IJPSR (2017), Vol. 8, Issue 2 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 July, 2016; received in revised form, 19 September, 2016; accepted, 26 September, 2016; published 01 February, 2017

TRANSDERMAL DRUG DELIVERY SYSTEM, ADVANCE DEVELOPMENT AND EVALUATION-A REVIEW

Garima Verma

Shambhunath Institute of Pharmacy, Jhalwa, Allahabad, Uttar Pradesh - 211012, India.

Keywords:

TDDS, Transdermal film, Drug polymer etc

Correspondence to Author:
Garima Verma

Shambhunath Institute of Pharmacy, Jhalwa, Allahabad, Uttar Pradesh-211012, India.

Email: garima.srivastava2111@gmail.com

ABSTRACT: It is the most important part of pharmaceutical dosage forms; transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. On the application of Transdermal patches, the delivery of the drug across dermis gives the systemic effect. TDDS is costly alternative to conventional formulation. It is also important due to its unique advantage. Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal drug delivery. Development of controlled release transdermal dosage form is a complex process involving extensive efforts. This review article describes the methods of preparation of different types of transdermal patches. In addition, the various methods of evaluation of transdermal dosage form and advance development in TDDS have also been reviewed.

INTRODUCTION: Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body- through its layers, to the circulatory system. 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 enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. Another advantage is convenience, especially notable in patches that require only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy. Designing and development of transdermal patches can be described as state of the art.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(2).385-00

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (2).385-00

The development of TDDS is multidisciplinary activity that encompasses fundamental feasibility A studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an ex vivo and in vivo model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical and stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important the economy [1].

Transdermal Permeation: Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration [2].

Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows: [3-4]

- Diffusion of drug from drug reservoir to the rate controlling membrane.
- Diffusion of drug from rate limiting membrane to stratum corneum.
- Sorption by stratum corneum and penetration through viable epidermis.
- Uptake of drug by capillary network in the dermal papillary layer.

Advantages of transdermal drug delivery systems: [3, 4] Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivery drugs across the skin to achieve systemic effects are:

- Avoidance of first pass metabolism
- Avoidance of gastro intestinal incompatibility
- Predictable and extended duration of activity
- Minimizing undesirable side effects
- Provides utilization of drugs with short biological half lives, narrow therapeutic window
- Improving physiological and pharmacological response
- Avoiding the fluctuation in drug levels
- Inter and intra patient variations
- Maintain plasma concentration of potent drugs
- Termination of therapy is easy at any point of time
- Greater patient compliance due to elimination of multiple dosing profile
- Ability to deliver drug more selectively to a specific site
- Provide suitability for self administration
- Enhance therapeutic efficacy

TDDS Classification Based on their Technical Sophistication:

A) Rate pre-programmed drug delivery system
B) Activation modulated drug delivery system
C) Feedback regulated drug delivery system
D) Carrier based drug delivery system

A) Rate Pre Programmed Drug Delivery System: It involves the system designs that deliver medicaments by controlling molecular diffusion of drug molecules across the skin barrier within or surrounding the delivery system.

1. Polymer membrane permeation controlled drug delivery system: It involves the system in which the drug is enclosed within a drug reservoir. This is covered by the semi permeable membrane of polymer that regulates the release and having a specific permeability. There are some potential development with process of membrane permeation are as micro porous membrane permeation controlled gastrointestinal delivery device, gastric fluid resistance intestinal targeted controlled release gastrointestinal device and gel diffusion controlled drug delivery system [5].

2. Polymer matrix diffusion controlled drug delivery system: It is developed by dispersing drug particles in carrier matrix (in a homogenous manner) that is rate controlling. For e.g. Nitro Dur – It is designed for application onto intact skin for 24 hrs that provide consistence transdermal infusion of nitroglycerine [6].

3. Microreservoir partitioned controlled drug delivery system: It involves dispersion of micro particles of suspension of drug (aqueous in nature) in a polymer using high energy dispersion. E.g. Syncromate implant – Engineered to deliver subdermal administration of norgestomet [7].

B) Activation Modulated Drug Delivery System: This type of delivery system can be achieved by

1. Physical means:

- Osmotic pressure activated drug delivery system.
- Hydrodynamic pressure controlled drug delivery system.
- Vapour pressure activated drug delivery system.
- Mechanically activated drug delivery system.
- Magnetically activated drug delivery system.
- Electrically activated drug delivery system.
- Ultrasound activated drug delivery system.
- Hydration activated drug delivery system**.**

2. Chemical means:

- pH activated drug delivery system
- Ion activated drug delivery system
- Hydrolysis activated drug delivery system

3-Biochemical means:

- Enzymes activated drug delivery system

C) Feedback Regulated Drug Delivery System: The release of the drug molecules from the transdermal system is facilitated by an agent that triggers the release of drug, such as biochemical in the body and also regulated by its concentration through some feedback mechanism.

- Bio-erosion regulated drug delivery system.
- Bio-responsive drug delivery system.
- Self regulated drug delivery system. [8]

D) Carrier Based Drug Delivery System:

Colloidal particulates carrier system: This involves vesicular system like hydrogels, liposomes, niosomes, nanocapsules, nanoparticles, polymeric complexes, microspheres, nanoerythrosomes, transferosomes, dendrimers, aquasomes, etc.

Basic Principle of TDDS: The skin represents an important barrier of the penetration of exogenous substances into the body and, on the other hand, a potential avenue for the transport of functional active principles into the skin and/or the body. Several studies have shown the modalities through which these molecules cross the horny layer, which represents the most important limiting factor of the process of diffusion and penetration, and have discussed how to increase the penetration of pharmacologically active substances [9-11].

The stratum corneum has a very peculiar structure: the corneocytes (the bricks: about 85% of the mass of horny mass) and intercellular lipids (15%) are arranged in approximately 15-20 layers. It consists of about 70 percent proteins, 15 percent lipids, and only 15 percent water. In the corneocytes contain keratin, filagrin, and demolition products. The corneocyte lacks lipids, but is rich in proteins. The lipids are inside extracellular spaces, in a bilayer organization surrounding corneocytes [12]. The very low permeability of the horny layer to hydrosoluble substances is because of this extracellular lipid matrix. Cutaneous penetration of hydrophilic substances is limited because of the convoluted and tortuous intercellular space and hydrophobicity of three lipidic constituents: ceramides, cholesterol, and free fatty acids that are present in the molar ratio: 1: 1: 1 (weight ratio: ceramides 50%, cholesterol 35-40%, free fatty acids 10-15%) [13]. This ratio is critical: the diminution of the concentration of one of these types of lipids alters the molar ratio functional to the normality of the barrier and modifies its integrity [14]. The variations of this lamellar structure and/or its lipid composition are the structural and biochemical basis of permeability variations along with the thickness of the horny layer [15, 16]. The extracellular matrix forms also the so-called reservoir of the horny layer (some substances are partially retained in the corneous layer and are slowly released).

Various processes carried out serially or in parallel, are involved in cutaneous penetration of substances and these may cross the stratum corneum via an intercellular or a transcellular route. Moreover, entrance through pilosebaceous units and eccrine glands is possible. Many efforts to obtain therapeutic effects in tissues far from the skin have been made. We may have: topical administration, with a pharmacological effect limited to skin, with some unavoidable systemic absorption; loco-regional delivery, when the therapeutic effect is obtained in tissues more or less deeply beneath the skin (muscles, articulations, vessels, etc.) with limited systemic absorption; and transdermic delivery that aims to obtain, through application of preparations on the skin, pharmacologically active levels for the treatment of systemic diseases through skin vascular network.

Stratum corneum barrier and intradermal delivery: The penetration through the stratum corneum involves partition phenomena of applied molecules between lipophilic and hydrophilic compartments. For many substances the penetration takes place through an intercellular way, more than transcellular, diffusing around the keratinocytes. Intercellular movement. The lipid lamellae of the intercellular spaces (each one including 2 or 3 bilayers and made mainly of ceramides, cholesterol, and free fatty acids) are the intercellular structure of the horny layer, with the main role in barrier function. Most solute substances, non-polar or polar, penetrate across intercellular lipid avenues. The permeability of very polar solutes is constant and similar to the transport of ions (es. potassium ions). Lipophilic solute permeability increases according to specific lipophilic properties.

Transcellular movement. Stratum corneum intracellular components are essentially devoid of lipids and lack a functional lipid matrix around keratin and keratohyalin. This results in an almost impenetrability of corneocytes [17]. Degradation of the corneodesmosomes causes formation of a continuous lacunar dominio ("aqueous pore") allowing intercellular penetration; the lacunae formed are scattered and not continuous, and form as a result of occlusion, ionophoresis, and ultrasound waves. These may become larger and connect forming a net ("pore-way"). Various methods can induce this type of permeability increase [18]. Transport through follicular and gland structures. Movement through hair follicles, pilosebaceous units, and eccrine glands is limited. The orifices of the pilosebaceous units represent about 10 percent in areas where their density is high (face and scalp) and only 0.1 percent in areas where their density is low.

This is a possible selective way for some drugs. Follicular penetration may be influenced by sebaceous secretion, which favors the absorption of substances soluble in lipids. The penetration through the pilosebaceous units is dependent upon the property of the substance and type of preparation.

a) Pharmacokinetic parameters Vehicle / corneous layer partition: For the purpose of the study of the mechanisms of transport and the functions of the skin barrier, it can be considered as a membrane or a cluster of membranes (mathematical principles can be applied) [19]. On the whole, transport through the horny layer is mainly a molecular passive diffusion. The physico-chemical and structural properties of the substance determine the capacity of diffusion and penetration through the membrane: important determinants are solubility and diffusibility. The diffusibility and the ability of a solute to penetrate through the barrier is influenced by several factors including the tortuosity of the intercellular route. This passive process of absorption follows Fick's law of diffusion: the velocity of absorption - flow - is proportional to the difference of concentration of the substance in relation to that within the barrier. It can finally be noted that the permeability coefficient relates flow and concentration, resulting from partition coefficient, diffusion coefficient, and length of diffusion route [20].

b) Role of the vehicle and excipients and interaction with the active principles: A vehicle is defined by the type of preparation (cream, ointment, gel) and the excipients (water, paraffin, propylene glycol); the terms "vehicle" and "excipient" refer to different entities. Vehicle and excipients deeply influence the velocity and magnitude of absorption and consequently the bioavailability and efficacy. The excipients of the vehicle modulate the effects of partition and diffusion in the stratum corneum. A lipid preparation that promotes occlusion may enhance the penetration of the drug, but ointments and lipid preparations and are not always more powerful than creams. Creams, gels and solutions may be formulated so as to obtain an effect equivalent to that of ointments. Topical corticosteroids, of different classes of potency, e.g., may show the same activity when formulated in different vehicles' [21]. A gel preparation of kellin, obtaining better penetration, has demonstrated important results in the treatment of vitiligo [22]. Also transfollicular penetration is influenced by vehicle and excipients; in this case better results are given by lipophilic and alcoholic vehicles. Relevant factors include dimension and charge of the molecules of the solute [23, 24].

c) Conditions that modify the barrier function: During hydration the greater part of the water is associated with intracellular keratin; the natural factor of hydration or natural moisturizing factor (NMF) absorbs a noticeable amount of water (10% of the weight of the corneocyte). Corneocytes swell and the barrier properties of the stratum corneum are deeply altered. In the intercellular space the small amount of water linked to polar groups by hydration does not alter the organization of lipids and does not reduce of permeability [25]. The effect of the hydration however has a discontinuous effect; the increment may be by ten times for some substances and very limited for others [26]. Occlusion partially hinders the loss of humidity of the skin, increasing the content of water of the horny layer. However the NMF level in the horny layer is almost zero.

It seems therefore that there is a homeostatic mechanism that prevents hyper hydration of the skin [17]. Occlusion may increase the absorption by several times, especially for hydrophilic compounds. However, in some conditions it may promote the formation of a reservoir effect. The acidity of the cutaneous surface, controlling homeostasis and enzymatic activities, influences permeability [27]; the metabolic activity of the skin (enzymatic oxidoreductive processes) may modify the substances applied, influencing permeability and effects. Absorption is also influenced by other skin properties that vary at different cutaneous anatomical sites.

For instance, the absorption diminishes greatly as one move from the palpebral skin to the plantar surfaces [28]. Age influences skin absorption. Various biological activities are lower in the skin of the aged individual. Great variation is also noted for the premature infant and neonate, who have greater cutaneous permeability [29]. There are no experimental data confirming the validity of friction on transcutaneous absorption [10]. Alterations of the barrier induce modifications of TEWL[13].

In addition, the horny layer may be defined as a biosensor; alterations of external humidity regulate proteolysis of filaggrin, synthesis of lipids, DNA, and proteins within keratinocytes, which can lead also to inflammatory phenomena [30]. The cutaneous bioavailability of most commercial dermatological formulations is low (within 1-5% of applied dose) [31]. The active substances of topical formulations are generally absorbed in small quantities; only a reduced fraction passes from the vehicle into the stratum corneum. The greater part remains on the surface of the skin, subject to loss in several ways such as by sweating, chemical degradation, and removal. The absorption of the drug is on the order of 1-5 percent of the applied dose. Future standards would therefore aim to make formulations not merely high in concentration, but pharmaceutically optimized to have an elevated (50-100%) bioavailability.

On the other hand, one must consider the marked variations of the different cutaneous areas and skin conditions that make uncertain the therapeutic equivalence when compared with other ways of administration in clinical conditions [32].

Basic Component of TDDS:

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. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status [33]. 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 micro porous polypropylene and Searle Pharmacia concentrates on silicon rubber [34]. Similarly Colorcon, UK uses HPMC for matrix preparation for propranolol transdermal delivery and Sigma uses ethyl cellulose for isosorbide dinitrate matrix [35-37]. The polymers utilized for TDDS can be classified as [2-3]:

Natural Polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc [38].

Synthetic Elastomers: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butyl rubber etc.

Synthetic Polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc*. The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose are used as matrix formers for TDDS. Other polymers like, silicon rubber and polyurethane are used as rate controlling membrane.

Drug:

Drug substance: Drug is in direct contact with release liner.

Ex: Nicotine, Methotrexate and Estrogen.

The selection of drug for transdermal drug delivery depends upon various factors.

Physicochemical properties: [38, 39]

a) The drug should have some degree of solubility in both oil and water (ideally greater than 1 mg/ml).

b) The substance should have melting point less than 200 °F. Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point (in degree absolute of the drug). In order to obtain the best candidates for TDD, an attempt should be made to keep the melting point as low as possible.

c) Substances having a molecular weight of less than 1000 units are suitable.

d) A saturated aqueous solution of the drug should have a pH value between 5 and 9. Drugs highly acidic or alkaline in solution are not suitable for TDD; because they get ionized rapidly at physiological pH and ionized materials generally penetrate the skin poorly.

e) Hydrogen bonding groups should be less than 2.

Biological properties: [40]

a) Drug should be very potent, i.e., it should be effective in few mgs per day (ideally less than 25 mg/day).

b) The drug should have short biological half life.

c) The drug should be non irritant and non allergic to human skin.

d) The drug should be stable when in contact with the skin.

e) The drug should not stimulate an immune reaction to the skin.

f) Tolerance to drug must not develop under near zero order release profile of transdermal delivery.

g) The drug should not get irreversibly bound in the subcutaneous tissue.

h) The should not get extensively metabolized in the skin.

Permeation Enhancers: These are the chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate [41]. Penetration enhancers interact with structural components of stratum corneum i.e., proteins or lipids. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability[42]. 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.

Permeation enhancers used for TDDS:

a. Solvents; Methanol, Ethanol, Dimethyl sulfoxide, Propylene glycol, 2- Pyrrolidone, Isopropyl myristate.

b. Anionic Surfectants; Sodium lauryl sulphate.

c. Nonionic surfectants; Sorbiton monolaurate, Pluronic.

d. Essential oils; Cardamom oil, Caraway oil, Lemon oil, Menthol, d-Limonene, Linoleic acid.

Pressure sensitive adhesives: A PSA is a material that helps in maintaining 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 [43, 44]. Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDSs [45]. 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 physicochemically and biologically compatible and should not alter drug release [46].

Backing Laminate: While designing a backing layer, the consideration of chemical resistance of the material is most important. 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. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate [47, 48]. Examples of some backing materials are vinyl, polyethylene and polyester films.

Release Liner: During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. 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 [49].

Other excipients: Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir [50]. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch [51, 52].

Types of Transdermal Drug Delivery Systems:

Membrane permeation controlled system: In this type of system (**Fig.1**), the drug reservoir is totally encapsulated in a shallow compartment moulded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane e.g. Ethylene vinyl acetate with defined drug permeability. The drug molecules are permitted to release only through the rate-controlling membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid-polymer matrix or suspended in a viscous liquid medium to form a paste like suspension. A thin layer of adhesive polymer is applied to the external surface of the rate-controlling membrane to achive an intimate contact of the transdermal system and the skin surface. For example Transderm-Nitro, Transderm-Scop, Catapress, Estraderm**.**

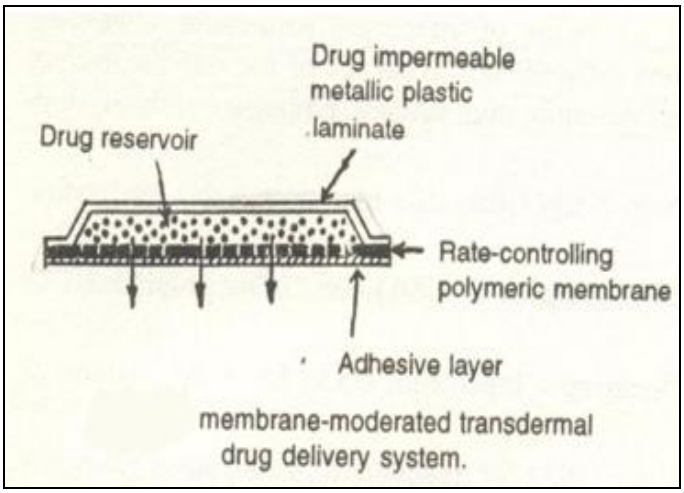

FIG. 1: MEMBRANE PERMEATION CONTROLLED SYSTEM

Matrix Diffusion controlled system: In this approach shown in **Fig.2**, the drug reservoir is prepared by homogenously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness. This drug reservoir containing polymer disc is then pasted on to an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing. The adhesive polymer is then spread along the circumference to form a strip of adhesive rim around the medicated disc, e.g. Nitro-Dur System.

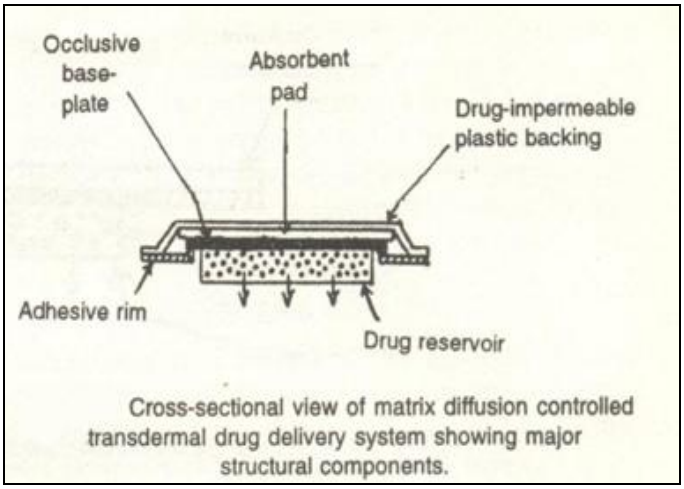

FIG.2: MATRIX DIFFUSION CONTROLLED SYSTEM

Adhesive Dispersion type system: This is a simplified form of the membrane permeation-controlled system as shown in **Fig.3.** The drug reservoir is formulated by directly dispersing the drug in an adhesive polymer eg. polyisobutylene and then spreading the medicated adhesive , by solvent casting or hot melt onto a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the top of the drug reservoir layer, thin layers of non- medicated, rate-controlling adhesive polymer of a specific permeability are applied to produce an adhesive diffusion - controlled delivery system, e.g. Deponit, Frandol Tape.

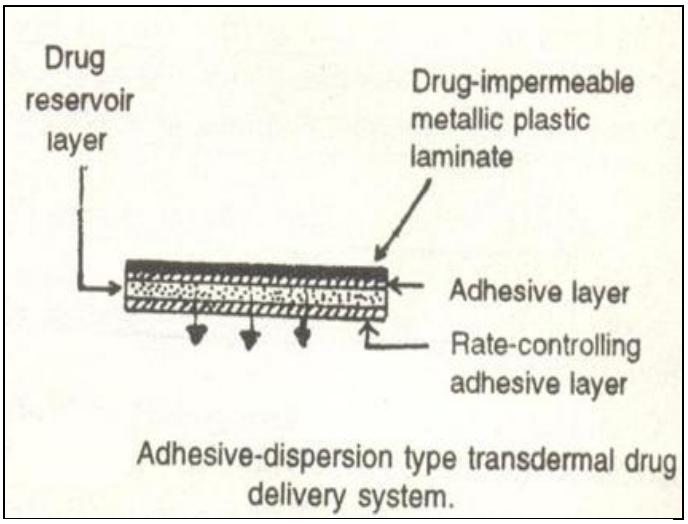

FIG.3: ADHESIVE DISPERSION TYPE SYSTEM

Microreservoir type or microsealed dissolution controlled systems: Here, the drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water soluble liquid polymer and then dispersing the drug suspension homogenously in a lipophilic polymer by high shear mechanical force to form a large number of microreservoirs as shown in **Fig. 4**. These are unleachable microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediate addition of cross linking polymers like Gluteraldehyde the polymer which produces a medicated polmer disc with a constant surface area and a fixed thickness. A transdermal therapeutic system is produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim and then it is spread on to the occlusive base plate with adhesive foam pad.

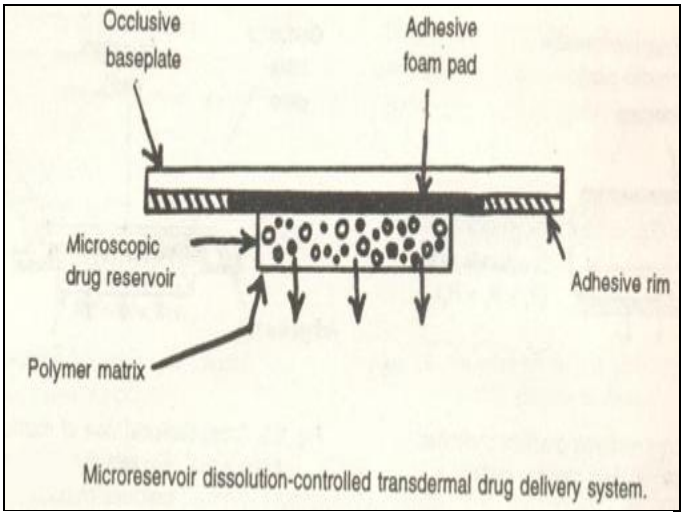

FIG. 4: MICRORESERVOIR TYPE OR MICROSEALED DISSOLUTION CONTROLLED SYSTEMS

Various Methods for Preparation of TDDS:

1. Asymmetric TPX membrane method: [53] A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1 pentene)} asymmetric membrane, and sealed by an adhesive. [(Asymmetric TPX membrane preparation): These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°c to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a Gardner knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs].

2. Circular Teflon mould method: [54] 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.

3. Mercury substrate method: [55] 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.

4. By using "IPM membranes" method: [56] In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers 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.

5. By using "EVAC membranes" method: [57] In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (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.

6. Aluminium backed adhesive film method: [58] Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one for preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custammade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

7. Preparation of TDDS by using Proliposomes: [59, 60] The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°c temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in desiccators 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.

8. By using free film method: [61] 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: [62, 63] Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other

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

2. Thickness of the patch: [64] 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: [65] 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: [66] 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: [66] 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: [67] The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

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

7. Water vapour permeability (WVP) evaluation: [68] Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula

$$WVP=W/A$$

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

8. Drug content: [69] A specified area of patch is to be 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: [70] An accurately weighed portion of the patch is to be 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 was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2µm membrane filter and analyzed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.

10. Polariscope examination: [71] This test is to be performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.

11. Shear Adhesion test: [72] This test is to be performed for the measurement of the cohesive strength of an adhesive polymer.

It can be influenced by the molecular weight, the degree of cross linking 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: [73] 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.

13. Thumb tack test: [74] It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.

14. Flatness test: [75] Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

15. Percentage Elongation break test: [76] The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula

$$\text{Elongation percentage} = \frac{L1-L2}{L2} \times 100$$

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

16. Rolling ball tack test: [77] This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

17. Quick Stick (peel-tack) test: [78] In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required to break 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: [79] 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: [80] 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: [80] An *in vitro* permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant.

The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2).

21. Skin Irritation study: [81] Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

22. Stability studies: [81] Stability studies are to be 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 and 180 days and analyze suitably for the drug content.

Advance Development in TDDS:

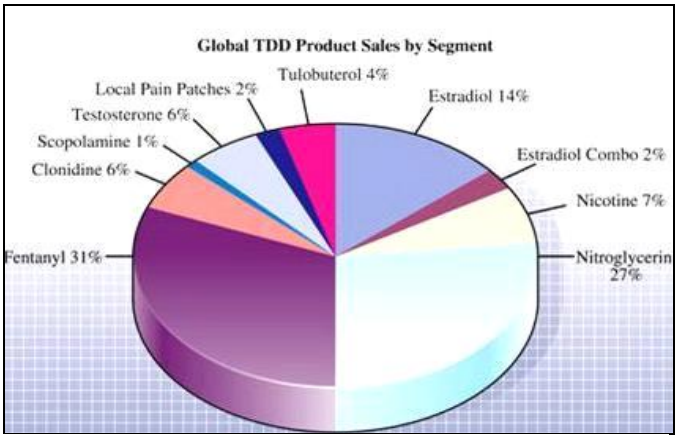

FIG. 5: TRANSDERMAL DRUG DELIVERY PRODUCT SALE GLOBALLY

Drug in adhesive technology has become the preferred system for passive transdermal delivery, two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch.

A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. These so-called "active" transdermal technologies include iontophoresis (which uses low voltage electrical current to drive charged drugs through the skin), electroporation (which uses short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules). Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin.

Transdermal Drug Delivery System Market: [81]
Table 1 gives a list of companies in transdermal drug delivery systems with their current products and technologies in the market. 3M Pharmaceuticals is a leader in pioneering the technological components in transdermal drug delivery system and components made by 3M are used for manufacturing the complete spectrum of drugs delivered transdermally [92]. **Fig. 5** shows a graph showing the range of transdermal drug delivery system currently sold in the market. On the X-axis are the drugs that are administered transdermally, while the Y-axis in the graph shows percentage of the total transdermal products that are being sold in the market.

TABLE 1: COMPANIES AND THEIR TRANSDERMAL DRUG DELIVERY TECHNOLOGIES & PRODUCTS [80]

Company Name	Transdermal Products/Technology in Market
3M Pharmaceuticals	MinitranTM, Pioneer in the field of Manufacturing Transdermal Components
Acrux Ltd.	ACROSSR, MDTSR, Patchless PatchR
Adhesives Research, Inc	ETATM, HRT Adhesives, PIB Adhesives, MTT Adhesives
Adherex Technologies, Inc.	ExherinTM
Altea Therapeutics Corp.	PassPortR Patch
Alza Corp.	D-TransR System, E-TransR System, MacrofluxR System
Antares Pharma, Inc.	ATDTM Gel Technology
Biochemics, Inc.	PENtoCORER
Boehringer Ingelheim Corp.	CATAPRES-TTSR
Dermisonics, Inc.	U-Strip
Elan Transdermal Technologies, Inc.	Buspirone Patch
Inovio Biomedical Corp.	MedPulser Electroporation Therapy System
ImaRx Therapeutics, Inc.	SonoDermTM Technology
Iomed, Inc.	Iontophoreris Electrodes: TransQR Flex, IOGELR, TransQR E, OptimaAR ; Numby StuffR, IONTOCAINER, PhoresorR
Noven Pharmaceuticals, Inc.	VivelleR, Vivelle-DotTM, CombiPatchTM, EstalisR, MethyPatchR
L.A.M. Pharmaceuticals LLC	IPM Wound GelTM, Polymer MatrixTM Technology
Macrochem Corp.	MacroDermTM, SEPAR
Norwood Abbey Ltd.	Laser Assisted Drug Delivery(LAD), Micro-needle Drug Delivery
Sontra Medical Corp.	SonoPrepR
Travanti Pharma, Inc.	Wearable Electronic Disposable Drug (WEDDR)
Vyteris, Inc.	LidoSiteTM Topical System

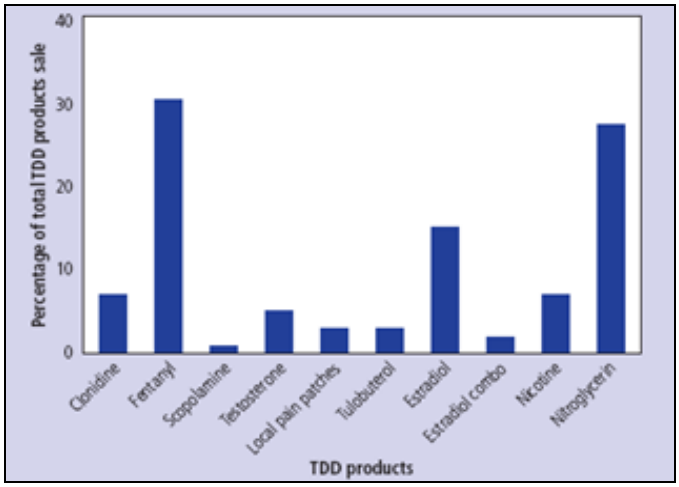

FIG. 6: GRAPH OF TRANSDERMAL DRUG DELIVERY PRODUCTS VS. PERCENTAGE TOTAL SOLD

Transdermal Drug Delivery Products: [83] The range of the current drugs that are administered by using Transdermal drug delivery technique is still limited due to the skin posing as a barrier against the drug diffusion or permeation.

This barrier of stratum corneum is overcome by use of active transdermal drug delivery techniques that are relatively new to the market but are considered to have great potential towards increasing the range and variety of drugs that could be administered transdermally. The annual market for transdermal Drug Delivery systems is more than $3 billion.

FDA Regulation and TDDS: [81] The first FDA approved Transdermal Drug Patch was in the year 1979. Since then, the transdermal drug delivery systems have come a long way. **Fig 6 s**hows the graph of trandermal drug delivery products Vs percentage total sold. The FDA regulation process for Transdermal drug delivery system is very stringent.

Transdermal Drug Delivery system is a combinational device as defined in 21 CFR § 3.2(e) by Food and Drug Administration. Transdermal drug delivery system have to undergo premarket approval (PMA) and hence requires substantial evidence including biomechanical testing, animal testing, clinical trials studies before the transdermal patch can get approval for use in the market. The most recent approval in the field of transdermal drug delivery system was the approval of Nuepro patch for treatment of Parkinson's disease.

In the case of Passive transdermal drug delivery system, the factor that requires consideration is ensuring that the drug in the drug-reservoir or the drug-in-adhesive is present and being delivered in a stable as well as controlled form.

It is also important to understand the reactivity of the drug on the skin and ensure that the material used for manufacturing the transdermal patch do not have an adverse reaction on the skin, for instance itching, inflammation, etc. The patch also needs to be kept on from several hours to, in some cases, several days (e.g., contraceptive patch) and hence the properties of the patch like the type of polymers, adhesives used in the making also need special consideration. The material used for making the patch is polymers. There are various types of polymeric materials that are utilized for the construction of transdermal drug delivery system. The following section in the paper describes the polymeric materials along with their properties that are used in the making of transdermal drug delivery system.

The Future of Transdermal Drug Delivery: The statical data showed a market of $ 12.7 billion in the year 2005 which is assumed to increase by $ 21.5 billion in the year 2010 and $ 31.5 billion in the year 2015. Almost all the pharmaceutical companies are developing TDDS [99]. TDDS may be ideal for many injected as well as orally given drugs, but many drugs cannot penetrate the skin membrane effectively because of low permeability of skin barrier. Pharmaceutical companies are now developing new adhesives, substances that enhance molecular absorption as well as penetration that will ultimately affect skin permeation and greatly increase the list of drugs which can be delivered transdermally. Well known technologies that are iontophoresis and phonophoresis (sonophoresis) considered to acheive significant plasma concentration levels via skin membrane. A micro needle technology is more promising for drug administered via skin. These systems use an arrangement of small needle-like structures to open pores in the stratum cornea and facilitate drug transport without any sensation of pain because these are not reachable to nerve endings. These systems are reported to greatly enhance the permeability of macromolecules across skin[100].

CONCLUSION: Transdermal drug delivery systems have been used as rational drug therapy (safe, effective and economic) drug delivery devices. 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. Different methods are used to prepare these patches by using basic components of TDDS. After preparation of transdermal patches, they are evaluated for physicochemical studies, *in vitro* permeation studies, skin irritation studies and stability studies. But all prepared and evaluated transdermal patches must receive approval from FDA before sale. Future developments of TDDS 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. Kandavilli S, Nair V, Panchagnula R. Polymers in transdermal drug delivery systems, Pharmaceutical Technology 2002, 62-78.
2. Guy RH. Current status and future prospects of transdermal drug delivery, Pharm Res 1996, 13, 1765-1769.
3. Guy RH, Hadgraft J, Bucks DA. Transdermal drug delivery and cutaneous metabolism, Xenobiotica 1987, 7, 325-343.
4. Chein YW. Transdermal Controlled Systemic Medication. New York and Basel, Marcel Dekker Inc. 1987; 159 – 176.
5. Weiner E, Victor A, Johansson ED. Plasma levels of d-Norgestel after oral administration. Contraception 1976, 14: 563-570.
6. Keith AD, Polymer matrix consideration for Transdermal Devices. Drug Dev Ind Pharm. 1983, 9: 605-625.
7. Karim A. Transdermal absorption: a unique opportunity for constant delivery of nitroglycerin. Drug Dev Ind Pharm. 1983, 9: 671.
8. Helier J, Trescony PV. Controlled drug release by polymer dissolution II, Enzyme mediated delivery device. J. Pharm. Sci. 1979, 68: 919.
9. Dermatological and Transdermal Formulations. Marcel Dekker, Inc. New York 2002.
10. Bronaugh RL, Maibach HI. Percutaneous Absorption: Drugs - Cosmetics - Mechanisms - Methodology (Drugs and the Pharmaceutical Sciences). Informa Healthcare; 4th Ed., 2005.
11. Smith EW, Maibach HI. Penetration percutaneous enhancers. Taylor and Francis, 2nd Ed, 2006.
12. Lampe MA, Burlingame AL, Whitney J, Williams ML, Brown BE, Roitman E. Human stratum corneum lipids: characterization and regional differences. J Lipid Res 1983; 24: 120-30.
13. Elias PM, Menon GK. Structural and lipid biochemical correlates of the epidermal permeability barrier. Adv Lipid Res 1991; 24: 1-26.

14. Elias PM, Tsai JC, Menon GK. Skin barrier, percutaneous drug delivery and pharmacokinetics. Dermatology, 2003. Chap 125, p 1235-52.
15. Elias PM, Feingold KR, Menon JK. The stratum corneum, two compartments model and its functional implication. In Basel, Karger Shroot B, Shaefer H, editors. Skin Pharmacokinetics 1987. Vol.1. p 1-9.
16. Surber C, Davis AF. Bioavailability and Bioequivalence of Dermatological Formulations p401-498. in: Dermatological and Transdermal Formulations.vol 119. Marcel Dekker, Inc. New York 2002.
17. Roberts MS, Cross SE, Pellett MA. Skin transport p 89-195 in: Dermatological and Transdermal Formulations.vol 119. Marcel Dekker, Inc. New York 2002.
18. Menon GK, Elias PM. Morphologic basis for a pore-pathway in mammalian stratum corneum. Skin Pharmacol 1997; 10:235-46.
19. Watkinson AC, Brain KR. Basic mathematical principles in skin permeation p 61-88: in Dermatological and Transdermal Formulations.vol 119. Marcel Dekker, Inc. New York.
20. Franz TJ. Kinetics of cutaneous drug penetration. Int J Dermatol 1983; 499-505.
21. Franz TJ. Pharmacokinetics and skin in: Skin barrier, percutaneous drug delivery and pharmacokinetics in Dermatology, vol II, 2003.p 1969-78
22. Orecchia G, Sangalli ME, Gazzaniga A, et al. Topical photochemotherapy of vitiligo with a new khellin formulation: preliminary clinical results. J Dermatol Treat 1998; 9: 65-9.
23. Roberts M, Cross SE, Pellett MA. Skin transport in Dermatological and Transdermal Formulations.vol 119. Marcel Dekker, Inc. New York 2002.
24. Middleton JD. The mechanism of water binding in stratum corneum. Br J Dermatol 1968; 80:437-50
25. Horii I, Nakajama Y, Obate Ml. Stratum corneum hydration and aminoacids contant in xerotic skin. Br J Dermatol Res 1989; 121: 588-64.
26. Imokawa G, Kuno H, Kawai M. Stratum corneum lipids serve as bound-water modulator. J Invest Dermatol 1991; 96: 845-51.
27. Mauro T, Hollerann WM, Grayson S, Gao WN, Man MQ, Kriehuber E, et al. Barrier recovery is impeded at neutral pH, independent of ionic effects: implications for extracellular lipid processing. Arch Dermatol Res 1998; 290: 215-22.
28. Rougier A, Lotte C, Corcuff TP. Relationship between skin permeability and cornecyte size according to anatomic site, age and sex in man. J Soc Cosmet Chem 1988; 39: 15-21.
29. Berardesca E, Maibach HI. Racial differences in skin pathophysiology. J Am Acad Dermatol 1996; 34: 667-72.
30. Menon GK, Elias PM, Feingold KR. Integrity of the permeability barrier is crucial for manteinance of the epidermal calcium gradient. Br J Dermatol 1994; 130: 139-47.
31. Surber C, Davis AF. Bioavailability and Bioequivalence of Dermatological Formulations p401-498. in: Dermatological and Transdermal Formulations.vol 119. Marcel Dekker, Inc. New York 2002.
32. Hauck WW. Bioequivalence studies of topical preparations: statistical considerations. Int J Dermatol 1992; 31 (suppl. 1): 29-33.
33. Keith AD. Polymer matrix considerations for transdermal devices, Drug Dev. Ind. Pharm 1983, 9, 605.
34. Baker RW, Heller J. Material selection for transdermal delivery systems; In: Hadgraft J, Guys RH, editors. Transdermal Drug Delivery: Development Issues and Research Initiatives. New York, Marcel Dekker Inc. 1989; 293-311.
35. Guyot M, Fawaz F. Design and in vitro evaluation of adhesive matrix for transdermal delivery of propranolol, Int J Pharm 2000, 204, 171-182.
36. 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.
37. 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.
38. Misra, A.N., In;Jain, N.K., Eds., Controlled and Novel Drug Delivery, 1st Edn., CBS Publishers and Distributors, New Delhi, 2002, 101-107.
39. Gordon RA, Peterson TA. Four myths about transdermal drug delivery, Drug Delivery Technology 2003, 3, 1-7.
40. Williams AC, Barry BW. Penetration enhancers, Advanced drug delivery reviews 2004, 56, 603-618.
41. Franz TJ. Transdermal Delivery. In: Kydonieus A, ed. Treatise on controlled drug delivery: Fundamentals, optimization, applications. New York, Marcel Dekker Inc. 1991; 341-421.
42. Tan HS, Pfister WR. Pressure sensitive adhesives for transdermal drug delivery, Pharm Sci Technol Today 1999, 2, 60-69.
43. 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.
44. Godbey KJ. Improving patient comfort with nonocclusive transdermal backings, American Association of Pharmaceutical Scientists 1996, 1-2.
45. Foco A, Hadziabdic J, Becic F. Transdermal drug delivery systems, Med Arch 2004, 58, 230-234.
46. 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).
47. Rao PR, Diwan PY. Permeability studies of cellulose acetate free films for transdermal use: Influence of plasticizers, Pharm Acta Helv 1997, 72, 47-51.
48. Gondaliya D, Pundarikakshudu K. Studies in formulation and pharmacotechnical evaluation of controlled release transdermal delivery system of bupropion, AAPS PharmSciTech 2003, 4, Article3.
49. 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.
50. Wiechers J. Use of chemical penetration enhancers in Transdermal drug delivery-possibilities and difficulties. Acta pharm. 1992: 4: 123.
51. 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.
52. Ning YM, Rao YF, Liang WQ. Influence of permeation enhancers on transdermal delivery of anemonia, Zhonqquo Zhong Yao Za Zhi 2007, 32, 393-396.
53. Budhathoki U, Thapa P. Effect of chemical enhancers on in vitro release of salbutamol sulfate from transdermal patches, Kathmandu University of Science Engineering and Technology 2005, 1(1), 1-8.

54. Zurdo SI, Franke P, Schaefer UF, Lehr CM. Delivery of ethinylestradiol from film forming polymeric solutions across human epidermis in vitro and in vivo in pigs, J. Controlled Release 2007, 118, 196-203.
55. Babu RJ, Pandit JK. Effect of permeation enhancers on the transdermal delivery of bupranolol through rat skin, Drug Delivery 2005, 12, 165-169.
56. Oquiso T, Iwaki M, Paku T. Effect of various enhancers on transdermal penetration of indomethacin and urea and relationship between penetration parameters and enhancement factors, J Pharm Sci 1995, 84, 482-488.
57. Parikh DK, Tapash KG. Feasibility of transdermal delivery of fluoxetine, AAPS PharmSciTech. 2005, 6, 144-149.
58. Nokodchi A, Shokri J, Dashbolaghi A, Hassan Zadeh D, Ghafourian T, Barzegar Jalali M. The enhancement effect of surfactants on the penetration of lorazepam through rat skin, Int J Pharm 2003, 250, 359-369.
59. Mukherjee B, Kanupriya, Mahapatra S, Das S, Patra B. Sorbitan monolaurate 20 as a potential skin permeation enhancer in transdermal patches, J Applied Research 2005, 5, 96-107.
60. El-Kattan AF, Asbill CS, Kim N, Mickniak BB. Effect of formulation variables on the percutaneous permeation of ketoprofen from gel formulations, Drug Delivery 2000, 7, 147-153.
61. Al- Khamis K, Davis S.S and Hadgraft J. Microviscosity and drug release from topical gel formulations. Pharm. Res. 1986; 3: 214-217.
62. Anon. Transdermal delivery systems-general drug release standards. Pharmacopeial Forum, 1980; 14: 3860-3865.
63. Mayorga P, Puisieux F and Couarraze G. Formulation study of a Transdermal delivery system of primaquine. Int. J. pharm. 1996; 132: 71-79.
64. 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.
65. 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.
66. 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.
67. Singh J, Tripathi K.T and Sakia T.R. Effect of penetration enhancers on the *in vitro* transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. Drug Dev. Ind. Pharm. 1993; 19: 1623-1628.
68. Wade A, Weller P.J. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical Publishing Association; 1994: 362-366.
69. Rhaghuram reddy K, Muttalik S and Reddy S. Once – daily sustained- release matrix tablets of nicorandil: formulation and invitro evaluation. AAPS Pharm.Sci.Tech. 2003; 4:4.
70. 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: 179-184
71. 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.
72. Wade A and Weller P.J. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical Publishing Association 1994; 362-366.
73. 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.
74. Vyas S.P and Khar R.K. Targetted and controlled Drug Delivery Novel carrier system1stEd., CBS Publishers and distributors, New Delhi, 2002; 411-447.
75. Singh Somnath. "An Overview of Transdermal Drug Delivery". Industry Overview and Deals. Drug Delivery Report Autumn/Winter 2005; (s):35-40. Available at: http://www.drugdeliveryreport.com/ articles/ ddr_w2005_ article06.pdf (Accessed on 11/18/ 2008).
76. Prausnitz Mark. R., Mitragotri Samir., Langer Robert. "Current Status and Future Potential of Transdermal Drug Delivery". Nature review, Drug Discovery, February 2004; Vol. 3. Page(s): 115-124.
77. Segal Marian: "Patches, Pumps and Timed Release: New Ways to Deliver Drugs". FDA Consumer Magazine October 1991; Available at http://www.fda.gov/bbs/topics/ consumer/CON00112.html (Accessed on 11/21/2008).
78. Definition of a Combination Product: "Title 21: Food and Drugs". 21 CFR Food and Drugs CHAPTER I Food and Drug Administration, Department of Health and Human Services Subchapter A- General Part 3-Product Jurisdiction. 2005; Available at http://www.fda.gov/oc/ ombudsman/ part3&5.htm#21:1.0.1.1.3.1.31.2 (Accessed on 11/21/2008).
79. Brannon-Peppas Lisa: "Polymers in Controlled Drug Delivery". Medical Plastics and Biomaterials Magazine [Online]. 1987; Available at http://www. devicelink.com/ mpb/archive/97/11/003.html (Accessed on 10/31/2008).
80. Langer Robert.: "Transdermal Drug Delivery: past progress, current status, and future prospects" Advanced Drug Delivery Reviews. 2004; Issue: 56 Page(s): 557-558.
81. Samad, Ullah A, Alam Z, Wais M I, Shams M, Mohammad S. Transdermal Drug Delivery System: Patents Reviews. Recent Pat Drug Deliv & formul 2009; 3(2):143-52.

How to cite this article:
Verma G: Transdermal drug delivery system, advance development and evaluation-a review. Int J Pharm Sci Res 2017; 8(2): 385-00.doi: 10.13040/IJPSR.0975-8232.8(2).385-00.