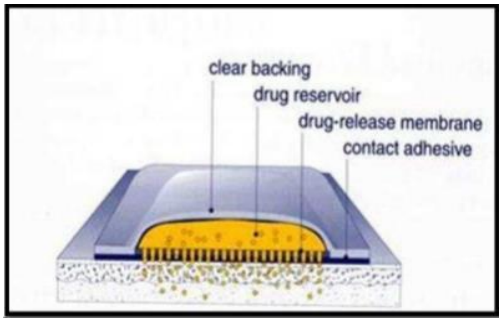

Figure: Components of trandermal patches.

A. Polymers

Polymers are the important parameter 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. Companies involved in the field of transdermal delivery concentrate on a few selective polymeric systems. For example, Alza Corporation mainly concentrates on ethylene vinyl acetate (EVA) copolymers or microporous polypropylene and Searle Pharmacia concentrates on silicon rubber. The polymers utilized for TDDS can be classified as,

- Natural Polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums
- Synthetic Elastomers: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon acrylonitrile, neoprene, butylrubber etc.
- Synthetic Polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone etc.

The following criteria should be satisfied for a polymer to be used in transdermal system.

Molecular weight and chemical functionality of the polymer should be such that specific drug diffuses properly and get released through it.

The polymer should be stable, non reactive, easily manufactured and fabricated into the desired product.

The polymer and its degradation product must be non-toxic to the host.

B. Drug

For successfully developing a TDDS, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery. Physiochemical properties

The drug should have a molecular weight less than approximately 1000 Dalton.

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The drug should have affinity for both lipophilic and hydrophilic phases.
The drug should have low melting point.

Biological properties
The drug should be potent with a daily dose of the order of a few mg/day.
The half life should be short.
The drug must not induce a cutaneous irritant or allergic response.
Drug which degrade in the GI tract are suitable for transdermal delivery.
Drugs which have to be administered for a long period of time can be formulated for transdermal system.

Permeation Enhancers

To increase the permeability of stratum corneum so as to attain higher therapeutic levels of the drug penetration enhancer interact with structural component of stratum corneum i.e protein and lipids. The enhancement of absorption of oil soluble drugs is apparently due to partial leaching of the epidermal lipids by chemical enhancers, resulting in the improvement of skin condition for wetting and transepithelial and transfollicular penetration.
Permeation enhancer is classified into two- chemical and physical enhancer.
Chemical enhancer: Chemicals that promote the penetration of topically applied drugs are commonly referred to as accelerants, absorption promoters, orpenetration enhancers.

Classification of chemical enhancer

- Terpenes : e.g. menthol, carvone etc.
- Pyrollidones : e.g. N-methyl-2-pyrollidone, azone etc.
- Fatty acids : e.g. oleic acid, lauric acid etc.
- Sulfoxides : e.g. dimethyl sulfoxide.
- Alcohols : e.g. ethanol, octyl alcohol etc.
- Miscellaneous enhancer : e.g. phospholipid,cyclodextrin,amino derivative etc.

Physical Enhancers

The iontophoresis and ultra sound (also known as phonophoresis or sonophoresis) techniques are examples of physical means of enhancement that have been used for enhancing percutaneous penetration (and absorption) of various therapeutic agents.

Adhesives

The pressure sensitive adhesive maintains an intimate contact between patch and the skin surface. E.g. polyacrylates, polyisobutylene and silicon based adhesive. Adhesive system should fulfill the following criteria
Should not irritate or sensitize the skin.
Should adhere to the skin aggresively during the dosing interval without its position being disturbed by activites such as bathing, exercise e.t.c.
Should be easily removed
Should not leave an unwashable residue on the skin.
Should have excellent contact with skin.

Backing Laminate

The primary function is to provide a good bond to the drug reservoir, prevent drug from leaving the dosage forms through the top. It is impermeable substance that protect the product during use on the skin.eg metallic plastic laminate, occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) etc.

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Release Liner

During storage release liner prevents the loss of the drug that has migrated into adhesive layer. It is therefore regarded as a part of primary packaging material. E.g paper fabric, polyethylene, polyvinylchloride etc.

Other Excipients

Solvents such as chloroform, methanol, acetone are used to prepare drug reservoir. In addition plasticizers such as castor oil, propylene glycol etc are added to provide plasticity to the patch.

Factors affecting transdermal permeation:

Physicochemical properties of the penetrant molecules:

Partition coefficient

A lipid/water partition coefficient of 1 or greater is generally required for optimal transdermal permeability.
It may be altered by chemical modification without affecting the pharmacological activity of the drug.

pH conditions

Applications of solutions whose pH values are very high or very low can be destructive to the drug.
With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.

Penetrant concentration

Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux.
At concentration higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug constitution for a prolonged period of time.

Physicochemical properties of the drug delivery system

A. Release characteristics

Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on the following factors:
Whether the drug molecules are dissolved or suspended in the delivery systems.
The interfacial partition coefficient of the drug from the delivery system to the skin tissue.
pH of the vehicle

B. Composition of the drug delivery systems

The composition of the drug delivery systems e.g., boundary layers, thickness, polymers, vehicles not only affects the rate of drug release, but also the permeability of the stratum corneum by means of hydration, making with skin lipids, or other sorption promoting effects e.g., benzocaine permeation decreases with PEG of low molecular weight.

Advantages of transdermal drug delivery system

- Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivering drug across skin to achieve systemic effect are
- Avoidance of first pass metabolism.
- Avoidance of gastrointestinal incompatibility.
- Predictable and extended duration of activity.
- Minimizing undesirable side effect.
- Provides utilization of drug with short biological half life, narrow therapeutic window.
- Avoiding the fluctuation in drug level.
- Maintain plasma concentration of potent drug.

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- Termination of therapy is easy at any point of time.
- Greater patient compliances due to elimination of multiple dosing profile.
- Ability to deliver the drug more selectively to a specific site.
- Provide suitability for self administration.
- Enhance therapeutic efficacy.

Disadvantages of TDDS:

- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- Higher cost.
- Should not use ionic drug.
- May cause allergic reactions.
- A molecular weight less than 500 Da is essential.
- Sufficient aqueous and lipid solubility, a log P (octanol/water) between 1 and 3 is required for permeate to transverse SC and underlying aqueous layers.
- Transdermal therapy is feasible for certain potent drugs only.
- Transdermal therapy is not feasible for ionic drugs.
- It cannot deliver drug in pulsatile fashion.
- Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin‟s impermeability.

Limitations of TDDS:

- Limited skin permeability.
- Restricted to potent drug
- Cannot use for large molecule (>500 Dalton)
- Significant lag time
- Difficulty for adhesion.
- The drug undergoes degradation in the skin.
- Variation in absorption efficiency at different sites of skin.

Recent Advances in Transdermal delivery system

Latest research done in field of transdermal patches are stated below:

Patch technology for protein delivery

Transdermal delivery of large protein is a novel and exciting delivery method.transpharma uses its unique printed patch technology for transdermal delivery of protein thereby complementing its via Derm delivery technology It is postulated that the highly water soluble proteins are dissolved by the interstitial fluid that is secreted from the skin through the RF MicroChannels, forming a highly concentrated protein solution in situ.The delivery of the dissolved molecules is then carried out, via the RF□Micro Channels, into the viable tissues of the skin, diffusing across a steep concentration gradient.

Testosterone transdermal patch system in young women with spontaneous premature ovarian failure

In premenopausal women, the daily testoterone production is approximately 300 µg, of which approximately half is derived from the ovaries and half from the adrenal glands. Young women with spontaneous premature ovarian failure (sPOF) may have lower androgen levels, compared with normal ovulatory women. Testosterone transdermal patch (TTP) was designed to deliver the normal ovarian production rate of testosterone.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
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Impact Factor: 7.301

Transdermal patch of oxybutynin used in overactive bladder

The product is a transdermal patch containing Oxybutynin HCl and is approved in US under the brand name of Oxytrol and in Europe underthe brand name of Kentera. OXYTROL is a thin, flexible and clear patch that is applied to the abdomen, hip or buttock twice weekly and provides continuous and consistent delivery of oxybutynin over a three to four day interval. OXYTROL offers over active bladder(OAB) patient's continuous effective bladder control with some of the side effects, such as dry mouth and constipation encountered with an oral formulation.

Nanotechnology gaining hold

Another enhancer that is gaining advancement is microneedles. This technology combines the advantage of a needle and the transdermal patch. The devices are dime□sized pieces of polymer with hundreds of hollow microneedles between 100 and 1,000 micrometers long.These small needles penetrate the top layers of skin and allow the drug to pass through with ease. This technology can be combined with an electronically controlled micropump that delivers the drug at specific times or upon demand. Alza is using a slightly different variation on the use of needles. . The company has developed the patented Macroflux transdermal technology that uses microprojections to create superficial pathways through the dead skin barrier.

Pain relief

Pain relief routinely benefits from transdermal patch technology. Most of the readers are aware of the Duragesic patch. One is Lidoderm, a lidocaine percent patch, which is used for post herpetic neuralgia. Other exciting advancements in pain control include the E Trans fentanyl HCl patch. . This credit card size patch is an active delivery device that has a self contained battery that delivers pulses of fentanyl HCl, a strong narcotic. This mimics the use of intravenous self controlled analgesic systems that are very expensive.

Molecular absorption enhancement technology

Considerable research has been done on absorption enhancers, compounds that promote the passage of drugs through the stratum corneum. Terpene derivatives as well as certain phenols seem to improve transdermal absorption. For example Limonene, menthone, and eugenol were found to enhance transdermal absorption of tamoxifen.

Phloretin, a polyphenol, enhanced the absorption of lignocaine.

Microfabricated microneedle

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 a some projections (microneedles as shown in fig. extending from the reservoir, these helps in penetrating the stratum cornea and epidermis to deliver the drug

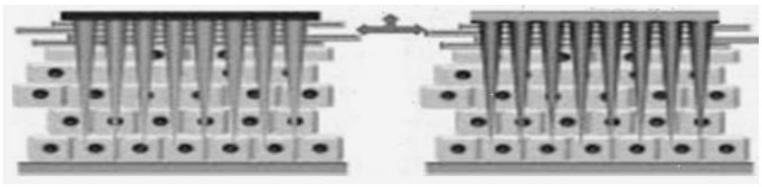

Figure: Delivery site for microneedle technology.
(a) Hollow microneedles with applied formulation; (b) Solid microneedles

Microneedles are tiny and very sleek devices that are manufactured by the silicon etching technology and micro-mechanical system manufacturing (MEMS) technique, which do not penetrate deep enough into the skin to reach up to the nerve endings and thus there is no pain sensation during the microneedles insertion into the skin. There are number of delivery approaches that have been employed to use the microneedles for TDDS. These includes-

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-

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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.

Future Technologies and Approaches

Thermal Poration is the formation of aqueous pathways across stratum corneum by the application of pulsed heat, this approach has been used to deliver conventional drugs .
Jet injectors are receiving increased attention now days, which is opening doors for improved device design for controlled, needle free injection of drug solutions across the skin and into deeper tissue.
Small needle is inserted a few millimeters into skin and drug solution is flowed through the needle into the skin at controlled rates using a micro□infusion pump that is contained within a large patch affixed to skin, morphine has been delivered to humans using this approach.
During the past decade several theories have been put forward in addressing the combinations of chemicals and iontophoresis; chemicals and electroporation; chemicals and ultrasound; iontophoresis and ultrasound; electroporation and iontophoresis; and electroporation and ultrasound.
TransPharma is focused on products for which our technology will provide clear benefits over existing therapies. Such benefits could include improving safety and compliance through the use of a drug patch or enhancing efficacy with the use of sustained release patch formulations, among others.
The ViaDerm system may be applied to the delivery of local medications for topical applications in the fields of dermatology and cosmetics. The ViaDerm system may also allow enhanced immunizations, providing a nonpainful, safe and effective alternative to current intramuscular or subcutaneous vaccination methods.
Altea Therapeutics is currently in clinical development of a transdermal patch designed to address a major unmet need by preventing ‘off’ periods and provide an improved therapeutic option for managing Parkinson’s disease.

VI. CONCLUSION

Transdermal drug delivery systems represent a beneficial innovation for drug delivery, particularly in patients who cannot swallow or remember to take their medications. Clinicians and other allied health professionals should understand the appropriate administration techniques for transdermal systems to ensure optimal patient outcomes and to ensure the safety of all who encounter patients who use TDDS.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.

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