Transdermal Patch: An Overview

Keywords: Transdermal drug delivery systems, structure of skin, skin permeation,

ABSTRACT

Now a day about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system has emerged. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. Transdermal drug delivery systems (TDDS) are dosage forms that involve drug transport to viable epidermal and dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. Several important advantages of transdermal drug delivery are the limitation of hepatic first-pass metabolism, enhancement of therapeutic efficiency and maintenance of a steady plasma level of the drug. This review article provides an overview of TDDS, its advantages over conventional dosage forms, drug delivery routes across human skin, permeation enhancers, and various components of the transdermal products. Transdermal patches are pharmaceutical preparation of varying sizes, containing, one or more active ingredients, intended to be applied to the unbroken skin to deliver the active ingredient to the systemic circulation after passing through the skin barriers, and it avoid first-pass effect.
INTRODUCTION

Transversal drug delivery is defined as dosage form which when applied to the intact skin it delivers the drug through the skin at a controlled rate to the systemic circulation. Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. The occurrence of systemic side-effects with some of these formulations is indicative of absorption through the skin. Several drugs have been applied to the skin for systemic treatment. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Moreover, it overcomes various side effects like painful delivery of the drugs and the first-pass metabolism of the drug occurred by other means of drug delivery systems. So, this transdermal drug delivery system has been a great field of interest in recent times. Many drugs that can be injected directly into the bloodstream via skin have been formulated. The main advantages of this system are that there is a controlled release of the drug and the medication is painless. The drug is mainly delivered to the skin with the help of a transdermal patch that adheres to the skin. A transdermal patch has several components including liners, adherents, drug reservoirs, drug release membranes which play a vital role in the release of the drug via the skin. Various types of patches along with various methods of applications have been discovered to deliver the drug from the transdermal patch. Because of its great advantages, it has become one of the high research fields among the various drug delivery system. Here, a general view over the transdermal patch has been discussed along with its advantages, disadvantages, methods of applying, care taken while applying, types and applications of the transdermal patch and recent advances and marketed products.

Advantages

The advantages of delivering drugs through the skin include the administration of therapeutic agents offers more. Hepatic first-pass metabolism, salivary metabolism, and intestinal metabolism are avoided.

2. The ease of usage makes it possible for patients to self-administer these systems. They can easily apply on the body surface.
3. In case of an emergency, removing the patch at any point of time during therapy can instantly stop drug input.

4. Since the composition of skin structurally and biologically is the same in almost all humans.

5. Drugs showing gastrointestinal irritation and absorption can be suitably administered through the skin.

6. The continuous, non-invasive infusion can be achieved for drugs with short biological half-lives, which would otherwise require frequent dosing.

7. Due to the reduced frequency of dosing, there is better patient compliance.

8. Therapeutic failures associated with irregularities in the dosing with conventional therapies can be avoided.

9. The adverse effects are minimized due to the steady and optimum blood concentration-time profile.

10. The risks, pain, and inconvenience associated with parenteral therapy are evaded.

11. The release is more prolonged than oral sustained drug delivery systems.

12. At times the maintenance of the drug concentration within the bio-phase is not desired; therefore transdermal systems are suitable in this case.

13. The daily dose of the drug required is lower than that with conventional therapies.

14. The drug release is such that there is a predictable and extended duration of the activity.

Disadvantages:

1. There is a possibility of skin irritation due to one or many of the formulation components.

2. Binding of the drug to the skin may result in dose dumping.

3. It can be used only for chronic conditions where drug therapy is desired for a long period including hypertension, angina, and diabetes.
4. Lag time is variable and can vary from several hours to days for different drug candidates.

5. Cutaneous metabolism will affect the therapeutic performance of the system.

6. Transdermal therapy is feasible for certain potent drugs only.

7. Transdermal therapy is not feasible for ionic drugs.

8. It cannot deliver the drug in a pulsatile fashion.

Figure No. 1: Structure of skin

**Structure of skin:** The skin can be considered to have four distinct layers of tissues including non-viable epidermis (stratum corneum), viable epidermis, viable dermis and (subcutaneous administration)connective tissue here is minimal inter and intrapatient variation. The epidermis is relatively thin, tough, outer layer of the skin. The epidermis has keratinocytes. They originate from cells in the deepest layer of the epidermis called the basal layer. New keratinocytes slowly migrate up to wart the outermost portion of the epidermis, relatively waterproof and, when undamaged, prevents most bacteria, viruses, and other foreign substances from entering the body. The epidermis also protects the internal organs, muscles, nerves, and blood vessels against trauma. The outer keratin layer of the
The epidermis (stratum corneum) is much thicker. The viable Epidermis layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50-100 μm. The structure of the cells in the viable epidermis is physicochemically similar to other living tissues. Cells are held together by tonofibrils the water content is about 90%. The dermis, the skin’s next layer, is a thick layer of fibrous and elastic tissue (made mostly of collagen, elastin, and fibrillin) that gives the skin its flexibility and strength.

The dermis contains nerve endings, sweat glands, and oil glands, hair follicles, and blood vessels. The subcutaneous tissue also known as hypodermis is not accepted as a true part of the structured connective tissue. It is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels. Most investigators consider the drug permeating through the skin enter the circulatory system before reaching the hypodermis where the fatty tissue serves as a depot of the drug (Barry 1983; Alexander et al., 2012).

**Pathways of Skin Permeation:** Drug molecules permeate through skin surface by the different potential pathways including through the sweat ducts, through the hair follicles and sebaceous glands or directly across the stratum corneum (Flaynn et al., 1985; Kasting et al., 1992; Potts and Guy 1992). Since the last few years, there is a point of debate among scientists for the relative importance of the shunt or appendageal route of transport across the stratum corneum and is further complicated by the lack of a suitable experimental model to permit separation of these pathways (Scheuplein et al., 1969; Scheuplein and Bank 1971).

A recent review by Menon (2002) provides a valuable resource. *In-vitro* experiments tend to involve the use of hydrated skin or epidermal membranes and the lipid phase behavior is different from that of other biological membranes (Scheuplein 1967). The stratum corneum consists of 10 to 15 layers of corneocytes (Anderson and Cassidy 1973; Holbrook and Odland 1974; Bouwstra et al., 1991).

**FACTORS THAT INFLUENCE TRANSDERMAL DRUG DELIVERY:**

Biological factors include

1. Skin condition
2. Skin age
3. Blood flow
4. Regional skin sites

5. Skin metabolism

6. Species differences

Physiological factors include:

1. Skin hydration

2. Temperature and pH

3. Diffusion coefficient

4. Drug concentration

5. Partition coefficient

6. Molecular size and shape

BASIC COMPONENTS OF TDDS:

1. The drug

2. Polymer matrix

3. Permeation enhancers

4. Adhesive

5. Backing layer.

**DRUG**

The drug is in direct contact with the release liner. Ex: Nicotine, Methotrexate, and Oestrogen. Some of the desirable properties of a drug for transdermal delivery: 1. The drug molecule should possess an adequate solubility in oil and water. 2. The drug should have a molecular weight of less than approximately 1000 daltons. 3. The drug should have a low melting point. 4. The drug molecule would require a balanced partition coefficient to penetrate the stratum corneum. 2. POLYMER MATRIX These polymers control the release of the drug from the drug reservoir. Natural polymers: shellac, gelatin, waxes, gums, starch,
etc., Synthetic polymers: polyvinyl alcohol, polyamide, polyethylene, polypropylene, Polyurea, polymethylmethacrylate, etc. 3. PERMEATION ENHANCERS: Substances exist which temporarily diminish the impermeability of the skin are known as accelerants or sorption promoters or penetration enhancers. These include water, pyrolidones, fatty acids and alcohols, azone and its derivatives, alcohols, and glycols, essential oils, terpenes and derivatives, sulfoxides like dimethyl sulfoximide and their derivatives, urea and surfactants. Surfactants are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant alter penetration is a function of the polar head group and the hydrocarbon chain length. Anionic surfactants: sodium lauryl sulfate.

Nonionic surfactants: Pluronic F 127, Pluronic F68, etc., Enhancer actions can be classified by lipid-protein partitioning concept. This hypothesis suggests that enhancers act by one or more ways selected from three main possibilities. The enhancer interacts with the organized intracellular lipid structure of the stratum corneum to disrupt it and make it more permeable to drug molecules. Very many enhancers operate in this way. Some solvents act by extracting the lipid Components and thus make the horny layer more permeable. Protein modification Ionic surface active molecules, in particular, tend to interact well with the keratin in the corneocytes, to open up the dense keratin structure and make it more permeable. The intracellular route is not usually prominent in drug permeation, although drastic reductions to this route's resistance could open up an alternative path for drug penetration. Partitioning promotion many solvents can enter the stratum corneum, change its solvent properties.

TRANSDERMAL PATCH

A transdermal patch or skin patch is a medicated adhesive applied on the skin surface of the epidermis. Stratum corneum. A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream (Figure 1). Often; this promotes healing to an injured area of the body. The first commercially available prescription patch was approved by the U.S. Food and Drug
Administration. Polymer selection and design must be considered when striving to meet the diverse criteria for the fabrication of effective transdermal delivery systems. The main challenge is in the design of a polymer matrix, followed by optimization of the drug-loaded matrix not only in terms of release properties but also concerning its adhesion cohesion balance, physicochemical properties, compatibility and stability with other components of the system as well as with skin. The polymers utilized for TDDS can be classified as (1) natural polymers include cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc, (2)synthetic elastomers includes polybutadiene, hydration rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butyl rubber, etc, (3) synthetic polymers include polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinyl pyrrolidone, polymethylmethacrylate, etc. The polymers like cross linked polyethylene glycol, eudragits, ethylcellulose, polyvinyl pyrrolidone, and hydroxyl propyl methylcellulose.

The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in.

COMPONENTS OF TRANSDERMAL PATHCHES.

(I) Polymer Matrix1

Transdermal patches.

(a) Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.

(b) The polymer should be stable.

(c) The polymer should be nontoxic.

(d) The polymer should be easy of manufactured.

(e) The polymer should be inexpensive.

(f) The polymer and its degradation product must be nontoxic or non-antagonistic to the host.

(g) Large amounts of the active agent are incorporated into it.
Types of polymer

(a) Natural polymers

Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.

(b) Synthetic Elastomers

Hydration rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.

(b) Synthetic polymers

Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamide, polyurea, epoxy.

IV) Other Excipients

(a) Adhesives

The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device. Adhesive attach to body parts.

i) It should not be irritant and compatible to body parts.

ii) It should be easily removed.

iii) It should not leave a unwashable residue on the skin.

iv) It should have excellent contact with the skin.

vi) Permeation of drugs should not effect.

(V) Linear

Protect the patch during storage. The linear is Physical & chemical compatibility with the drug and body parts removed before use.

It prevents the loss of drug which migrated into the adhesive layer during storage.

It also prevents contamination.
(VI) Backing

The primary function of the backing membrane is to provide supports. It protect the patch from the outer environment.

Hypermethylcellulose are used as matrix formers for TDDS. Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membranes.

Drug

The most important criteria for TDDS are that the drug should possess the right physicochemical and pharmacokinetic properties. Transdermal patches offer much to drugs which undergo extensive first-pass metabolism, drugs with narrow therapeutic window, or drugs with short half-life which causes non-compliance due to frequent dosing. For example, drugs like rivastigmine for Alzheimer's and Parkinson's dementia, rotigotine for Parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS.

3. Permeation enhancers

To increase the permeability of stratum corneum to attain higher therapeutic levels of the drug permeation enhancers interact with structural components of stratum corneum i.e., proteins or lipids. The enhancement in the absorption of oil soluble drugs is apparently due to the partial leaching of the epidermal lipids by the chemical enhancers, resulting in the improvement of the skin conditions for wetting and for trans-epidermal and trans-follicular permeation. The miscibility and solution properties of the enhancers used could be responsible for the enhanced transdermal permeation of water soluble drugs. Pharmaceutical. The scientists have made great efforts in transdermal permeation studies using various
enhancers (Table 1) for several drug moieties (Parivesh et al., 2010). The permeation of drugs across the skin may also be enhanced by physical means including iontophoresis, electroporation, application of ultrasound (sonophoresis), and use of microscopic projection. Iontophoresis passes a few milli amperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Mainly used for pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test. Iontophoretic delivery of lidocaine appears to be a potential approach for the rapid onset of anesthesia (Schultz et al., 2002).

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the skin for the diffusion of drugs is increased by 4 or stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum (Neumann et al., 1982; Sugar and Neumann 1984). Application of ultrasound, particularly low-frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis. Ogura et al., (2008) reported on the use of low-frequency sonophoresis for topical delivery of EMLA cream. Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 μm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the permeation or pain. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in the development of cutaneous vaccines for tetanus and influenza. Various other methods are also used for the application of the transversal patches like thermal poration, magnetophoresis, and photomechanical waves. However, these methods are in their early stages of development and require further detailed studies.

Compounds that promote the penetration of topically applied drugs are commonly referred to as absorption promoters, accelerants, penetration enhancers. Penetration enhancers are incorporated into a formulation to improve the diffusivity and solubility of drugs through the skin that would reversibly reduce the barrier resistance of the skin. Thus allow the drug to penetrate to the viable tissues and enter the systemic circulation. Desired properties for penetration enhancers: i. It should be non-irritant, non-sensitizing, nonphototoxic, and non-
comedogenic. ii. The onset of action should be rapid and the duration of activity should be predictable and reproducible. iii. Have no pharmacological activity in the body i.e. should not bind to the receptor site. iv. Upon removal of the enhancer, the upper layer should immediately and fully recover its normal barrier property. v. The barrier function of the skin should reduce in one direction only. Endogenous material should not be lost to the environment by diffusion out of the skin. vi. The accelerants should be chemically and physically compatible with all drugs and adjuvants to be formulated in topical preparations and devices. vii. It should be inexpensive, tasteless and colorless, viii. It should readily be formulated into dermatological preparations. ix. It should have a desired solubility parameter that approximates that of the skin. x. It should adhere and spread well on the skin with a suitable skin feel. Some of the examples of the widely used classical enhancers involve various classes that include water, hydrocarbons alcohols, acids amines, amides, esters, surfactant terpenes, terpenoids and essential oil, sulfoxides, lipids and miscellaneous such as cyclodextrin derivatives, chitosan, etc.

Table No. 1: Permeation enhancer

<table>
<thead>
<tr>
<th>Classes</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acid</td>
<td>Oleic acid, undecanoic acid.</td>
</tr>
<tr>
<td>Fatty alcohol</td>
<td>Octanol, ethanol.</td>
</tr>
<tr>
<td>Terpin</td>
<td>Menthol, thymol.</td>
</tr>
<tr>
<td>Sulfoxide</td>
<td>Dimethyl sulfoxide.</td>
</tr>
<tr>
<td>Unionic surfactant</td>
<td>Sodium lauryl sulfate.</td>
</tr>
<tr>
<td>Non-ionic surfactant</td>
<td>Polysorbate.</td>
</tr>
<tr>
<td>Amides</td>
<td>N, N-Dimethyl m-tolbutamide.</td>
</tr>
</tbody>
</table>

Other excipients: Plasticizers: Plasticizers have also been used in many formulations ranging from 5 to 20% (w/w, dry basis). Along with the brittleness and ductility of the film, it is also responsible for adhesiveness of the film with other surfaces or membranes and improvement in the strength of the film. Some of its examples are glycerol or sorbitol, at 15%,w/w, dry basis, phosphate, phthalate esters, fatty acid esters and glycol derivatives such as PEG 200, and PEG 400. Solvents: Various solvents such as methanol, chloroform, acetone, isopropanol, and dichloromethane, etc. are used to prepare a drug reservoir.
Pressure sensitive adhesive (PSA)

A PSA maintains intimate contact between the patch and the skin surface. It should adhere to not more than applied finger pressure, be aggressively and permanently tacky, and exert a strong holding force. These include polyacrylates, polyisobutylene, and silicon based adhesives. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. PSA should be physicochemically and biologically compatible and should not alter drug release. The PSA can be positioned on the face of the device (as in the reservoir system) or in the back of the device and extending peripherally (as in the case of matrix system).

![Figure No. 2: Pressure sensitive adhesive](image)

Types of Transdermal Patches

There are four types of transdermal patches:

(I) **Single-layer drug in–adhesive**

The adhesive layer of this system also contains the drug. In this type of patches, the adhesive layer not only serves to adhere to the various layer together, along with the entire system to the skin but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner.
Figure No. 3: Single–layer drug in–adhesive

(II) The multi-layer drug in adhesive

The multi-layer drug in the adhesive is similar to the single-payer system in that both adhesive layers is also responsible for the releasing of the drug. But it is different however that it adds another layer of a drug in – adhesive, usually separated by a membrane. This patch also has a temporary liner – layer and a permanent backing.

Figure No. 4: The multi-layer drug in adhesive

5. Backing laminate

The primary function of the backing laminate is to provide support. The backing layer should be chemically resistant and excipients compatible because the prolonged contact between the backing layer and the excipients may cause the additives to leach out or may lead to diffusion of excipients, drug or permeation enhancer through the layer. They should have a low moisture vapor transmission rate. They must have optimal elasticity, flexibility, and tensile strength. Examples of some backing materials are aluminum vapor coated layer, plastic film (polyethylene, polyvinyl chloride, polyester) and heat seal layers are believed to form tréester foil and metalized laminate. Backing laminate: While design the backing layer following points must be in consideration: Must be flexible. → Having low water vapor transmission
rate so as to promote skin hydration and thus greater skin permeability of drug should be compatible with transdermal system as remain in use while applying. Should be chemical resistance. Having good tensile strength. Nonirritant Examples of backings laminate are polyethylene film, polyester film, and polyolefin film, and aluminum vapor coated layer.

7. Other excipients

Various solvents such as chloroform, methanol, acetone, isopropanol, and dichloromethane are used to prepare a drug reservoir. Also, plasticizers such as dibutyl phthalate, triethyl citrate, polyethylene glycol and propylene glycol are added to provide plasticity to the triethyl citrate, polyethylene glycol and propylene glycol are added to provide plasticity to transient aqueous pores in the capillary network. The various steps involved in the transport of drug from patch to systemic circulation are as follows:

1. Diffusion of a drug from a drug reservoir to the rate-controlling membrane.

2. Diffusion of a drug from rate-limiting membrane to stratum corneum.

3. Sorption by stratum corneum and permeation through the viable epidermis.

4. Uptake of a drug by the capillary network in the dermal papillary layer.

Release liner

During storage, release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than a part of the dosage form for delivering the drug. The release liner is composed of a base layer which may be non-occlusive (paper fabric) or occlusive (polyethylene and polyvinyl chloride) and a release coating layer made up of silicon or Teflon. Other materials used for TDDS release liner include polyester foil and metalized laminate.

The patch is covered by a protective liner during storage until it is used. The release liner removed and discarded just before the application of patch over the skin since release liner is in intimate contact with the transdermal system hence it should be physically as well as chemically inert. The 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 as release liner in transdermal patches include polyester foil.

Polymers used in the transdermal system in a versatile manner such as Rate controlling membrane: It controls the release of drug by dispersing through an inert polymer matrix. The polymer powder blended with drug moiety by the physical manner and then molded into the desired shape with the required thickness and surface area. Adhesive: make intimate contact between the skin and transdermal system. It carries the drug which is dissolved or dispersed in solution or suspension form. The quality of drugs diffused into the skin depending on the holding power. Pressure sensitive adhesive:

Hitherto the rapidity of transdermal system can be done by pressure sensitive adhesive.

Table No. 2: Components of TDDS

<table>
<thead>
<tr>
<th>polymer</th>
<th>category</th>
<th>role</th>
</tr>
</thead>
<tbody>
<tr>
<td>gelatin</td>
<td>Natural polymer</td>
<td>base</td>
</tr>
<tr>
<td>Na-alginate</td>
<td>base</td>
<td></td>
</tr>
<tr>
<td>Gum arabic</td>
<td>Natural polymer</td>
<td></td>
</tr>
<tr>
<td>Tragacanth</td>
<td>Natural polymer</td>
<td>base</td>
</tr>
<tr>
<td>carmellose</td>
<td>Semisynthetic polymer</td>
<td>base</td>
</tr>
<tr>
<td>Polyhydroxymethacrylate(PHMA)liner</td>
<td>Semi synthetic polymer</td>
<td>Base with adhesive polymer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liner backing membrane</td>
</tr>
</tbody>
</table>

Single layer drug in adhesive

In this type, the adhesive layer contains the drug. The adhesive layer not only serves to adhere to the various layers together and also responsible for releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

a) Multi -layer drug in adhesive

This type is also similar to the single-layer but it contains an immediate drug-release-layer and another layer will be a controlled release along with the adhesive layer. The adhesive
layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

b) Vapour patch

The patch containing the adhesive layer not only serves to adhere to the various surfaces together but also serves as to release the vapor. The vapor patches are new to the market, commonly used for releasing the essential oils in decongestion. Various other types of vapor patches are also available in the market which is used to improve the quality of sleep and reduces cigarette smoking conditions.

c) Reservoir system

In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate-controlling membrane which can be microporous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic on target organ organ.

d) Matrix system

i. Drug-in-adhesive system

This type of patch is formulated by mixing the drug with an adhesive polymer to form a drug reservoir. It then followed by spreading on an impervious backing layer by solvent casting or melting method. The top of the reservoir is protected by an unmediated adhesive polymer layer. It may further be categorized into single-layer and multi-layer drug-in-adhesive. The System is considered to be compatible with a wide variety of drugs. Moreover, the system is Competent to deliver more than one drug in a single patch. It offers advantages in reduced Size and thickness and improved conformability to the application site, helping drive patient Preference.

ii. Matrix-dispersion system

The drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. It is then altered into a medicated disc with definite shape and thickness. This drug containing Polymer
disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug.

e) Micro reservoir system

The system consists of microscopic spheres of drug-reservoirs that release a drug at a zero-order rate for maintaining constant drug levels. The micro-reservoir system is a combination of Reservoir and matrix-dispersion system. The aqueous solution of water-soluble polymer is Mixed with the drug to form a reservoir. It is then followed by dispersing the solution homogeneously using high shear mechanical force in a lipophilic polymer to form thousands of microscopic drug reservoirs. Cross-linking agents are added to stabilize the Thermodynamically unstable dispersion by in-situ cross-linking the polymer. Reservoir, it is spread.

**Various methods for the preparation of TDDS**

1. **Circular Teflon mold method** (Baker and Heller 1989)

Solutions containing polymers in various ratios are used in an organic solvent. Calculated Amount of drug is dissolved in half the quantity of the same organic solvent. Enhancers in with the circudifferent concentrations are dissolved in the other half of the organic solvent and then added. Plasticizer (e.g., Di-N-butylphthalate) is added into the drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular Teflon mold. The molds are to be placed on a leveled surface and covered with an inverted funnel to control solvent Vaporization in a laminar flow hood model with an airspeed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. The dried films are to be stored for another 24 h at 25±0.5°C in a desiccator containing silica gel before evaluation to eliminate aging effects. These types of films are to be evaluated within one week of their preparation. Alanazi et al., (2007) have studied bioadhesive film containing ketorolac. Films were cast from organic and aqueous solvents using various bioadhesive polymers namely: sodium carboxy methylcellulose (Na-CMC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) and Carbopol 934. The prepared films were subjected to investigations for their physical and mechanical properties, swelling behaviors, in-vitro adhesion, drug permeation via bovine buccal mucosa and in-vitro drug release. These properties were found to vary significantly depending on the preparation methods, the type of the polymers and the ratio of the addition of both plasticizer (i.e. polyethylene glycol) and film-forming agent.
(ethylcellulose and polyvinylpyrrolidone). The obtained results indicated that the concentration of ketorolac in the oral cavity was maintained above 4.0 μg/mL for a period of at least 6 h. This film showed promising results for using the ketorolac buccoadhesive route of administration.

2. Asymmetric TPX membrane method (Berner and John 1994)

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. The drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive. These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and non solvent 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 the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in a coagulation bath (maintained the temperature at 25°C). After 10 minutes of immersion, the membrane can be removed, air dried in a circulation oven at 50°C for 12 h. Wang et al., (1998) have studied that asymmetric poly(4-methyl-1-pentene) (TPX) membranes, fabricated by the dry/wet inversion method, were applied to transdermal delivery of nitroglycerin (NTG), a drug for treating angina pectoris. The flux of NTG through the TPX membrane was measured in-vitro by a Franz cell. The results indicated that the NTG flux through asymmetric TPX membranes is strongly dependent on the membrane structure, which can be varied by adding non-solvents in the casting solution. By adding different kinds of non-solvents and adjusting the added amounts, membranes with different NTG-release rates can be fabricated. It was also found that, with suitable drug formula, the NTG dissolution rate of a prototype TPX patch is comparable to that of a commercial patch, Transderm-Nitro.

3. Mercury substrate method

The drug is dissolved in polymer solution along with plasticizer. It is followed by stirring for 10-15 minutes to produce a homogenous dispersion and poured into a leveled mercury surface, covered with the inverted funnel to control solvent evaporation (Wiechers 1992). Rathore et al., (2006) have studied that transdermal matrix type patches of terbutaline sulfate were fabricated using ethylcellulose and cellulose acetate polymer. The transversal

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patches of terbutaline sulfate were prepared by the solvent casting technique employing a mercury substrate. In the present investigation various polymeric transdermal patches of terbutaline sulfate was prepared. The effect of permeability enhancer on the permeability of drugs from cellulose acetate and ethylcellulose patches was studied. The polymeric combinations showed good film forming properties and the method of casting on mercury substrate was found to give good films. Patel et al., (2009) have studied transdermal patches containing glibenclamide (1.06 % w/v, i.e. 13.5 mg/cm2) were prepared by solvent casting technique employing mercury as substrate to formulate transdermal patches using Eudragit RL 100, Eudragit RS 100, Polyvinyl pyrollidone (PVP) as polymers, glycerol and propylene glycol as a plasticizers and Span 80 as a permeation enhancer by solvent casting method. The formulation containing Eudragit RL 100 with propylene glycol as plasticizer showed complete and prolonged release with 98.02 % at the end of 24 h.

4. “IPM membranes” method

The drug is dispersed in a mixture of water and propylene glycol containing carbomer-940 polymers and stirred for 12 h in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of tri-ethanolamine. Buffer (pH 7.4) can be used to obtain solution incorporated in the IPM (isopropyl myristate) membrane (Tang et al., 2010). Xi et al., (2010) have studied the drug-in-adhesive transdermal patch and evaluated for the site-specific delivery of anastrozole. Different adhesive matrixes, permeation enhancers and amounts of anastrozole were investigated for promoting the passage of anastrozole through the skin of rat-in-vitro. The best skin permeation profile (in-vitro) was obtained with the formulation containing DURO-TAK® 87-4098 (pressure sensitive adhesive), IPM 8% and anastrozole 8%. For local tissue disposition studies, the anastrozole patch was applied to mouse abdominal skin, and blood, skin, and muscle samples were taken at different times after removing the residual adhesive from the skin. High accumulation of the drug in the skin and muscle tissue beneath the patch application site was observed in mice and compared with that after oral administration. These findings showed that anastrozole transdermal patches were an appropriate delivery system for application to the breast tumor region for site-specific drug delivery to obtain a high local drug concentration.
5. “EVAC membranes” method

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. The 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 a 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. Friend et al., (1991) have studied the irritation of transdermal devices delivering levonorgestrel and the permeation enhancer ethyl acetate with or without ethanol was evaluated in rabbits. Erythema and edema were assessed 24, 48 and 72 h and 7 days after application of the 24-h delivery system. The devices were found to be mild to moderately irritating, with erythema the primary manifestation. No differences were observed between devices using pure ethyl acetate or ethyl acetate-ethanol (7:3 v/v) as enhancers. Devices using pure ethanol as an enhancer gave levels of irritation similar to those using ethyl acetate ethanolor pure ethyl acetate.

Aluminum backed adhesive film method

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than the preparation of same, chloroform is the choice of solvent because most of the drugs as well an adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom-made aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks. Shamset al., (2010) developed medicated films (containing Losartan Potassium - LP) using the polymers, Eudragit E 100 (EE 100) and polyvinyl pyrrolidone VA 64 (PVP VA 64), were prepared in a film casting assembly with aluminum foil. It was planned to design the system in such a way that it provides the delivery of LP at a controlled rate across intact skin to achieve the anti-hypertensive effect for a longer period. The films were evaluated for physical properties, in-vitro drug release studies, in-vitro skin permeation studies, and pharmacodynamic studies. The physical parameters were found to be very satisfied with high drug content (>99%). The pharmacodynamic studies were carried out using a tail-cuff method in Wistar albino rats. Hypertension was induced by methyl prednisolone acetate subcutaneously for 2 weeks. The developed matrix patch was found to decrease the blood
pressure significantly (P < 0.001) in the proximity of the normal value and it was maintained for 24 h. Jeans and Heard (1999) have investigated the permeation of primaquine across full thickness excised human skin from two acrylate transdermal adhesives. Primaquine base was formulated with National Starch 387-2516 and 387-2287 to provide aluminum foil-backed 1-cm diameter patches, each loaded with 10 mg drug. The patches were applied to cadaver skin in Franz-type diffusion cells and the permeation of primaquine determined. 10 mg. Aluminum preparation of the same, chloroform is the 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 custom-made aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks. Shams et al., (2010) developed medicated films (containing Losartan Potassium - LP) using the polymers, Eudragit E 100 (EE 100) and polyvinyl pyrrolidone VA 64 (PVP VA 64), were prepared in a film casting assembly with aluminum foil. It was planned to design the system in such a way that it provides the delivery of LP at a controlled rate across intact skin to achieve the anti-hypertensive effect for a longer period. The films were evaluated for physical properties, in-vitro drug release studies, in-vitro skin permeation studies, and pharmacodynamic studies. The physical parameters were found to be very satisfied with high drug content (>99%). The pharmacodynamic studies were carried out using a tail-cuff method in Wistar albino rats. Hypertension was induced by methyl prednisolone acetate subcutaneously for 2 weeks. The developed matrix patch was found to decrease the blood pressure significantly (P < 0.001) in the proximity of the normal value and it was maintained for 24 h. Jeans and Heard (1999) have investigated the permeation of primaquine across full thickness excised human skin from two acrylate transdermal adhesives. Primaquine base was formulated with National Starch 387-2516 and 387-2287 to provide aluminum foil-backed 1-cm diameter patches, each loaded with 10 mg drug. The patches were applied to cadaver skin in Franz-type diffusion cells and the permeation of primaquine determined. Adhesive film method freezing temperature until characterization (Deo et al., 1997). Vora et al., (1998) have studied the proniosome based transdermal drug delivery system of levonorgestrel (LN) was developed and extensively characterized both in-vitro and in-vivo. The system was evaluated in-vitro for drug loading, rate of hydration (spontaneity), vesicle size, polydispersity, entrapment efficiency and drug diffusion across rat skin. The effect of the composition of formulation, amount of drug, type of spans, alcohols and sonication time on transversal permeation profile was observed. The stability studies were performed at 4°C and room temperature. The biological assay for progestational activity included endometrial assay and
inhibition with the formation of corpora lutea. The study demonstrated the utility of proniosomal transdermal patch bearing levonorgestrel for effective contraception. Alam et al., (2010) have studied the anti-inflammatory effect of celecoxib incorporated in proniosomes. A low dose of proteasomal gel containing celecoxib was developed for the treatment of osteoarthritis. All the prepared formulations were subjected to physicochemical evaluations and anti-inflammatory studies. The entrapment efficiency was found to be more than 90%. The vesicle shape was determined with the help of transmission electron microscopy. It showed that the vesicles were spherical and discrete with sharp boundaries. The vesicle size, size distribution, and polydispersity studies were performed using a photon correlation size of 449.4 nm. An admirable uniformity in particle size distribution was obtained as indicated by a low polydispersity index (PI < 1). Anti-inflammatory studies were performed using the rat hind-paw edema induced by carrageenan (1% w/v) method. The optimized proniosomal gel on spectro.

8. Free film method

A free film of cellulose acetate is prepared by casting on a mercury surface. A polymer solution (e.g., 2% w/w) is prepared using an organic solvent (e.g., chloroform). The optimized concentration of plasticizer is incorporated into the polymer solution (e.g., 40% w/w of polymer weight). A small volume (e.g., 5 ml) of the polymer solution is poured in a glass ring that 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 the complete evaporation of the solvent. The dried film is separated 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 polymerscropy. Das et al., (2010) studied the transdermal drug delivery system of metformin hydrochloride. It was prepared using combinations of a hydrophobic polymer, ethyl cellulose and a hydrophilic polymer, polyvinyl pyrrolidone in different ratios (e.g., 1:2, 1:4, 1:6, 1:8, 2:1, 4:1, 6:1 and 8:1 w/w) by solvent evaporation technique. Polyvinyl alcohol was used to prepare the backing membrane and dibutyl phthalate as a plasticizer. The prepared polymeric films were characterized by various physicochemical parameters like film thickness, tensile strength, moisture content, moisture uptake, water vapor transmission rate. Permeation studies were carried out for patches through the commercial semi-permeable membrane as well as rat abdominal skin using Keshary-Chien diffusion cell. The optimized
formulation exhibited excellent drug release (e.g., 96.92%) from the patch within 24 h. Alam et al., (2009) developed transdermal patches containing celecoxib for the treatment of osteoarthritis.

Different ratios of ethyl cellulose/polyvinyl pyrrolidone (EC/PVP) were used for the vesicles for development of the system. The release rates and flux increased linearly when an increase in the fraction of PVP was mixed with the formulations. In-vitro studies showed enhanced performance in the presence of an enhancer (5% v/v oleic acid). The cumulative amount of drug permeated was found to be proportional to the square root of time. The optimized formulation produced 100% inhibition of paw edema in rats (anti-inflammatory effect) up to 6 h. The anti-inflammatory effect (in-vivo) was studied by carrageenan-induced (1% w/v) rated from proniosomes.

FACTORS AFFECTING TRANSDERMAL BIOAVAILABILITY:

Two major factors affect the bioavailability of the drug through transdermal routes:

(1) Physiological factors

(2) Formulation factors Physiological factors include:

i. Stratum corneum layer of the skin

ii. The anatomic site of application on the body

iii. Skin condition and disease

iv. Skin metabolism

v. Skin irritation and sensitization

Formulation factors include:

Penetration enhancers use

Vehicles and membrane used

Physical chemistry of transport

Method of application
Approaches used in the development of the transdermal patch

Membrane moderated systems: The system consists of a drug reservoir molded from a drug impermeable metallic plastic laminate and a rate-controlling polymeric membrane. The drug reservoir compartment contains the drug solids that are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium (e.g., silicon fluid). The rate-controlling membrane can be microporous or nonporous polymeric membrane e.g., ethylene-vinyl acetate copolymer on the external surface of the polymeric membrane, a skin layer of drug, compatible hypo-allergic adhesive polymer may be applied to achieve an intimate contact of TDDS with the skin surface. The membrane moderated transdermal systems are available under the various brand names including Transderm-Nitrosystem (once a day provide continuous controlled release of nitroglycerin for the prevention of angina pectoris due to coronary artery disease), Transderm-Scop system (3 days medication for prevention of nausea and vomiting), and Catapres-TTS.

Adhesive diffusion-controlled system: It is the simplest version of the membrane moderated drug delivery systems. In this system, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting onto a flat sheet of drug impermeable metallic plastic backing to form thin drug reservoir layer. On the top of the reservoir layer, layers of the non-medicated rate-controlling adhesive polymer of constant thickness are applied (Figure 3). Drug-in-adhesive patch may be a single layer or multi-layer. The multi-layer system is different from the single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane. Characteristics of the drug in the adhesive patch may account for improved patient compliance due to ease of remembering once-weekly patch application, improved cosmetic acceptance and better adhesion. The system is available under the various brand names including Climara® (designed to release both estradiol and levonorgestrel for the treatment of moderate to severe vasomotor symptoms associated with menopause and postmenopausal osteoporosis), Nicoderm® (for smoking cessation), and Deponit patches (containing glycercyl trinitrate for the prevention of angina attacks).

C. Matrix dispersion system: The drug reservoir is formed by homogeneously dispersing niosomes a dispersion type. In this, the drug reservoir is formed by suspending the drug solids in an aqueous solution of water-soluble polymer followed by dispersing the drug suspension homogeneously in the lipophilic polymer (Figure 5). The dispersion is carried out
by a high shear mechanical force to form unleachable microscopic spheres of the drug reservoir. This dispersion is stabilized immediately by cross-linking the polymer chains which produces a medicated. Foredisc with constant surface area and thickness. The system is available as Nitrodisc®(containing nitroglycerin for the prevention of chest pain (angina) in people with a certain heart condition) in the mark.

Evaluation of Transdermal Patches

The development of controlled release transdermal dosage form is a complex process involving extensive research. Transdermal patches have been developed to improve the clinical efficacy of the drug and to enhance patient compliance by delivering a smaller amount of drug at the drug and to enhance patient compliance.

**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 (Samanta et al., 2003).

**Drug content determination:** It can be determined by completely dissolving a small area (1 cm²) of the polymeric film in a suitable solvent of definite volume. The solvent is selected in which the drug is freely soluble. The selected area is weighed before dissolving in the solvent. The whole content is shaken continuously for 24 h in a shaker incubator followed by sonication and filtration. The drug in solution is assessed by an appropriate analytical method.

**Content uniformity test:** The test is applied as the gold standard to determine chemically the content of active constituent for each unit dose. The test is completed by performing an assay to find out the content of drug material contained in polymeric film of the patch. According to USP, the procedure consists of two stages. The first stage consists of assaying random lympiance by deselected ten units. It is followed by the second stage to be performed on twenty more units when the first stage fails. Initially, ten patches are selected and content is determined for individual patches. The test passes when all 10 unit doses have content ≥ 85 % and ≤ 115 % (RSD < 6%). 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 RSD of all
the 30 units is < 7.8%, not more than one value is outside 85–115% and no value is outside 75–125%, the batch passes the test if not fails the test.

**Moisture content:** The prepared films are weighed individually and kept in a desiccators veering smaller amount containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight.

**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 a saturated solution of potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below. **Flatness:** A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with a flatness study. For flatness determination, one strip is cut from the center 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.

**Adhesive studies:**

**Shear adhesion test:** The cohesive strength of an adhesive polymer is determined by this test. The value of strength can be affected by the degree of cross-linking, the molecular weight, the composition of the polymer and the number of tackifiers added. An adhesive coated patch is stacked on the plate made of stainless steel and specified weight hung from the patch parallel to this plat. The time taken to pull off the patch from the plate determines the cohesive strength. The more time taken, the greater is the shear strength.

![Shear strength test](image)

**Figure No. 5: Shear strength test**
Peel tack or quick stick test

**Peel tack or quick stick test:** the bond between The peel force is the force required to break the adhesive and the test substrate. The patch is pulled away from the substrate at 90° with speed 12 inches/minute. The value of force is Expressed in grams/inch or ounces/inch.

![Figure No. 6: Peel tack or quick stick test](image)

**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 breaks. The number of times the films could be folded at the same place without breaking gives the folding Endurance value.

**Rolling ball tack test:** This test involves the measurement of distance traveled by stainless steel along the upward face of adhesive. The diameter of the ball is 7/16 inches and it released on inclined track having angle 22.5°. More the distance traveled, less the tacky polymer. Distance traveled by ball is measured in inches which determine the tackiness of polymer.

![Figure No. 7: Rolling Ball Tack Test](image)
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 gives the folding endurance value.

Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately. ‘F’ is the force required to break; ‘a’ is the width of the film; ‘b’ is the thickness of the film; ‘L’ is length of Film; ‘l' is elongation of film at breakpoint.

In another study, the tensile strength of the film was determined with the help of a texture analyzer.

The force and elongation were measured when the films broke.

Water vapor transmission studies (WVT): WVT is determined by taking one gram chloride in previously dried empty vials having equal diameters. The polymer films are pasted over the brim with the help of adhesives like silicon adhesive grease and then allowed to set for 5 minutes. The vials are accurately weighed and placed in the humidity chamber maintained at 68 % RH. The vials are then weighed repeatedly up to seven consecutive days and an increase in weight was considered as a quantitative measure of Moisture transmitted through the patch.

In other reported methods, desiccators are used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution are placed. The desiccators are tightly closed and humidity inside the desiccators is measured by using a hygrometer. The vials are then weighed before and after placing in the desiccators and procedure is repeated by determining water vapor transmission.

Microscopic studies: Distribution of drug and polymer in the film can be studied using a Scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double sided adhesive tape. The sections are then coated with gold palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under the scanning electron microscope.
Adhesive studies:

**Peel Adhesion properties:** It is the force required to remove the adhesive coating from the test percent constriction drug at a substrate. It is tested by measuring the force required to pull a single coated tape, applied to the substrate at a 180° angle. The test is passed if there is no residue on the substrate. Minghetti et al., (2003) performed the test with a tensile testing machine Acquati model AG/MC 1(Aquati, Arese, Italy).

**Tack properties:** The polymer can adhere to the substrate with little contact pressure. Tack is dependent on the molecular weight and composition of the polymer as well as on the use of tackifying resins in the polymer (Gutschke et al., 2010; Satas 2002; Horstmann et al.,1999). It includes thumb tack test, rolling ball test, quick stick (Peel tack) test, and probe tack test. Thumb tack test is performed by touching the surface of a pressure sensitive adhesive with the thumb and feeling the force required to break the bond. Thus the force required to remove the thumb from adhesive is a measure of tack. Rolling ball test involves measurement of the distance that stainless steel ball travels along with an upward facing adhesive. The less tacky the adhesive, the further the ball will travel. Tack is the ability of the polymer to adhere to a substrate with little finger pressure It’s important in transdermal systems that are applied with little figure pressure. Tack is dependent on molecular weight as well as the composition of polymer and tackifying resins used in the polymer.

**Tests for tack include:**

**Thumbtack test:** This is a subjective test in which evaluation is done by pressing the thumb into the adhesive. Experience is required for using the test. Distance traveled by stainless steel along the upward face.

**Probe tack test:** In this, the tip of the probe with defined surface roughness brought in to contact with the adhesive and when the bond is formed between the adhesive a probe, removal of a probe at a fixed rate away from the adhesive which breaks the bond. The force required to break the bonds recorded as a tack and it is expressed in grams.

**Skin irritancy studies:**

The skin irritancy can be performed transdermal system can be evaluated by a modified Draize test. The dorsal surface of the given test animal is to be cleaned and remove the hair.
from the clean surface then applied rectified sprit. Applied the transdermal formulation over the clean surface for 24 hours. After this period, remove the formulation and observed the status of the skin. The score is given from 0 to 4 depending the degree of erythema as follows: zero-point given for no erythema, 1 point for slight on healthy rabbits / mice albino / rats and potential of erythema-(barely perceptible-light pink), 2 point for moderate erythema (dark pink), 3 points for moderate to severe erythema (dark pink) and 4 points for severe erythema (extreme redness).

Confocal laser scanning microscopy (clsm):  

The depth of skin penetration of a patch can be assessed using CLSM. The transdermal formulation is applied non-occlusive for 8 hours to the dorsal skin. The mice are sacrificed by heart puncture, dorsal skin is excised and washed with distilled water. The excised skin is then placed on aluminum foil and the dermal side of the skin is generally teased off any adhering fat and/ or subcutaneous tissue. These are then cut into pieces of 1mm2 and tested for probe penetration. The full skin thickness is optically scanned at different increments through the z-axis of a CLS microscope.

Stability studies: The stability of the active component is a major criterion in determining acceptance or rejection of the transdermal system. The stability studies were performed according to ICH guidelines at different temperatures and relative humidity 25-30oC (60% relative humidity) and 45-50oC (75% relative humidity) over 60 days. The sample was withdrawn at 0,3,6, and 9 weeks respectively and was analyzed for their physical appearance, drug content and in-vitro diffusion studies.

Paddle over disc apparatus (USP apparatus 5): this apparatus is quite similar to paddle apparatus (USP apparatus II) except that the patches were stuck on a disc or holder placed at the bottom of the apparatus and temperature of the medium maintained at 0oC.

Cylindrical apparatus (USP apparatus 6): This apparatus also used for the evaluation of transdermal formulations and it is identical to the rotating apparatus (USP apparatus 1). In this apparatus, stainless steel is used to hold the sample. The sample is placed on an inert porous cellulose material and adhered to the cylinder.

Reciprocating disc: In this apparatus, the sample are placed on disc-shaped holders using inert porous cellulosic support which reciprocating vertically using drive inside a glass
container containing dissolution medium. The test is performed at 32°C and reciprocating frequency maintained at 30 cycles/min. The samples were withdrawn at the appropriate interval of time and an equal amount of buffer is replaced by the buffer. The samples were diluted suitably and absorbance determined spectrophotometrically.

**In-vitro skin permeation and release kinetics studies:**

The design and development of the transdermal patch are greatly influenced by in vitro studies. In-vitro studies greatly help in investigating the route of skin permeation and the rate of transfer through the skin by which drugs entered into the systemic circulation. These studies can easily be performed and the methodology used allowed flexibility in adapting the model in addressing different aspects involved in preliminary or feasibility studies in the development of transdermal patch.

**Franz Diffusion Cell:** The in-vitro skin permeation of transdermal patches can be studied using Franz diffusion cell (most commonly used) with an effective permeation area of 1.0cm² and reaches cell volume of 10 ml. The temperature is maintained at 32°C ±1°C. The receptor compartment is filled with 10 ml PBS and is constantly stirred in a magnetic stirrer at 100rpm. The skin is mounted on the receptor compartment with the stratum corneum side facing upward into the donor compartment. Samples are withdrawn through the sampling port of the diffusion cell at a predetermined time interval over 24 hours and are analyzed. The receptor phase is immediately replenished with an equal volume of fresh diffusion buffer.

**Quick stick (Peel tack) test:** and the substrate is measured by pulling the tape away from the substrate at 90° at the speed of 12 inches/min. Probe tack test is performed using a probe that is pushed forward into contact The peel force required breaking the with the adhesive surface and then retracted at a predefined speed. The force required to break the bond after a short period of contact is measured. The test may be performed with the help of Texture Analyser.

**Shear strength properties or creep resistance:** Shear strength is the measurement of the cohesive strength of an adhesive polymer i.e., the device should not slip on application determined by measuring the time it takes to pull an adhesively coated tape off a stainless plate. Minghetti et al., (2003) performed the test with an apparatus that was fabricated according to PSTC-7 (pressure-sensitive tape council) specification.
2. In-vitro studies

A) In-vitro release studies

The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films (Alam et al., 2009). Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence their in-vivo performance. Several mathematical models have been developed to describe the drug dissolution kinetics from controlled release drug delivery systems e.g., Higuchi, First-order, Zero-order and Peppas and Korsenmeyer models. The dissolution data is fitted to these models and the best fit is obtained to describe the release mechanism of the drug. Various methods are available for the determination of drug release from TDDS (Mutilak and Udupa 2005; Kalia and Guy 2001; Higuchi 1963; Desai et al., 1966; Ritger and Peppas 1987; Tymes 2006). The paddle over disc method (USP apparatus 5/PhEur 2.9.4.1) 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 paddle over disk method in conjunction with a watch glass-patch-screen sandwich experimentally almost the same release profile when compared with other more complicated methods (Shah et al., 1989). The cylinder modified USP basket (USP apparatus 6 / PhEur2.9.4.3) 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 a medium at 32 ±5°C. The reciprocating disc (USP apparatus 7) method consists of attaching the patches to holders and oscillated in small volumes of the medium, allowing the apparatus to be useful for systems delivering a low concentration of a drug. Paddle over-extraction cell method (PhEur 2.9.4.2) may system is thought to also be used. Diffusion cells include Franz-diffusion cell and its modification Keshary-Chien Cell. In this method, the transdermal system is placed in between the receptor and donor compartment of the diffusion cell. The transdermal system faces the receptor compartment in which receptor fluid (e.g., drug solution) is placed. The agitation speed and temperature are kept constant. The whole assembly is kept on a magnetic stirrer and the solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals, the receptor fluid is removed for analysis and is replaced with an equal volume of fresh receptor fluid. The concentration of the drug is preferable.
(B) *In-vitro* permeation studies

After release from the polymeric films, the drug reaches the skin surface is then passed to the dermal microcirculation by permeation through cells of the epidermis and/or between the cells of the epidermis through skin appendages. Usually, permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between the receptor and donor compartment in a vertical diffusion cell such as Franz diffusion cell or Keshary-Chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with a lipophilic side in contact with receptor fluid. The receiver compartment is maintained at a specific temperature (usually 32±5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals method an equal amount of buffer is replaced each time. The samples are diluted appropriately and estimated by a suitable analytical method. The amount of drug permeated per square centimeter at each time interval is calculated. Many variables including design of the system, patch size, the surface area of skin, the thickness of skin and temperature may affect the *in-vitro* properties of a drug. Thus, the permeation studies involve preparation of the skin, mounting of skin and. It is easier, more permeation cell, the setting of experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux (i.e., drug permeated per unit area per unit time) (Alam et al., 2009; Murthy and Hiremath 2001).

3. *In-vivo* Studies

*In-vivo* evaluations are the true depiction of drug performance. The variables which can not be taken into account during *in-vitro* studies can be fully explored during *in-vivo* studies (Sun et al., 2012; Park et al., 2012). *In-vivo* evaluation of TDDS may be carried out using either animal models or human volunteers.

A. Animal models

Considerable time and resources are required to carry out human studies, so animal studies are preferred on a small scale. The most common animal species used for evaluating transdermal drug delivery systems are a mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig, etc. Based on the experiments conducted so far it is concluded that hairless animals are preferred over hairy animals in both *in-vitro* and *in-vivo* experiments. Rhesus monkey is one of the most reliable models for *in-vivo* evaluation.
B. Human models

The final stage of the development of a transdermal device involves the collection of pharmacokinetic and pharmacodynamic data following the application of the patch to human volunteers. Clinical trials are conducted to assess the transdermal systems including the efficacy, risk involved, side effects, and patient compliance. Phase-I clinical trials are conducted to determine mainly safety in volunteers and phase-II clinical trials determine short term safety and mainly effectiveness in patients. Phase-III trials indicate the safety and effectiveness in a large number of the patient population and phase-IV trials at post-marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources they are the best to assess the performance of the transdermal drugs.

Recent advances in the field of transdermal patches

Recently several therapeutically active substances are delivered transdermally including large proteins, testosterone, oxybutynin, and patches for the relief of pain. Drug delivery (Chein 1987; Walker.

1. Patch technology for protein delivery

Transdermal delivery of large proteins is a novel and exciting delivery method. There is non-commercial technology currently available that incorporates proteins into transdermal patches. TransPharma uses its unique printed patch technology for transdermal delivery of proteins thereby complementing its Via Derm delivery technology. Such printed patches contain accurate doses of proteins in a dry state. It is postulated that the highly water soluble proteins are dissolved by the interstitial fluid that is secreted from the skin through the RF-Micro Channels, 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.

2. Pain-free diabetic monitoring using transdermal patches

The patch (about 1cm2) is made using polymers and thin metallic films. The metallic interconnections and sampling array can be seen. When the seal is compromised, the interstitial fluid and the biomolecules contained therein becomes accessible on the skin.
surface. Utilizing micro-heating elements integrated into the structural layer of the patch closest to the skin surface, a high-temperature heat pulse can be applied locally, breaching the stratum corneum. During this ablation process, the skin surface experiences temperatures of 130°C for 30 ms duration. The temperature diminishes rapidly from the skin surface and neither the living tissue nor the nerve endings are affected. This painless and bloodless process results in disruption of a 40–50 μm diameter region in the dead skin layer, approximately the size of a hair follicle, allowing the interstitial fluid to interact with the patch's electrode sites.

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

In premenopausal daily testosterone 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. The addition of TTP to cyclic E2/MPA therapy in women with sPOF produced mean free testosterone levels that approximate the upper limit of the normal release of the drug.

4. Transdermal Patch of Oxybutynin used in overactive Bladder (OAB)

The product is a transdermal patch containing Oxybutynin HCl and is approved in the US under the brand name of Oxytrol and in Europe under the 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 the four-day interval. Oxytrol offers OAB patient’s continuous effective bladder control with some of the side effects, such as dry mouth and constipation encountered with and oral formulation.

5. Pain relief

Pain relief routinely benefits from transdermal patch technology. Most of the readers are aware of the Duragesic patch (Park et al., 2011). Several others are available in the market. Lidoderm, a lidocaine patch (5%), 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, cumbersome, and require considerable nursing care.

6. Molecular absorption enhancement technology

Absorption enhancers are the compounds that promote the passage of drugs through the stratum corneum. Terpene derivatives, as well as certain phenols, seem to improve transdermal absorption (Ahad et al., 2011; Parhi et al., 2012). For example, linalool, alpha terpineol, and carvacrol were studied in conjunction with haloperidol (a commonly prescribed neuroleptic drug). All three enhanced haloperidol absorption, but only linalool increased it to the therapeutic level (Vaddi et al., 2002). Limonene, menthone, and eugenol were found to enhance the transdermal absorption of tamoxifen (Zhao and Singh, 1998). Phloretin, a polyphenol, enhanced the absorption of lignocaine (Valenta et al., 2001). The enhancement in permeation of celecoxib through rat skin was estimated using transcutol and oleic acid as permeation enhancers. A comparative flux pattern of formulations containing these enhancers (oleic acid and enhancement research has been done with excised animal skin (rat, pig or rabbit) or human skin obtained from cadavers or plastic surgery procedures.

Table No. 3: Classification of permeation enhancers

<table>
<thead>
<tr>
<th>Permeation Enhancers</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terpenes (essential oils)</td>
<td>Nerodilol, Menthol, Cineol, Limonene, Carvone</td>
</tr>
<tr>
<td>Pyrrolidones</td>
<td>N-methyl-2-pyrrolidone (NMP), Azone.</td>
</tr>
<tr>
<td>Fatty acids and esters</td>
<td>Oleic acid, Linoleic acid, Lauric acid, Capric acid</td>
</tr>
<tr>
<td>Sulfoxides and similar compound</td>
<td>Dimethyl sulfoxide(DMSO), Dimethylformamide.</td>
</tr>
<tr>
<td>Alcohols, Glycols and Glycerides</td>
<td>Ethanol, Propylene glycol, Octyl alcohol.</td>
</tr>
<tr>
<td>Miscellaneous enhancers</td>
<td>Phospholipids, Cyclodextrins, Aminoacid derivatives, Enzymes.</td>
</tr>
</tbody>
</table>
(I) Preparation of individual matrix solution Raw material [Polymer, tackifier, softening agent] is dissolved in an organic solvent to obtain a standard or stock soln. The matrix solution then prepared from the stock solution by mixing it with ingredients specified by the formulation. The active ingredient and other non-soluble additives are added.

The process and equipment involved in the manufacture of an adhesive dispersion system

Figure No. 8: Method of preparation

Figure No. 9: The process and equipment involved in the manufacture of an adhesive dispersion system
(II) Coating the individual matrix layers

The individual layers are made by coating the solution (above). On the smooth paper or film web and removing the solvent by drying using.

(a) Coating unit

The solvent based formulations are coated onto the appropriate web. Depending on the viscosity, solid contents, flowability and surface tension of the matrix solution.

(b) Drying Unit

Closed to the environment and is directly connected to the drying unit to avoid solvent and this active agent evaporation. The solvent is evaporated from the adhesive mars by running the coated web through a drying channel using a transport system like a cranked shaft, conveyor belt.

(I) Building the multilayer laminate

Lamination is used to build up the multilayer matrix system. Here two matrix layers, each adhering to one side of the web are laminated. Then a carrier material of this two layer laminate is removed and a third layer, with the laminated side to the laminated side of the two layer laminate is pressed. This procedure is repeated until the final laminate is complete.

(II) Separating unit of the multilayer laminate

The bulk product is slit longitudinally and the individual unit is punched quit from the narrow rolls so obtained. The precision of the operations is of paramount importance here hence it affects the release rate of the active ingredient. Then the liner is applied with the necessary release aids to the system.

(III) Packaging

Primary packaging is done using sealed, four-cornered while secondary packaging in cardboard boxes precedes the shipment coating machine. This machine consists of two units.
CONCLUSION

Transdermal drug delivery represents one of the most rapidly advancing areas of novel drug delivery. Due to recent advances in technology and the ability to deliver the drug systemically without rupturing the skin membrane, the transdermal route is becoming a widely accepted route of drug administration. TDDS are designed for the controlled release of drugs through the skin into systemic circulation maintaining consistent efficacy. It offers the delivery of drugs at a lowered dose that can save the recipient from the harm of large doses with improved bioavailability. This may be achieved by by-passing the hepatic first metabolism. Almost all major and minor pharmaceutical companies are developing TDDS. Potential development in drug delivery systems includes the use of improved adhesive and/or enhancer technologies; and systems that exploit thermal, electrical, ultrasonic, or other forms of energy.

REFERENCES

(1) Type, preparation and evaluation of transdermal patch; A review intake Alam* Alam* Vikramjit Singh, Md. Sarfaraj Alam, Md Sajid Ali Tarque Anwer, Mohamad M. Safi College of Pharmacy, Patti, Amritsar, Punjab, India.
(2) A review article Pantejaswini, Y. Soujanya, U. Swapna, V. Sarika, G. Moulika, Department of Pharmacy, Maheshwara Institute of Pharmacy Hyderabad.
(3) A review Rajesh Mujoriya and Kishordhamande, Sardar Patel College of Technology, Balghat, (M.P)481001
(4) A review Dipenpatel*, Sunita A. Chaudhary, Bhavesh Parmar, Nikunj Bhura, Arihant School of Pharmacy and Bio-Research Institute, Gandhinagar, Gujrat, India.
(5) A review article Richa Sachan, Meenakshi Bajpai Uttarhand Technical University, Deharadun (248001).
(7) A review Archana K Gaikwad Aurangabad 430001 Maharashtra India.