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Review Article

Transdermal drug delivery system: A review

Zainab E. Jassim*, Halah Talal Sulaiman, Saba Abdul Hadi Jabir

ABSTRACT

Transdermal drug delivery has made an important contribution to medical practice but has yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs through the skin to the systemic circulation. A transdermal patch is an adhesive patch that has a coating of drug; the patch is placed on the skin to deliver particular amount of drug into the systemic circulation over a period of time. The transdermal drug delivery systems (TDDS) review articles provide information regarding the transdermal drug delivery systems and its evaluation process as a ready reference for the research scientist who is involved in TDDS.

KEY WORDS: Permeation enhancers, Polymer matrix, Transdermal drug delivery systems

INTRODUCTION

The most common form of drug delivery is the oral route. In this route of administration has notable advantages and also has significant drawbacks such as first-pass metabolism, drug degradation in gastrointestinal tract due to enzymes, and pH. To overcome these difficulties a novel drug delivery system was developed.[1]

Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin.[2]

Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation. Transdermal patch uses a special membrane to control the release rate at which the liquid drug contained patch reservoir can pass through the skin and into the bloodstream.

Several important advantages of transdermal drug delivery are limitation of hepatic first-pass metabolism, enhancement of therapeutic efficiency, and maintenance of steady plasma level of the drug.[3]

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Advantages[4]

- Transdermal medication delivers a steady infusion of the drug over prolonged period of time, therefore, avoiding adverse side effects and therapeutic failure frequently associated with intermittent dosing can also be avoided.
- Alternative route of administration for the patients who cannot tolerate oral dosage forms such as vomiting patient.
- Increases therapeutic value of many drugs by avoiding specific problems associated with the drug, for example, gastrointestinal irritation, low absorption and drug interaction with food, drink, and other administered drugs.
- Avoidance of first pass metabolism because it bypasses the liver.
- Self administration is possible, and they are non-invasive, avoiding the inconvenience of parenteral therapy.
- They are easily and rapidly identified in emergencies (for example, unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.

Disadvantages[5]

Although transdermal drug delivery systems possess numerous advantages, these also have some disadvantages as follow:

- Difficult to administer the large dose, i.e. more than 10 mg/day.
- Ionic drugs create problems.

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- Drugs having size more than 500 Dalton are not suitable for TDDS.
- Drugs in high concentration may cause skin irritation.
- Difficult to achieve high plasma drug concentration.
- Long-term adherence creates discomfort to patients.
- Drugs with very low or high partition coefficient fail to reach systemic circulation.

ANATOMY AND PHYSIOLOGY OF SKIN[6]

The skin has evolved into an extremely efficient barrier, which prevents both excessive water loss from the body and the ingress of xenobiotics. It enables us to withstand a considerable range of environmental challenges. The reasons for this are manifold and may be summarized simply for the purposes of this chapter. The outer layer of the skin, the stratum corneum, forms the rate-controlling barrier for diffusion for almost all compounds. It is composed of dead, flattened, keratin-rich cells, and the corneocytes. These dense cells are surrounded by a complex mixture of intercellular lipids. They comprise ceramides, free fatty acids, cholesterol, and cholesterol sulfate. Their most important feature is that they are structured into ordered bilayer arrays. The predominant diffusional path for a molecule crossing the stratum corneum appears to be intercellular. The penetration across epithelial borders is a slow process due to the effect of the barrier properties. The skin, in particular, the stratum corneum, possesses a barrier to drug penetration due to its high density (1.4 g/cm^2 in the dry state), its low hydration of 15–20%. The barrier function is further facilitated by the continuous replacement of stratum corneum, thereby limiting the topical and transdermal bioavailability. Therefore, in recent years, numerous studies have been conducted in the area of penetration enhancement. Limitations include slow penetration rates, lack of dosage flexibility and a restricted to relatively low dosage drugs. The structure of skin was shown in Figure 1.

FACTORS THAT INFLUENCE TRANSDERMAL DRUG DELIVERY[1,7]

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.
6. Release linear.
7. Other excipients such as plasticizers and solvent.

Desirable Properties for Transdermal Candidate[8]

Physicochemical properties

1. The drug should have a molecular weight <500 daltons.
2. The drug should have an affinity for both lipophilic and hydrophilic phases.
3. The drug should have a low melting point.

Biological Properties

1. The drug should be potent with a daily dose of the order of a few mg/day.
2. The half-life (t1/2) of the drug should be short.
3. The drug must not induce a cutaneous irritation or allergic response.
4. Drugs which degrade in the G.I. tractor/are inactivated by hepatic first-pass effect are suitable candidates for transdermal delivery.
5. Tolerance to the drug must not develop under the near zero-order release profile of transdermal delivery.
6. Drugs which have to administer for a long period of time or which cause adverse effects to non-target tissues can also be formulated for transdermal delivery.

Polymer Matrix or matrices[9]

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

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

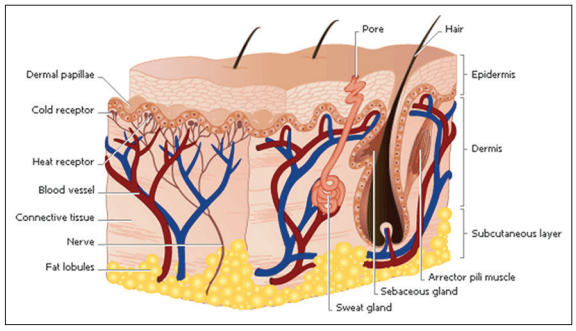

Figure 1: Structure of human skin

b. The polymer should be stable.
c. The polymer should be nontoxic
d. The polymer should be easily of manufactured
e. The polymer should be inexpensive
f. The polymer and its degradation product must be non-toxic or non-antagonistic to the host.
g. Large amounts of the active agent are incorporated into it.

Polymer Used in TDDS[10]

Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of the drug in liquid or solid state synthetic polymer base. In addition, they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status.

- Natural Polymers: For example, cellulose derivatives, gelatin, shellac, waxes, gums, and chitosan.
- Synthetic elastomers: For example, polybutadiene, polyisobutylene, silicon, nitrile, acrylonitrile, neoprene, and butyl rubber.
- Synthetic polymers: For example, polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, and polyvinyl pyrrolidone.

Penetration Enhancers[11]

The penetration enhancers facilitate the drug absorption by altering the barrier properties of stratum corneum. Penetration enhancer must be non-toxic, non-allergic, pharmacologically inert, tasteless, inexpensive, and compatible with drug and excipients.

Skin permeability can be enhanced by the interaction of intercellular lipids causing disruption of their cellular organization and hence increasing their fluidity.

Other Excipients[12]

Adhesives

The fastening of all transdermal devices to the skin has so Farben done by using a pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally. Both adhesive systems should fulfill the following criteria:

1. Should adhere to the skin aggressively, should be easily removed.
2. Should not leave an unwashable residue on the skin.
3. Should not irritate or sensitize the skin. For example Silicones, and polyisobutylene.

Backing membrane

Backing membranes are flexible, and they provide a good bond to the drug reservoir, prevent the drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects the product during use on the skin, for example, metallic plastic. For example, Cellulose derivatives and polypropylene silicon.

Linear

Protect the patch during storage. The linear is removed before use.

Types of Transdermal Patches[13,14]

Single layer drug-in-adhesive

The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. To the outer side of adhesive layer there is lining of temporary liner and a backing.

Multi-layer Drug-in-adhesive

It is similar to the single layer system in the respect that both adhesive layers are also responsible for the releasing of the drug. The multilayer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also surrounded by a temporary liner-layer and a permanent backing [Figure 2].

Reservoir System

In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The rate controlling membrane can be microporous or nonporous only which can release the drug. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix [Figure 2].

Micro Reservoir System

In this type, the drug delivery system is a combination of reservoir and matrix system. The drug reservoir is formed by suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogenously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs [Figure 2]. This thermodynamically unstable dispersion is stabilized quickly by immediately crosslinking the polymer *in situ* using crosslinking agents.

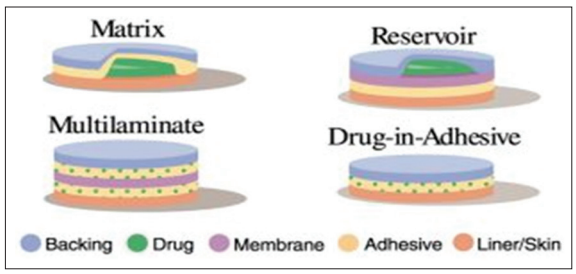

Figure 2: Representative designs of transdermal drug delivery systems

Matrix System

Drug in adhesive system

In this type, the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting (in the case of hot melt adhesive) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose [Figure 2].

Matrix dispersion system

In this type, the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer [Figure 2]. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

Characterization of Transdermal Patches

***Physical evaluation*[15]**

Drug content uniformity

It is determined by taking specific no. of patches and completely dissolving then in specific media. Resulting solution is filtered out through membrane filter. The samples so obtained are analyzed by high-performance liquid chromatography (HPLC) or ultraviolet (UV) spectrophotometer.

Determination of surface pH

Specific number of patches is kept in contact with distilled water and excess water is drained and pH noted by pH meter.

Holding endurance

It is calculated by cutting the patch in specific size using sharp blade. Folding endurance was determined by repeatedly following a small strip of the patch at the same place till it broke. The number of time the patch could be folded at the same place without breaking gave the value of folding endurance.

Thickness of patches

The thickness of transdermal patches is measured using micrometer screw gauge.

Weight of patches

Specific number of patches of each formulation is weighed individually in digital balance and calculated standard deviation.

Moisture content

The prepared patches are cut into strips of specific size. The strips are then weighed individually and kept in a desiccator containing activated silica at 30°C for 12 h. The films are reweighed individually until a constant weight is obtained.

Percentage (%) of moisture content = Loss in wt./ Initial wt. × 100.

Water absorption studies

Transdermal films are into strips of specific size. A strip is weighed and kept in a desiccator at 40°C for 24 h, removed and exposed to 75% RH (Containing saturated solution of sodium chloride) at room temperature weight is taken until a constant weight is obtained.

Water absorption capacity = Increase in weight/Initial weight × 100.

Drug carrier interaction

Thin layer chromatography or HLPC method is used for the drug carrier interaction studies.

Tack properties

Tack is the ability of a polymer to adhere to a substrate with little contact pressure. It is depends on the molecular weight and composition of polymer.

***Tensile strength*[16]**

To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen, and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted.

The tensile strength can be calculated using the following equation.

Tensile strength= F/a.b (1+L/l)

F is the force required to break; a is width of film; b is thickness of film; L is length of film; l is elongation of film at break point.

In vitro Drug Release Studies[17]

Franz diffusion cell: The cell is composed of two compartments: Donor and receptor. The receptor compartment has a volume of 5–12 ml and effective surface area of 1–5 cm^2. The diffusion buffer is continuously stirred at 600 rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds the receptor compartment.

In vitro Drug Permeation Studies[18]

It is done using Franz diffusion cell. Abdominal skin with full thickness of male Wistar rats (200–250 g weight) is act as a semipermeable membrane. The membrane (abdominal skin) was isolated from rat abdomen and it is cleared properly, the tissues and

the blood vessels present over the skin also removed. Then, the skin is equilibrated in medium for 1 h before starting the experiments and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of diffustant. The temperature of the cell was maintained at 32°C + 5°C using thermostatically controlled heater. The isolated rate spin is mounted between the donor receptor compartments of the cell, with the epidermis facing upward into the compartment. The specified volume is taken out from the receptor compartment and it is repeated with fresh medium. Then, the samples are filtered and analyzed by UV (or) HPLC.

Skin Irritation Test[19]

Skin permeation and sensitization testing are performed using healthy rabbits. The formulated patches are applied on the dorsal surface of the skin rabbits. Before affixing the patch the hair is removed from the skin of the rabbits. After 24 h the skin is to be observed.

Stability Studies[20]

It is carried out according to ICH guidelines. The formulated transdermal patches are stored at 40°C ± 0.5°C and 75 ± 5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90, and 180 days and it analyses suitably for drug content.

Advance Development in TDDS[21]

Drug in adhesive technology has become the preferred system for passive transdermal delivery; two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch. A rich area of research over the past 10–15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. These so-called "active" transdermal technologies include Iontophoresis which uses low voltage electrical current to drive charged drugs through the skin.

- Electroporation which uses short electrical pulses of high voltage to create transient aqueous pores in the skin.
- Sonophoresis (which uses low-frequency ultrasonic energy to disrupt the stratum corneum) and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules).
- Even magnetic energy, coined magnetophoresis has been investigated as a means to increase drug flux across the skin.

Another advanced technology is microneedles[22].

Microneedle, a microstructured transdermal system, consists of an array of microstructured projections coated with a drug or vaccine that is applied to the skin to provide intradermal delivery of active agents, which otherwise would not cross the stratum corneum. Microneedles are somewhat like traditional needles, but are fabricated on the micro scale. They are generally 1 μ in diameter and range from 1 to 100 μ in length. Microneedles have been fabricated with various materials such as metals, silicon, silicon dioxide, polymers, glass, and other materials. It is smaller than hypodermic needle, the less it hurts when it pierces skin and offer several advantages when compared to conventional needle technologies. The major advantage of microneedles over traditional needles is, when it is inserted into the skin it does not pass the stratum corneum, which is the outer 10–15 μm of the skin. Conventional needles which do pass this layer of skin may effectively transmit the drug but may lead to infection and pain. As for microneedles they can be fabricated to be long enough to penetrate the stratum corneum, but short enough not to puncture nerve endings. Thus reduces the chances of pain, infection, or injury.

CONCLUSION

Nowadays, the TDDS becoming a most widely used routes of drug administration directly into bloodstream without any pain and without rupturing skin membrane. This article gives valuable information about the formulation and evaluation of transdermal patches. We can overcome the challenges associated with current popular drug delivery by formulating the drug as transdermal patches. Some advanced techniques are also developed in TDDS, so it might be one of the best novel drug delivery system in future.

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