

## Patches: A Novel approach for development of topical drug delivery system

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### ABSTRACT

Transdermal drug delivery systems (TDDS) allow delivery of contained drug into the systemic circulation via permeation through skin layers at a controlled rate. These systems are easy to apply and remove as and when desired. Skin is an effective medium from which absorption of the drug takes place. Various types of transdermal patches are used to incorporate the active ingredients into the circulation system via skin. The patches have been proved effective because of its large a advantages over other controlled drug delivery systems. This review article covers the introduction of transdermal drug delivery system, anatomy of skin, principles of transdermal permeation, various components of transdermal patch, approaches of transdermal patch, release kinetics of drug from transdermal patch, advantages and disadvantages of transdermal patch.

**Keywords:** Transdermal drug delivery system, Transdermal patches, Skin .

### INTRODUCTION

Treatments of acute and chronic diseases have been accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. This dosage form is known to provide a prompt release of drug. But recently several technical advancements have been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release. At present, the most common form of delivery of drug is the oral route, while this has a notable advantage of easy administration, it also has significant drawbacks – namely poor bioavailability due to hepatic metabolism and tendency to produce rapid blood level spikes (both high and low) leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient [1]. To overcome these difficulties there is need for development of new drug delivery system; which will improves the therapeutic efficacy and safety of drug by more precise (i.e. site specific),

special and temporal placement within the body there by reducing both the size and number of doses. New drug delivery system are also essential for the delivery of novel, genetically engineered pharmaceuticals (peptide, proteins) to their site of action, without incurring significant immunogenicity or biological inactivation. One of method most often utilized has been transdermal delivery – meaning transport of therapeutic substances through the skin for systemic effect. Closely related is percutaneous delivery, which is transport in to target tissue, with an attempt to avoid side effect[2]. Being a non-invasive technique, Transdermal delivery causes very little, if any, pain or risk of infection to the patient. These benefits are summarized in following table.

**Table 1:** Transdermal drug delivery offers the best of IV and Oral administration

Routes of administration	IV	Oral	TDDS
Reduced first-pass effects	Yes	No	Yes
Constant drug levels	Yes	No*	Yes
Self-administration	No	Yes	Yes
Unrestricted patient activity	No	Yes	Yes
Non-invasive	No	Yes	Yes

\*Sometimes can be achieved with controlled release

Transdermal delivery not only provides controlled, constant administration of the drug, but also allows

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continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects.[3] A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Along with a predictable pharmacokinetic profile, the delivery rate of the drug from a transdermal device into the bloodstream can be controlled. Therefore, constant drug levels can be achieved over extended periods of time without the extreme peak and trough fluctuations inherent in oral administration. With transdermal devices, drug delivery can be localized and discontinuation of therapy can be achieved immediately by simply removing the patch. Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories — therapeutic and cosmetic), aroma patches and weight loss patches, and patches that measure sunlight exposure.

### Popular Transdermal Patch Applications

- Nicotine patch
- Fentanyl for severe pain
- Estrogen patches for hormone therapy
- Nitroglycerine for Angina
- Scopolamine for motion sickness
- Anti-hypertensive
- Anti-depressant
- Attention Deficit Hyperactivity Disorder (ADHD)
- Vitamin B12

### TRANSDERMAL PATCH



**Figure 2:** A Transdermal drug delivery patch

Transdermal drug delivery system is topically administered medicaments in the form of patch that

deliver drug for systemic effect at predetermined and controlled rate. A Transdermal drug delivery device which may be of an active or passive design is a device which provides an alternative route for administering medication. These devices, allow for Pharmaceuticals to be delivered across the skin barrier.[4] In theory transdermal patches work very simply. A drug is applied in relatively high dosage to the inside of patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the blood stream directly through the skin. Since there is high concentration on the patch low concentration in blood, the drug will keep diffusing into the blood for long period of time, maintaining the constant concentration of drug in the blood flow.[5] Transdermal drug delivery has many advantages over conventional drug delivery and can be discussed as follows

### Advantages [6-15]

1. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
2. They can substitute for oral administration of medication when that route is unsuitable, as with vomiting and diarrhea.
3. They avoid the first-pass effect, that is, the initial pass of drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.
4. They are noninvasive, avoiding the inconvenience of parenteral therapy.
5. They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
6. The activity of a drugs having short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.

7. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
8. They are easily and rapidly identified in emergencies (e.g., unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.
9. They are used for drugs with narrow therapeutic window.
10. Dose delivery unaffected by vomiting or Diarrhea. At the same time transdermal drug delivery has few disadvantages that are limiting the use of transdermal delivery.

#### Disadvantages [6-15]

1. Only relatively potent small, lipophilic drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
2. Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
3. The delivery system cannot be used for drugs requiring high blood levels.
4. The use of transdermal delivery may be uneconomic.
5. Adhesion may vary with patch type and environmental conditions
6. The barrier function of the skin changes from one site to another on the same person, from person to person and with age for better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways.

#### Principles of Transdermal Permeation [8,6]

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:

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary layer.
5. Effect on target organ

#### Brief review of skin structure [1,7,17,18]

The skin is largest and most external organ of body and hence provides a large surface area for drug application, combines with the mucosal lining of the respiratory, digestive, and urogenital tracts to form a capsule which separates the internal body structures from external environment. The pH of the skin varies from 4 to 5.6, Sweat and fatty acids secreted from sebum influence the pH of the skin surface.

#### Functions of skin [8,10]

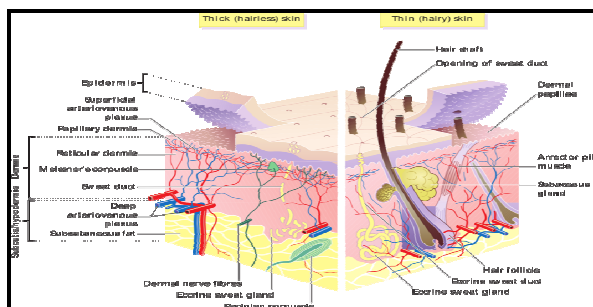
1. Protection – from invasion by microbes, chemicals, physical agents (e.g. mild trauma, UV light), and dehydration.
2. Reflex action – due to sensory nerves to stimuli
3. Regulation of body temperature – regulate body temperature about 36.8°C (98.4°F) with variation of 0.5°C to 0.75°C.
4. Formation of vitamin D – fatty substance present in skin, 7- dehydrocholesterol, in presence of UV light from sun is converted to vitamin D.
5. Absorption – absorbs some drug with low molecular weight as well as toxic chemicals like mercury.
6. Excretion – excretes sodium chloride in sweat, urea when kidney function is impaired, and aromatic substances (e.g. garlic and other spices)

#### Anatomy and Physiology of skin [17,18]

Human skin comprises of three distinct but mutually dependent tissues.

- A) The stratified, a vascular, cellular epidermis,

- B) Underlying dermis of connective tissues, and  
C) Hypodermis.



**Fig 3:** Human Skin (T.S.) Structure

### A. Epidermis

The multilayered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum and the remainder of the epidermis so called viable epidermis cover a major area of skin. The epidermis contains no blood vessels and hence nutrients and waste products must diffuse across the dermo-epidermal layer in order to maintain tissue integrity. Likewise, molecules permeating across the epidermis must cross the dermo-epidermal layer in order to be cleared into the systemic circulation. The source of energy for lower portions of epidermis is also glucose, and the end product of metabolism, lactic acid accumulates in skin. The epidermis contains four histologically distinct layers which, from the inside to the outside, are

- **Stratum Germinativum** (Growing Layer)
- **Malpighion Layer** (pigment Layer)
- **Stratum Spinosum** (Prickly cell Layer)
- **Stratum Granulosum** (Granular Layer)
- **Stratum Lucidum**
- **Stratum Corneum** (Horny Layer)

A representation of the 'Brick and Mortar' model of human stratum corneum

Lipid constituents vary with body site (neutral lipids, sphingolipids, polar lipids, cholesterol). Phospholipids are largely absent, a unique feature of mammalian membrane. The architecture of horny layer may be modeled as a wall-like structure. In this model, the keratinized cells function as a protein "bricks"

embedded in lipid "mortar." The lipids are arranged in a multiple bi layers, and it has been suggested that there is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bi layer form. In the basal layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead Horny cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

### B. Dermis

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

### C. Hypodermis (Subcutaneous Fat Layer)

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

### Fundamentals of skin permeation [8]

Until the last century the skin was supposed to be impermeable with exception to gases. However, in the

current century the study indicated the permeability to lipid soluble drugs like electrolytes. Also it was recognized that various layers of skin are not equally permeable i.e. epidermis is less permeable than dermis. After a large controversy, all doubts about stratum corneum permeability were removed and using isotopic tracers, it was suggested that stratum corneum greatly hamper permeation.

**Table 2:** Regional variation in water permeability of stratum corneum

Sr. No.	Skin Region	Thickness ( $\mu\text{m}$ )	Permeation ( $\text{mg}/\text{cm}^2/\text{hr}$ )	Diffusivity ( $\text{cm}^2/\text{sec} \times 10^{10}$ )
1	Abdomen	15	0.34	6.0
2	Volar forearm	16	0.31	5.9
3	Back	10.5	0.29	3.5
4	Forehead	13	0.85	12.9
5	Scrotum	5	1.70	7.4
6	Back of hand	49	0.56	32.3
7	Palm	400	1.14	535
8	Plantar	600	3.90	930

Intracellular regions in stratum corneum are filled with lipid rich amorphous material. In dry stratum corneum intracellular volume may be 5% to 1% in fully hydrated stratum corneum.

#### • Intracellular verses transcellular diffusion

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#### Permeation pathways [1,8]

Percutaneous absorption involves passive diffusion of the substances through the skin. A molecule may use two diffusional routes to penetrate normal intact skin, the appendageal route and the epidermal route.

#### Transcellular

Transcellular pathway means transport of molecules across epithelial cellular membrane. These include passive transport of small molecules, active transport of ionic and polar compounds, and endocytosis and transcytosis of macromolecules.

#### Paracellular

Paracellular pathway means transport of molecules around or between the cells. Tight junctions or similar situations exist between the cells. The principal pathway taken by a permeant is decided mainly by the partition coefficient ( $\log k$ ). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permeants ( $\log k > 2$ ) traverse the stratum corneum via the intercellular route. Most permeants permeate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route and major barrier to the permeation of most drugs.

#### Factors influencing transdermal drug delivery [8]

The effective Transdermal drug delivery can be formulated by considering three factors as Drug, Skin, and the vehicles. So the factors affecting can be divided in two classes as biological factors and physicochemical factors.

#### A) Biological factors

- **Skin condition** – Acids and alkalis; many solvents like chloroform, methanol damage the skin cells and promotes penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.
- **Skin age** – The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDSs.
- **Blood supply** – Changes in peripheral circulation can affect transdermal absorption.
- **Regional skin site** – Thickness of skin, nature of stratum corneum, and density of appendages vary site to site. These factors affect significantly penetration.
- **Skin metabolism** – Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.
- **Species differences** – The skin thickness, density of appendages, and keratinization of skin vary species to species, so affects the penetration.

## B) Physicochemical factors

**Skin hydration** – In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectants is done in Transdermal delivery.

**Temperature and pH** – The permeation of drug increase ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

**Diffusion coefficient** – Penetration of drug depends on diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

**Drug concentration** – the flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

**Partition coefficient** – The optimal  $K$ , partition coefficient is required for good action. Drugs with high  $K$  are not ready to leave the lipid portion of skin. Also, drugs with low  $K$  will not be permeated.

**Molecular size and shape** – Drug absorption is inversely related to molecular weight; small molecules penetrate faster than large ones. Because of partition coefficient domination, the effect of molecular size is not known.

## Factors affecting permeability [19]

### A. Physiological factors:

- Anatomic site of application on the body
- Skin condition and disease
- Age of the patient
- Skin metabolism
- Desquamation (peeling or flaking of the surface of the skin)
- Skin irritation and sensitization

- Race

### B. Formulation factors

- Physical chemistry of transport
- Vehicles and membrane used
- Penetration enhancers used
- Method of application
- Device used

### C. Physicochemical properties of enhancers

- Partition coefficient of 1 or greater is required
- pH value should be moderate, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their Transdermal permeability
- Concentration of penetrant higher than solubility, excess solid drug functions as a reservoir and helps in maintaining constant drug concentration for prolonged time.

## Technologies for developing Transdermal patches [16,20]

The technologies can be classified in four basic approaches,

### A) A Polymer membrane partition-controlled TDD systems:

In this type of systems, the drug reservoir is sandwiched between a drug impermeable backing laminate and a rate controlling polymeric membrane.

### B) Polymer matrix diffusion-controlled TDD systems:

In this system, the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix, and then the medicated polymer formed is molded into medicated disks with defined surface area and thickness. This drug reservoir containing polymer disk is then mounted on occlusive base plate in a compartment fabricated from a drug-impermeable plastic backing. Instead of coating adhesive polymer directly on the surface of medicated disk, it is applied along the circumference of the patch to form a strip of adhesive

rim surrounding the medicated disk. e.g. Nitro-Dur system and NTS system for angina pectoris. The rate of release from polymer matrix drug dispersion-type is, Only drug is dissolved in polymer matrix can release,  $C_p$  is practically equal to  $C_R$ . Alternately, the polymer matrix drug dispersion-type TDD system can be fabricated by directly dispersing drug in a pressure-sensitive adhesive polymer, e.g. polyacrylate, and then coating the drug-dispersed adhesive polymer by solvent casting or hot melt onto a flat sheet of a drug-impermeable backing laminate to form a single layer of drug reservoir. This yields a thinner patch. e.g. Minitran system, Nitro-Dur II system for angina pectoris.

### C) Drug reservoir gradient-controlled TDD systems:

Polymer matrix drug dispersion-type TDD systems can be modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multi laminate adhesive layers. The drug release from this type of drug reservoir gradient- controlled TDD systems can be expressed by

$$\frac{dQ}{dt} = \frac{K_a}{h a} A(h a)$$

In this system the thickness of diffusional path through which drug molecules diffuse increases with time, i.e.  $h a(t)$ . The drug loading level in the multi laminate adhesive layer is designed to increase proportionally i.e.  $L_d(h a)$  so as to compensate time dependent increase in diffusional path as a result of drug depletion due to release. Thus, theoretically this should increase a more constant drug release profile. E.g. Deponit system containing nitroglycerine for angina pectoris.

### D) Microreservoir dissolution-controlled TDD systems:

A hybrid of reservoir- and matrix dispersion-type drug delivery systems, which contains drug reservoir formed by first suspending the drug solids in an

aqueous solution of water-miscible drug solubilizer e.g. propylene glycol, then homogeneously dispersing the drug suspension, with controlled aqueous solubility, in a lipophilic polymer, by high shear mechanical force, to form thousands of unleachable microscopic drug reservoirs.

### Basic Components of Transdermal patches [8]

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

#### 1. Polymer matrix:

Polymers are the backbone of a Transdermal drug delivery system. Systems for Transdermal delivery are fabricated as multilayered polymeric laminates in which a drug reservoir or a drug polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane. 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 with respect to its adhesion- cohesion balance, physicochemical properties, and compatibility and stability with other components of the system as well as with skin. The polymers utilized for TDDS can be classified as,

- **Natural Polymers:** e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan *etc.*
- **Synthetic Elastomers:** e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber *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 EVA, silicon rubber and polyurethane are used as rate controlling membrane.

## 2. Drug

The most important criteria for TDDS is that the drug possesses 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 dementia, rotigotine for parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS.

### Biopharmaceutical parameters in drug selection for transdermal patch [16]

- ✧ Dose should be low i.e. <20mg/day.
- ✧ Half life should be 10 h or less.
- ✧ Molecular weight should be <400 Da.
- ✧ Partition coefficient should be  $\log P$  (octanol-water) between 1.0 and 4.
- ✧ Skin permeability coefficient should be  $<0.5 \times 10^{-3} \text{ cm/h}$ .
- ✧ Drug should be non irritating and non sensitizing to the skin.
- ✧ Oral bioavailability should be low.
- ✧ Therapeutic index should be low.

### 3. Permeation enhancers

To increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug penetration enhancers interact with structural components of stratum corneum *i.e.*, proteins or lipids. The enhancement in 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 transepidermal and transfollicular penetration. The miscibility and solution properties of the enhancers used could be responsible for the enhanced Transdermal permeation of water soluble drugs. Pharmaceutical scientists have made great efforts in Transdermal permeation studies using various enhancers for several drug moieties.

### Classification of penetration enhancers [9]

- **Terpenes(essential oils)** :e.g. Nerodilol, menthol, 1 8 cineol, limonene, carvone *etc.*
- **Pyrrolidones:** E.g. N-methyl-2-pyrrolidone(NMP), azone *etc.*
- **Fatty acids and esters:** E.g. Oleic acid, linoleic acid, lauric acid, capric acid *etc.*
- **Sulfoxides and similar compounds:** E.g. Dimethyl sulfoxide(DMSO), N,Ndimethyl Formamide Alcohols, Glycols, and Glycerides : E.g. Ethanol, Propylene glycol, Octyl alcohol *etc.*
- **Micellaneous enhancers:** E.g. Phospholipids, Cyclodextrins, Amino acid derivatives, Enzymes *etc.*

The permeation of drugs across is also enhanced by physical means like pulsed DC iontophoresis *i.e.* it passes a few milliamperes 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, sonophoresis *i.e.* application of ultrasound, particularly low frequency ultrasound, has been shown to enhance Transdermal transport of various drugs including macromolecules, electroporation *i.e.* application of short, highvoltage electrical pulses to the skin for increasing the permeability of the skin for diffusion of drugs by 4 orders of magnitude, use of micro projections *i.e.* Transdermal patches with microscopic projections called microneedles were used to facilitate Transdermal drug transport *etc.*

### 4. Pressure sensitive adhesive:



A PSA maintains an intimate contact between patch and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tacky, exert a strong holding force. For e.g. 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 reservoir system) or in the back of the device and extending peripherally (as in case of matrix system).

### 5. Backing laminate

The primary function of the backing laminate is to provide support. Backing layer should be chemical resistant and excipient 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 penetration 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 an aluminium vapor coated layer, a plastic film (polyethylene, polyvinyl chloride, polyester) and a heat seal layer.

### 6. 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 dosage form for delivering the drug. 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. Other materials used for TDDS release liner include polyester foil.

### 7. Other excipients:

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylphthalate, triethylcitrate, polyethylene glycol

and propylene glycol are added to provide plasticity to the transdermal patch.

### Evaluation of transdermal patch : [23]

1. Interaction studies
2. Thickness of the patch
3. Weight uniformity
4. Folding endurance
5. Percentage Moisture content
6. Percentage Moisture uptake
7. Water vapour permeability (WVP) evaluation
8. Drug content
9. Uniformity of dosage unit test
10. Polariscope examination
11. Shear Adhesion test
12. Peel Adhesion test
13. Thumb tack test
14. Flatness test
15. Percentage Elongation break test
16. Rolling ball tack test
17. Quick Stick (peel-tack) test
18. Probe Tack test
19. In vitro drug release studies
20. In vitro skin permeation studies
21. Skin Irritation study

### In-Vitro Skin Permeation and Release Kinetics Studies

The design and development of transdermal drug delivery systems is greatly aided by invitro studies. In vitro studies can help in investigating the mechanism of skin permeation of drug before it can be developed into a transdermal therapeutic system. The methodology used in the in vitro study is relatively easy to follow and generally affords the investigator better control over the experimental conditions than is possible in-vivo, The factors that require consideration when selecting an in vitro system include:

1. The rate limiting process: drug solubilization or diffusion in the vehicle, partitioning from the vehicle, diffusion through the test membrane or partitioning and removal by the receptor phase.

2. The intrinsic diffusivity of the permeate and apparent diffusivity.
3. The predominating route of diffusion during the experiment and the relative contents of drug binding and metabolism, occurring in the membrane, delivery and receptor phases.
4. The predominating route of diffusion during the experimentation and the relative extents of drug binding.
5. The intrinsic barrier potential of the membrane and the effects that vehicle components may have on retardative properties. Hydration of the membrane and the presence of penetration enhancers may be important here. The kinetics of skin permeation can be more precisely analyzed by studying the time course for the permeation of drug across a freshly excised skin mounted on a diffusion cell, such as the Franz diffusion cell. Keshary and Chien have pointed out certain deficiencies in the Franz cell and modified to obtain closer approximation to in vivo conditions. Some diffusion cells are designed to hold the skin at a vertical position between donor and receptor chambers. A more recent example is the valia, Chien cell, which is superior to similar earlier models in that it does not expose both, the donor and the receptor phases to the same temperature, and does not allow solvent loss from either phase. Moreover, the design overcomes another inadequacy of the Franz cell, namely the susceptibility of its donor phase to the changes in ambient temperature.

#### A) Physical design of diffusion cell

- Horizontal type
- Vertical type
- Flow-through type

#### B) Method of sampling and measurement

- Continuing system
  1. Fluid circulation system
  2. Noncirculation system
- Intermittent system: rotating agitation systems

### In-Vitro Dissolution Studies

In-vivo Evaluation of Transdermal Drug Delivery Systems:

In-vivo evaluation of TDDS can be carried out using,

- A. Animal models
- B. Human volunteers
- C. Biophysical models

A. Animal models:- In vivo animal models are preferred because considerable time and resources are required to carry out studies in humans. Some of the species that have been used for in vivo testing include; mouse, rat, guinea pig, rabbit, hairless mouse, which of the animal models provide the best prediction of the behavior of the device, being tested, in humans.

B. Human volunteers:- The final stage in the development of transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the device to human volunteers. An in vivo evaluation using human subjects should give pertinent information with minimum risk to the subjects within a reasonable period of time. In vivo evaluation using human models involve determination of percutaneous absorption by an indirect method.

1) Reservoir techniques

2) Mass balance techniques

C. Biophysical Models Models based on steady-state mass balance equation, solution of Fick's second law of diffusion for the device, stratum corneum and viable epidermis, as well as linear kinetics have been described in the literature. It can be concluded that many techniques for in-vivo evaluation of transdermal systems have been put forward there is scope for further refinement.

### General clinical considerations in the use of TDDS [7]

The patient should be advised of the following general guidelines. The patient should be advised of the importance of using the recommended site and rotating locations within the site. Rotating locations is important to allow the skin to regain its normal permeability and to prevent skin irritation.

TDDSs should be applied to clean, dry skin relatively free of hair and not oily, inflamed, irritated, broken, or callused. Wet or moist skin can accelerate drug permeation beyond onset time. Oily skin can impair the adhesion of patch. If hair is present at the site, it should be carefully cut, not wet shaved, nor should a depilatory agent be used, since later can remove stratum corneum and affect the rate and extent of drug permeation.

- Use of skin lotion should be avoided at the application site, because lotions affect the hydration of skin and can alter partition coefficient of drug.
- Cutting should not physically alter TDDSs, since this destroys integrity of the system.
- The protecting backing should be removed with care not to touch fingertips. The
- TDDS should be pressed firmly against skin site with the heel of hand for about 10 sec.

## CONCLUSION

A lot of progress has been done in this field of transdermal drug delivery system especially in transdermal patches. This system interests a lot of researchers due to large advantages of transdermal drug delivery system. To incorporate newer drugs via this system many new research are going on in the present days. Extensive research during the past decades, chemical enhancers have achieved only limited success in increasing the transdermal transport of small molecules and have only a relatively poor ability to increase macromolecular transport under conditions likely to have therapeutic action. Different devices which help in increasing the rate of penetration and absorption of the drug are also studied. The use of transdermal drug delivery is limited. But, with the invention of new drugs and new devices which can be incorporated via this system, it used is increasing rapidly in the present time.

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