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"TRANSDERMAL PATCHES"

A systematic review on Transdermal Patches

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Abstract

The advantage of transdermal medication delivery is that it is comparatively painless. The benefits of using the skin as a portal for medication entry include the ease of access, the skin's enormous surface area, systemic access via underlying circulatory and lymphatic networks, and the non-invasiveness of drug administration. Transdermal delivery, often known as medication distribution through the skin for systemic effects, was invented in 1981 when Ciba-Geigy released Transderm V (now sold as Transderm Scop) to treat motion sickness and stop nausea and vomiting. Transdermal medication delivery allows for consistent blood level profiles, regulated drug release into the patient, fewer systemic side effects, and occasionally higher efficacy than other dose forms.

Transdermal drug delivery systems' primary goal is to deliver medications into the bloodstream through the skin at a predefined pace with little inter- and intrapatient variation.

Keywords: Transdermal Patch, Polymer, Non-toxic, Controlled Release

Introduction

Recently, there has been a resurgence in interest in creating new methods for delivering current medicinal compounds. The creation of a novel delivery method for already-existing pharmacological molecules significantly increases patient compliance, overall therapeutic benefit, and the medicine's efficacy and safety performance[1].

Novel delivery systems can effectively deliver drugs with improved bioavailability by using the novel concepts of timed or pulsatile release, or gastro-resistant delivery[2].

when they are properly designed and developed for a particular drug. For example, drugs that partially or completely degrade before reaching the site of action could be effectively delivered.

Drug compositions have improved during the past 20 years, as have new administration methods. We now understand more about how drugs move through tissues. The use of the skin as a channel for systemic drug delivery is relatively new, despite the fact that topical treatments or drug delivery systems have been utilized for centuries to treat localized skin disorders[3].

The advantage of transdermal medication delivery is that it is comparatively painless. The large surface area of the skin, systemic access through underlying circulatory and lymphatic networks, and the noninvasive nature of drug delivery all contribute to its allure as a portal for drug entry. Transdermal delivery, often known as skin absorption, is the practice of administering medications to the body 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].

The transdermal patch has developed into a tested technology over the past 20 years that has a number of important clinical advantages over alternative dosing modalities[6]. It represents a fresh development in the field of controlled delivery systems and has broadened the scope of scientific advancements. Several

significant benefits of transdermal medicine delivery over conventional oral and intravenous delivery methods are offered. Drugs that are supplied via transdermal delivery forgo the risk and inconvenience of intravenous therapy, typically present a lower risk of overdose or underdose, permit simple cessation, and allow for both local and systemic therapeutic benefits.

Transdermal medication delivery allows for a constant blood level profile, regulated drug release into the patient, less systemic side effects, and occasionally higher efficacy than conventional dose forms.[7, 8]. Transdermal drug delivery systems' primary goal is to deliver medications into the bloodstream through the skin at a predefined pace with little inter- and intrapatient variation. Transdermal patches are also widely acknowledged to promote patient compliance due to their ease of application, convenience, painlessness, and multi-day dosage. By 2007 [9], it is anticipated that transdermal medication delivery systems will have grown 12% yearly.

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[12,12,13]

- 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]

In the transdermal medication delivery mechanism, the skin is crucial. In addition to receiving around one third of the blood that circulates through the body and serving as a permeability barrier against the transdermal absorption of various chemical and biological agents, the skin of an average adult body has a surface area of roughly 2 sq m. Transdermal medication delivery systems heavily rely on the top three layers of skin.

Structure of skin

1. **The subcutaneous fat layer**
   - It bridges between the overlying dermis and the underlying body constituents.
   - It is relatively thick in order of several millimetre's.
   - The layer of adipose tissue serves to insulate the body and to provide mechanical protection against physical shock.
   - It also provide supply of high energy molecules
   - Principal blood vessels and nerves are carried to the skin in this layer
2. **The dermis**

   - It contains blood and lymphatic vessels, nerve endings, pilosebaceous units (hair follicles and sebaceous glands) and sweat glands (eccrine and apocrine).
   - It provides physiological support for the epidermis.
   - It is typically 3-5 mm thick and is the major component of human skin.
   - 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).
   - It provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules.

3. **The epidermis**
   - It is 100 µm thick.
   - 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).
   - 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.
   - 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

Factors affecting transdermal permeation [11, 16]

Physicochemical properties of the penetrant molecules

1. **Partition coefficient**

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

2. 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.

3. 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

1. Release characteristics

Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on the following factors:

- Whether the drug molecules are dissolved or suspended in the delivery systems.
- The interfacial partition coefficient of the drug from the delivery system to the skin tissue.
- pH of the vehicle

2. 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.

3. 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

An essential and crucial part of transdermal medication delivery systems is polymer. Rate-controlled medication delivery has been made possible by the use of many kinds of polymeric materials. The physicochemical characteristics of the drug and the polymer employed in the device's construction determine the mechanism of drug release. To be employed in a transdermal system, a polymer must meet the following requirements.

- 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

- 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

To combine the benefits of the various polymers, they have been combined in a variety of ratios. The versatility of drug loading and other device features, such as hydration, degradation rate, and mechanical strength, are advantages of polymer blends.

- 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 substance's melting point should be lower than 200 °F, and the medicine should be somewhat soluble in both water and oil (preferably greater than 1 mg/ml). The reciprocal of the drug's melting point (measured in degrees absolute) and the log solubility of the drug in the membrane's lipid phase both directly relate to the concentration gradient across the membrane. An effort should be made to keep the melting point as low as feasible in order to obtain the finest candidates for TDD.
- 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 substances are regarded as essential components of the majority of transdermal formulations because they increase skin permeability by changing the way that a desired penetrant passes through the skin. It is necessary to lower the skin's barrier to drug diffusion in order to allow drug molecules to pass through skin and sustain therapeutic levels of drug concentration in blood. By interacting with the applied formulation or the skin itself, they can alter the skin's barrier to penetration 17. The penetration enhancer should have the following properties: the ability to work selectively, reversibly, and for a predictable period; it should be pharmacologically inactive; nontoxic; nonallergenic; and nonirritating. There shouldn't be any bodily fluid, electrolyte, or other endogeneous materials.

2.6 Drug reservoir components

It must allow for drug transport at the desired rate and be compatible with the drug. In order to ensure a dependable production process while using an ointment, the drug reservoir needs to have the required viscosity characteristics. To keep the system together, it must have the appropriate adhesive and cohesive qualities. Mineral oils, polyisobutylene, colloidal silica, and HPC are the materials used.

2.7 Backing laminates

The backing laminate's main purpose is to offer support. They ought to be able to stop the medication from coming out the top of the dose form. They must be resistant to medicines and permeation-enhancing substances. They ought to have a slow rate of moisture vapor transport. They need to be as elastic, flexible, and tensile as possible. Chemical compatibility with the medicine, enhancer, adhesive, and other excipients is required. They must support printing and adhesive lamination, and they must be reasonably priced. Type backing membranes are made up of a heat seal layer, a plastic film (polyethylene, polyvinyl chloride, or polyester), a pigmented layer, and an aluminum vapor coated layer.

2.8 Rate controlling membrane

Transdermal devices have membranes that control the rate at which drugs are released from the dosage form. For usage as rate-controlling membranes, natural polymeric materials like chitosan show considerable promise. Recent studies have examined composite poly-2-hydroxyethyl methacrylate (PHEMA) membranes as rate-controlling barriers for transdermal application [20] .

2.9 Adhesive layer

All transdermal devices must be fastened to the skin using a pressure-sensitive adhesive that can be applied to the face or the device's back. During its interaction with the skin, it shouldn't irritate, sensitize, or disturb the normal flora of the skin. It should firmly stick to the skin. The three main polymer classes considered for TDDS's possible medical uses are:

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

2.10 Release liners

Before applying the transdermal system, the release liner must be removed since it stops the loss of the medicine that has migrated into the adhesive layer during storage. Additionally, it aids in avoiding infection. It is made up of a silicon or Teflon release coating layer on top of a base layer that may or may not be occlusive. Polyesters, foil, Mylar, and metallized laminates are examples of additional materials.

3.0 Patch design and technology [21]

There are two major types of transdermal delivery system products:

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

4.0 Four major transdermal systems [22]

1. **Single layer drug in adhes**ive

The inclusion of the medicine directly within the skin-contacting glue is what distinguishes the single layer drug in adhesive system. In this transdermal system design, the adhesive doubles as the basis for the

formulation, holding the medicine and all excipients in one backing film while simultaneously serving as a means of attaching the system to the skin.

2. Multi layer drug in adhesive

Similar to the single layer drug in adhesive, the multi layer drug in adhesive incorporates the drug right into the glue. The term "multi layer" refers to the inclusion of either a membrane between two different pharmaceuticals in adhesive layers or the addition of numerous drugs in adhesive layers underneath a single backing film.

3. Reservoir

The presence of a liquid compartment containing a medication solution or suspension that is separated from the release liner by a semi-permeable membrane and adhesive defines the reservoir transdermal system design. Either a continuous layer between the membrane and the release liner, or a concentric design all around the membrane, can be used to incorporate the adhesive component of the product that is responsible for skin attachment.

4. Matrix

The addition of a semisolid matrix holding a medication solution or suspension that is in direct contact with the release liner characterizes the matrix system design. The element causing skin adherence is built into an overlay and arranges itself in a concentric pattern all around the semisolid matrix.

Ideal product requirements [23]

- Shelf life up to 2 years
- Small size patch (i.e., less than 40 cm2)
- 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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