Online Available at www.thepharmaresearch.info

THE PHARMA RESEARCH, A JOURNAL

The Pharma Research (T. Ph. Res.), (2010), 3; 139-149.
Published on- 15 June 2010



ISSN 0975-8216

*Original Article*

# A REVIEW ON TRANSDERMAL PATCHES

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## ABSTRACT

The administration of drugs by transdermal route offers the advantage of being relatively painless. The appeal of using the skin as a portal of drug entry lies in case of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks and the noninvasive nature of drug delivery. Delivery of drugs through the skin for systemic effect, called transdermal delivery was first used in 1981, when Ciba-Geigy marketed Transderm V (present day marketed as Transderm Scop) to prevent the nausea and vomiting associated with motion sickness. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variation.

**Keywords: Transdermal, Delivery, Patches**

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## 1.0 INTRODUCTION

During the past few years, interest in the development of novel drug delivery systems for existing drug molecules has been renewed. The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent[1]. When properly designed and developed for a particular drug, novel delivery system can overcome specific hurdles associated with conventional methods of delivery, e.g., drugs that undergo partial or complete degradation before reaching the site of action could be effectively delivered with improved bioavailability by using the novel concepts of timed or pulsatile release, or gastro-resistant delivery[2].

During the past 20 years, advances in drug formulations and innovative routes of administration have made. Our understanding of drug transport across tissues has increased. While topical products or drug delivery systems have been used for centuries for the treatment of local skin disorders, the use of the skin as a route for systemic drug delivery is of relatively recent origin[3]. The administration of drugs by transdermal route offers the advantage of being relatively painless. The appeal of using the skin as a portal of drug entry lies in case of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks and the noninvasive nature of drug delivery. Delivery of drugs through the skin for systemic effect, called transdermal delivery was first used in 1981, when Ciba-Geigy marketed Transderm V (present day marketed as Transderm Scop) to prevent the nausea and vomiting associated with motion sickness[4, 5].

Throughout the past 2 decades, the transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms[6]. It constitutes a new trend in controlled delivery system and has opened new scientific horizon in innovations. The delivery of drugs transdermally (through the skin) provides several important advantages over traditional oral and intravenous delivery routes. Transdermally delivered drugs avoid the risk and inconvenience of intravenous therapy, usually provide less chance of an overdose or underdose, allow easy termination, and permit both local and systemic treatment effects. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms [7, 8]. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variation. In addition, because transdermal patches are user

friendly, convenient, painless, and offer multi day dosing, it is generally accepted that they offer improved patient compliance 10. The growth rate for transdermal drug delivery systems is expected to increase 12% annually by 2007 [9].

### 1.1 Advantages of transdermal drug delivery systems [10]

Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivery drugs across the skin to achieve systemic effects are:

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

**Limitations of transdermal drug delivery systems [11, 12, 13]**

- Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin
- Cannot administer drugs that require high blood levels
- Drug of drug formulation may cause irritation or sensitization
- Not practical, when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin.
- Not suitable for a drug, which doesn't possess a favourable, o/w partition coefficient
- The barrier functions of the skin of changes from one site to another on the same person, from person to person and with age.

### 1.3 Human skin [14, 15]

The skin plays an important role in the transdermal drug delivery system. The skin of an average adult body covers a surface area of approximately 2 sq. m. and receives about one third of the blood circulating through the body and serves as a permeability barrier against the transdermal absorption of various chemical and

biological agent. The main three layers of skin play an important role in transdermal drug delivery system.

**Table 1: Structure of skin**

| | |
|---|---|
| The subcutaneous fat layer | ➢ It bridges between the overlying dermis and the underlying body constituents.<br>➢ It is relatively thick in order of several millimeters.<br>➢ The layer of adipose tissue serves to insulate the body and to provide mechanical protection against physical shock.<br>➢ It also provide supply of high energy molecules<br>➢ Principal blood vessels and nerves are carried to the skin in this layer. |
| The dermis | ➢ It contains blood and lymphatic vessels, nerve endings, pilosebaceous units (hair follicles and sebaceous glands) and sweat glands (eccrine and apocrine).<br>➢ It provides physiological support for the epidermis.<br>➢ It is typically 3-5 mm thick and is the major component of human skin.<br>➢ It is composed of a network of connective tissue, predominantly collagen fibrils providing support and elastic tissue providing flexibility, embedded in a mucopolysaccharide gel (Wilkes *et al*., 1973).<br>➢ It provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules. |
| The epidermis | ➢ It is 100 μm thick.<br>➢ It contains various layers. The stratum germinativum is the basal layer. Above the basal layer are the stratum spinosum, the stratum granulosum, the stratum lucidum, and finally, the stratum corneum (SC).<br>➢ SC is the rate limiting barrier that restricts the inward and outward movement of chemical substances consists of flattened keratin-filled cells (e.g., corneocytes). Upon reaching the SC, these cells are cornified and flatten. The corneocytes are then sloughed off the skin at a rate of about one cell layer per day, a process called desquamation.<br>➢ The main source of resistance to penetration and permeation through the skin is the SC. |

**1.4 Basic principles of transdermal permeation** [12]

Transdermal permeation is based on passive diffusion. Before a topically applied drug can act either locally or systemically, it must penetrate the stratum corneum – the skin permeation barrier. In the initial transient diffusion stage drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium through the intact

stratum corneum becomes the primary pathway for transdermal permeation.

The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process, which involves [15]

- Dissolution with in and release from the formulation
- Partitioning into the skin's outermost layer, the stratum corneum
- Diffusion through the SC, principally via a lipidic intercellular pathway
- Partitioning from the SC into the aqueous viable epidermis, diffusion through the viable epidermis and into the upper dermis, and uptake into the papillary dermis and into the microcirculation

**Table 2: Factors affecting transdermal permeation** [11, 16]

| Factors | Explanations |
|---|---|
| **Physicochemical properties of the penetrant molecules** | |
| Partition coefficient | A lipid/water partition coefficient of 1 or greater is generally required for optimal transdermal permeability.<br>It may be altered by chemical modification without affecting the pharmacological activity of the drug. |
| pH conditions | Applications of solutions whose pH values are very high or very low can be destructive to the skin. With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability. |
| Penetrant concentration | Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux. At concentration higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug constitution for a prolonged period of time. |
| **Physicochemical properties of the drug delivery system** | |
| Release characteristics | Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on the following factors:<br>Whether the drug molecules are dissolved or suspended in the delivery systems.<br>The interfacial partition coefficient of the drug from the delivery system to the skin tissue.<br>pH of the vehicle |
| Composition of the drug delivery systems | The composition of the drug delivery systems e.g., boundary layers, thickness, polymers, vehicles not only affects the rate of drug release, but also the permeability of the stratum corneum by means of hydration, making with skin lipids, or other sorption promoting effects e.g., benzocaine permeation decreases with PEG of low molecular weight. |
| Enhancement of transdermal permeation | Majority of drugs will not penetrate skin at rates sufficiently high for therapeutic efficacy. In order to allow clinically useful transdermal permeation of most drugs, the penetration can be improved by the addition of a permeation promoter into the drug delivery systems. |

## 2.0 Basic components of transdermal drug delivery systems

### 2.1 Polymer matrix

Polymer is an integral and foremost important component of transdermal drug delivery systems. Different classes of polymeric materials have been used to achieve rate controlled drug delivery. The mechanism of drug release depends upon the physicochemical properties of the drug and polymer used in the manufacture of the device. The following criteria should be satisfied for a polymer to be used in a transdermal system.

- Molecular weight, glass transition temperature, chemical functionality or polymer must allow diffusion and release of the specific drug.
- The polymer should permit the incorporation of a large amount of drug.
- The polymer should not react, physically or chemically with the drug
- The polymer should be easily manufactured and fabricated into the desired product and in expensive.
- The polymer must be stable and must not decompose in the presence of drug and other excipients used in the formulation, at high humidity conditions, or at body temperature.
- Polymers and its degradation products must be non toxic.

No single material may have all these attributes; e.g., cosolvents such as ethanol, propylene glycol, PEG 400 could be added to increase drug solubility.

Various techniques which are employed to modify the polymer properties and thus drug release rates [17, 18]

**Table 3: Techniques of matrix**

| Techniques | Description |
|---|---|
| Cross linked polymers | The higher the degree of cross linking, the more dense the polymer and slower the diffusion of drug molecules through the matrix. |
| Polymer blends | Polymers have been blended on varying ratios to combine the advantages of the individual polymers. Advantages of polymer blends include easy fabrication of devices, manipulation of drug loading and other devices properties such as hydration, degradation rate and mechanical strength. |
| Plasticizers | Plasticizers have been known to reduce the stiffness of the polymer backbone, thereby increasing the diffusion characteristics of the drug. Commonly used plasticizers are polyethylene glycol, propylene glycol, glycerol, dibutyl phthalate. |

### 2.2 Drug substance

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

### 2.3 Physicochemical properties [16,19]

- The drug should have some degree of solubility in both oil and water (ideally greater than 1 mg/ml)
- The substance should have melting point less than 200 °F. Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point (in degree absolute of the drug). In order to obtain the best candidates for TDD, an attempt should be made to keep the melting point as low as possible.
- Substances having a molecular weight of less than 1000 units are suitable.
- A saturated aqueous solution of the drug should have a pH value between 5 and 9. Drugs highly acidic or alkaline in solution are not suitable for TDD; because they get ionized rapidly at physiological pH and ionized materials generally penetrate the skin poorly.
- Hydrogen bonding groups should be less than 2.

### 2.4 Biological properties [12]

- Drug should be very potent, i.e., it should be effective in few mgs per day (ideally less than 25 mg/day)
- The drug should have short biological half life
- The drug should be non irritant and non allergic to human skin
- The drug should be stable when in contact with the skin
- The drug should not stimulate an immune reaction to the skin
- Tolerance to drug must not develop under near zero order release profile of transdermal delivery
- The drug should not get irreversibly bound in the subcutaneous tissue
- The should not get extensively metabolized in the skin

### 2.5 Penetration enhancers

These are the compounds, which promote skin permeability by altering the as a barrier to the flux of a desired penetrant and are considered as an integral part of most transdermal formulations. To achieve and maintain therapeutic concentration of drug in the blood, the resistance of skin to diffusion of drugs has to be reduced in order to allow drug molecules to cross skin and to maintain therapeutic levels in blood. They can modify the skin's barrier to penetration either by

interacting with the formulation that applied or with the skin itself [17].

The penetration enhancer should be pharmacologically inert, non toxic, non allergenic, non-irritating and ability to act specifically, reversibly and for predictable duration. It should not cause loss of body fluids, electrolytes or other endogeneous materials.

### 2.6 Drug reservoir components

It must be compatible with the drug and must allow for drug transport at the desired rate. If an ointment is used, the drug reservoir must possess the desired viscosity attributes to ensure reliable manufacturing process. It must possess the desired adhesive and cohesive properties to hold the system together. Materials used are: mineral oils, polyisobutylene, and colloidal silica, HPC.

### 2.7 Backing laminates

The primary function of the backing laminate is to provide support. They should be able to prevent drug from leaving the dosage form through top. They must be impermeable to drugs and permeation enhancers. They should a low moisture vapor transmission rate. They must have optimal elasticity, flexibility, and tensile strength. They must be chemically compatible with the drug, enhancer, adhesive and other excipients. They must be relatively inexpensive and must allow printing and adhesive lamination. Type backing membranes are composed of a pigmented layers, an aluminium vapor coated layer, a plastic film (polyethylene, polyvinyl chloride, polyester) and a heat seal layer.

### 2.8 Rate controlling membrane

Rate controlling membranes in transdermal devices govern drug release from the dosage form. Membranes made from natural polymeric material such as chitosan show great promise for use as rate controlling membranes. Recently composite poly-2-hydroxyethyl methacrylate (PHEMA) membranes have been evaluated as rate controlling barriers for transdermal application [20].

### 2.9 Adhesive layer

The fasting of all transdermal devices to the skin using a pressure sensitive adhesive that can be positioned on the face or in the back of device is necessary. It should not cause irritation, sensitization or imbalance in the normal skin flora during its contact with the skin. It should adhere to the skin aggressively. The three major classes of polymers evaluated for potential medical applications in TDDS include:

- Polyisobutylene type pressure sensitive adhesives
- Acrylic type pressure sensitive adhesives
- Silicone type pressure sensitive adhesives

### 2.10 Release liners

The release liner has to be removed before the application of transdermal system, and it prevents the loss of the drug that has migrated into the adhesive layer during storage. It also helps to prevent contamination. It is composed of a base layer, which may be nonocclusive or occlusive, and a release coating layer made of silicon or Teflon. Other materials include polyesters, foil, Mylar and metallized laminates.

### 3.0 Patch design and technology [21]

There are two major types of transdermal delivery system products:

- Thin flexible colored or nearly invisible matrix patches
- Flexible colored or transparent liquid or semisolid filled reservoir patches

### 4.0 Four major transdermal systems [22]

### 4.1 Single layer drug in adhesive

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

### 4.2 Multi layer drug in adhesive

The multi layer drug in adhesive is similar to the single layer drug in adhesive in that the drug is incorporated directly into the adhesive. However, the multi layer encompasses either the addition of a membrane between two distinct drugs in adhesive layers or the addition of multiple drugs in adhesive layers under a single backing film.

### 4.3 Reservoir

The reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.

### 4.4 Matrix

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

### 5.0 Ideal product requirements [23]

- Shelf life up to 2 years
- Small size patch (i.e., less than 40 $cm^2$)
- Convenient dose frequency (i.e., once a day to once a week)
- Cosmetically acceptable (i.e., clear, white color)

- Simple packaging (i.e., minimum number of pouches and steps required to apply the system)
- Easy removal of the release liner (i.e., for children and elderly patients)
- Adequate skin adhesion (i.e., no fall off during the dosing interval and easy removal without skin trauma)
- No residue (i.e., "cold flow" around the edge of the patch in storage or after application to skin or beneath the patch after removal)
- No unacceptable dermal reactions (i.e., contact dermatitis, skin sensitization, photo toxicity, photosensitization, erythema, itching, stinging, burning, etc.)
- Consistent biopharmaceutical performance (i.e., precision of the required pharmacokinetic and pharmacodynamic response between individuals and in the same individuals over time.

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