FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES


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ABSTRACT
Transdermal drug delivery system is the prominent route of administration with fewer side effects. Here, the drug is delivered in a discrete dosage form from a skin-sticker patch or other transdermal methods/device by crossing through the skin layers to the systemic circulation. This system has many advantages over conventional administration routes such as intravenous or oral administration for systemic and local drug delivery with simple administration. The technique works as a self-administered, non-invasive, avoid causing liver damage. This review article focuses towards the basic facts about the transdermal drug delivery system including the method of their preparation and some of the recent advancement. The recent Market Strategy of patch System increases Due to its significant advantages. Physicians should improve their knowledge of patch based wound healing products medications (patch) discuss with patients their possible benefits.

KEYWORDS: Transdermal, Patch, Skin, Polymer, Adhesive.

INTRODUCTION
Historically, after the successful launch of scopolamine patch as the first Transdermal Drug Delivery System (TDDS) to treat motion sickness and nausea, nicotine patches have turned out to be a mega medicine after a decade of launch, which has increased the acceptance and importance of transdermal delivery in therapy and prophylactics with greater interest for people in them.[1] The transdermal route for administering a drug also has great potential in the medical device markets for both over-the-counter and prescription drug segments. The current (CA-2019) market of transdermal patches in the US and globally is estimated to be very high at between 1500 million and 4500 million USD (US Dollars), respectively, and is
expected to rise at ~7% annually over the period until 2024, the patch is applied on the superficial layer of skin its gradual release of drug through skin permeation pathway.[2] This route of administration is prominent route for less side effect.

Chronic wound in diabetes undergoes a lifetime risk of developing into diabetic foot ulcer. Oxygen is crucial to wound healing by resulting cell proliferation, migration, and neovascularization.[3] However current oxygen therapies, including hyperbaric oxygen delivery, which is much less effective in penetrating the skin. Therefore, transdermal patch system is wonderful way to treat this type of wounds. Recently the patch dressing is design named algae-gel patch (AGP), that can simply cover the wound and deliver dissolved oxygen into wound bed.[4] Hydrogel beads 1mm in diameter containing living microalgae were filled in the patch, which can consume carbonates (co2- and HCO-3) added in advance to produce O2 and CO2 through respiration and photosynthesis. Hydrophilic (PTFE) membranes with a 0.22-micrometer aperture are used as the lining of AGP, to allow the bidirectional permeation of clean gases and water with bacteria filtration performance. When the affixed to wound, a sealing system is formed between the dressing and the wound owing to the impermeable polyurethane film used as the back liner of AGP the humidity can be regulated by AGP to repair the tissue full time aerobic and wet healing manner.[5]

Skin

The skin is the largest organ of the mammalian body with an estimated total weight of 5 kg, it represents a major physical and immunological protection against injury and infection. It provides a barrier to water loss and pathogens and protects against diverse forms of trauma, including thermal, chemical and ultraviolet radiations. Depending on the anatomical location, the skin can also be accompanied by a variety of ectodermal growths and glands such as nail
and hairs; mammary, sebaceous, and sweat glands; as well as a variety of immune and nerve cells. The hair and stratum corneum serve as a physical barrier. The stratum corneum is an impermeable cover that obstructs the entry of occupying microorganisms and prevents access to potentially toxic chemicals. It reflects and absorbs ultraviolet radiation, preventing damage to the deeper layers of the skin. It produces a complex immunological barrier with components. This immunological barrier protects against potentially harmful chemicals, microorganisms and neoplastic cells.[6]

A. Skin structure
The skin is structured into three layers: the epidermis, dermis, and subcutaneous fat tissue. The epidermis, the outermost layer of the skin, is subdivided into the stratum corneum, stratum lucidum, stratum granulosum, and stratum basales. The stratum corneum contains corneocytes, which are terminally differentiated keratinocytes. These cells are continuously replenished by keratinocytes localized in the stratum basales. The stratum lucidum is a thin and clear layer of dead keratinocytes. Instead of keratin, keratinocytes in the stratum lucidum contain eleidin, a clear intracellular protein, which gives this layer its transparent appearance. The stratum granulosum is a thin layer between stratum lucidum and stratum basales. Keratinocytes in the stratum granulosum contain cysteine and histidine rich granules, which bind keratin filaments together. The stratum basales contain basal keratinocytes, immune cells such as Langerhans cells and T cells, and melanocytes that provide the skin with pigmentation. Beneath the epidermis is the dermis, which is further categorized into the papillary and reticular sub layers. In humans, the papillary dermis forms extensions that reach out to the epidermis and it contains capillaries that facilitate the transport of the nutrients. Reticular dermis contains skin appendages such as hair follicles, sweat glands and sebaceous glands. The reticular dermis is significantly thicker than the papillary dermis due to the dense concentration of collagenous and reticular fibers that are interwoven within this layer. Both dermal layers house fibroblasts, myofibroblasts, and immune cells such as macrophages, lymphocytes, and mast cells. Underlying the dermis is the subcutaneous fat. This layer consists of fibrocytes and adipocytes and is rich in proteoglycans and glycosaminoglycans, which confer mucus like properties to the layer. This layer also produces a variety of mediators such as growth factors, adipokines, and cytokines, and contains multiple immune cells.[7][8]
B. Pathway of skin permeation

In order to simplify the calculation of a compound’s permeation profile through skin, scientists have adopted models for simple diffusion to explain the flux of compounds through SC lipid domains. The majority of molecules that cross the epidermis will travel through the intercellular space between the cells. As a result, a compound's major pathway greatly depends on its partition coefficient. Hydrophilic compounds may preferably partition into the intracellular domains, while lipophilic ones may cross the SC through the intercellular route. When considering polar and nonpolar pathways for penetration, it is usually assumed that polar compounds will penetrate through polar routes, while non-polar compounds will favor lipophilic routes and also, A molecule can enter through the skin via either the trans epidermal pathway (diffusing across the skin layers) or the appendageal pathway (through hair follicles or sweat ducts). The combined flux of these two pathways determines the overall observed flux across the skin.\(^9\)\(^{10}\)

C. Trans epidermal pathway

In the Trans epidermal pathway, the permeant traverses the intracellular / extracellular spaces, from the epidermis to the dermis and hypodermis. The molecule may perform this function intercellularly or transcellularly. The permeant must pass through the alternating layers of cells and extracellular matrix in order to travel the transcellular route. Partitioning and diffusion into alternate hydrophilic and lipophilic domains are required for this. In general, the interiors of cells are more hydrophilic than the extracellular matrix, though the cells and substances that make up the hydrophilic or lipophilic domains differ between skin layers.\(^{11}\) Without passing through the cells, the permeant travels the complicated
extracellular matrix in the intercellular route. Small hydrophilic molecules generally favor the transcellular route over the intercellular route and vice versa for lipophilic molecules.\textsuperscript{[12]}

\textbf{D. Appendageal pathway}

The appendageal (or shunt) pathway encompasses permeation through hair follicles (the trans follicular route) or sweat ducts. The trans follicular route has gained significant research interest in recent years.\textsuperscript{[13]}

\textbf{E. Relative contributions of permeation pathways}

The contribution of the appendageal pathway to percutaneous transport is generally considered secondary, since appendageal features typically account for only around 0.1 % of skin surface area. However, the relative contribution of these pathways will differ based on the formulation and the permeant's physicochemical characteristics. Highly lipophilic drugs may be retained in the lipophilic stratum corneum and resist partitioning into the more hydrophilic viable epidermis. The relative importance of each pathway may also change with time various studies have shown that the appendageal pathway rapidly but transiently predominates before being overtaken by the trans epidermal pathway at steady state.\textsuperscript{[14]}

\textbf{F. Transdermal drug delivery system}

In clinical practice, topical and transdermal drug delivery methods have demonstrated important benefits for medication targeting to the body's action site, which has decreased systemic adverse effects. Here, the drug is delivered in a discrete dosage form from a skin-sticker patch or other transdermal methods/device by crossing through the skin layers to the systemic circulation. For topical drug delivery, a variety of pharmaceuticals including creams, ointments, pastes, and gels have been employed; for transdermal drug delivery, suspensions, emulsions, and even gels have been used. The Iontophoresis, electroporation, sonophoresis, magnetophoretic, dermal patches, nanocarriers, needled and needle-less shots, and injectors are among some of the methods of transdermal delivery. However, more advancements in the TDDS methods and the development of delivery devices over time have made it possible to deliver both lipophilic and hydrophilic, as well as amphiphilic drugs, sometimes with the aid of delivery/permeation enhancers as well as more recent physical techniques of delivery with little harm to soft tissues of the skin.\textsuperscript{[15]}

\textbf{Advantages of TDDS}\textsuperscript{[16]}

1. The TDDS technique helps to decrease the dose.
2. Enhance the therapeutic efficacy and therapeutic value.
3. The technique also avoids therapeutic failures, losses of dose-frequency and chronological dosing’s for the patient.
4. The technique works as a self-administered, non-invasive, painless tool and typically allows less frequent or one-time dosing application in comparison to oral and other routes of administration.
5. It is also, by and large, inexpensive and convenient for patients who want to get rid of remembering to take tablets/pills, and is a relief for their care gives.
6. The estradiol patches, popular in millions of patients worldwide, avoid causing liver damage as compared to its oral formulations.
7. The delivery mode is helpful in maintaining the drug plasma levels due to consistent infusion and bioavailability of the drug.
8. The drug spreads in the systemic flow by escaping the first-pass metabolism in the liver, and no obliteration of the drug takes place.

Types of transdermal patches
There are 4 / Four major transdermal systems

1. Single–layer drug in–adhesive
The drug is also contained in this system's adhesive layer. The adhesive layer in these patches not only holds the various layers and the entire system to the skin together, but it also facilitates the drug release. The adhesive layer is surrounded by a temporary liner and a backing.[17]

![Figure 2: Single–layer drug in–adhesive.](image)

2. Multi-layer drug in adhesive
The multi-layer drug in adhesive is like the single layer system in that both adhesive layers are also responsible for the releasing of the drug. But it is different however that it adds
another layer of drug in – adhesive, usually separated by a membrane. This patch also has a temporary liner-layer and a permanent backing.[18]

Figure 3: -Multi - layer drug in adhesive.

3. Drug reservoir-in-adhesive
Reservoir transdermal system has a separate drug layer. The backing layer serves as a physical barrier between the drug layer and a liquid compartment containing a drug solution or suspension. The rate of release in this system is zero order.[19]

Figure 4: - Drug reservoir-in-adhesive.

4. Drug matrix-in-adhesive:
The drug layer in this matrix system is a semisolid matrix that contains a drug solution or suspension. This patch's drug layer is partially covered by an adhesive layer which surrounds it.[20]

Figure 5: -Drug matrix-in-adhesive.
Component of transdermal patches[21]

A. Drug
For transdermal application of film forming systems, the drugs need to have suitable properties which are independent of the dosage form. For the successful development of a transdermal drug delivery, the following are the desirable properties of a drug.

a) Physicochemical properties[22]
For passive and adhesive transdermal patches must be
i. Non-ionic
ii. A molecular weight of less than 1000 daltons is required.
iii. Melting point less than $200^\circ$C
iv. Must be potent means dose ideally less than 10 mg per day.

b) Biological properties[23]
i. The drug should have a short half-life.
ii. The drug does not show the irritant or allergic response.
iii. Tolerance of drug not be developed.
iv. The drug should be effective at doses of only a few mg per day.

B. Release liner[24]
i. Protects the patch during storage. The liner is removed prior to use.
ii. During storage the patch is covered by a protective liner which removes or discharges fastly before the application of the patch.
iii. It prevents the loss of drug and also protects against the contamination.
iv. It is capable of easily peeled off and does not interact with the functionality of the product.

C. Polymer matrix
The polymer is formulated either as a matrix to control the release of drug from the device.

a) Ideal characters[25]
i. It should be stable, non-reactive with the drug and easily manufactured.
ii. Polymer molecular weight, glass transition temperature and chemical functionality must allow proper diffusion and release of drug.
iii. The polymer and its degradation products must be nontoxic or non-antagonistic to the
iv. The mechanical properties of the polymer should not deteriorate excessively when the large amounts of the active agents are incorporated into it.

b) Polymer\textsuperscript{[26][27]}

The Polymer controls the release of the drug from the device. Possible useful polymers for transdermal devices are,

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Natural Polymers:  \\
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• e.g., Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.  \\
\hline
Synthetic Elastomers:  \\
\hline
• e.g., Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadiene rubber, Neoprene etc.  \\
\hline
Synthetic Polymers:  \\
\hline
• e.g., Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyanide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy etc.  \\
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D. Adhesive

It serves to adhere the components of the patch together along with adhering the patch to the skin.

E.g. - Acrylic, polyisobutylene (PIB), and silicone are the adhesives have many pharmaceutical applications. For applications in which the adhesive, the drug, and perhaps enhancers are compounded, the selection of a PSA is more complex (e.g., a matrix design).\textsuperscript{[28]}

E. Membrane

It controls the release of the drug from the reservoir and multi-layer patches.

Evaluation test of transdermal patches delivery system\textsuperscript{[29]}

a. Drug content

The patch must have a specific portion of the patch dissolve in a specific volume of an appropriate solvent. Then the solution is to be filtered through a filter medium and analyses
the drug content with the suitable method (UV or HPLC technique). Each value represents average of three samples.

b. Weight uniformity
The prepared patches are to be dried at 60°C for 4 hrs before testing. A specified patch area must be divided into various patches and weighed using a digital balance. From the individual weights, the average weight and standard deviation values should be calculated.

c. Skin irritation study
Healthy rabbits can be used for assessing skin sensitivity and irritation (average weight 1.2 to 1.5 kg). Cleaning the rabbit's dorsal surface, shaving off any hair, cleaning the area with rectified spirit, and applying the appropriate formulas to the skin are all necessary steps. After 24 hours, the patch is to be removed, and the skin is to be examined and graded into 5 categories based on the degree of skin damage.

d. Thickness of the patch
Using a digital micrometre, the thickness of the drug-loaded patch is measured at several sites in order to calculate the average thickness and standard deviation for the patch's thickness.

e. Flatness test
Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side and another one from the right side. Each strip's length was measured, and any variations in length due to non-uniform flatness were determined by calculating the percent constriction—0% constriction being equal to 100% flatness.

f. Percentage moisture uptake
In order to maintain 84% RH, the weighted films must be stored in desiccators for 24 hours at room temperature with saturated potassium chloride solutions. The films must be reweighed after 24 hours to calculate the percentage moisture uptake using the formula below.

Percentage moisture uptake = \( \frac{\text{Final Weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \)

\( g. \) Moisture loss
The prepared films are to be weighed individually and to be kept in a desiccator containing calcium chloride at 40°C. After 24 hrs. the films are to be reweighed and determine the percentage of moisture loss from the below formula.

\( \% \) Moisture Loss = \( \frac{\text{Initial wt} - \text{Final wt}/ \text{Final wt}}{\text{Final wt}} \times 100 \)
h. Water Vapor Transmission Rate (WVTR) Studies
Equal-diameter glass vials were used as transmission cells. These transmission cells were washed thoroughly and dried in oven at 100 0C for some time. The cells were filled with approximately 1g of anhydrous calcium chloride, and the corresponding polymer film was fixed over the brim. The cell was accurately weighed and kept in a closed desiccators containing saturated solution of potassium chloride to maintain a relative humidity of 84%. After storage, the cells were removed and weighed. The amount of water vapor transmitted was found using following formula.
Water Vapor Transmission Rate = Final Weight –Initial Weight/ Time X Area

It is expressed as the number of grams of moisture gained/hr/cm.sq

i. Swellability
The patches of 3.14 cm² was weighed and put in a Petri dish containing 10 ml of double distilled water and were allowed to imbibe. At predetermined time intervals, the patch's weight increased until a constant weight was noticed.
The degree of swelling (S) was calculated using the formula

\[ S\% = \frac{W_t - W_0}{W_0} \times 100 \]

Where, S is percent swelling
Wt. is the weight of patch at time t and Wo is the weight of patch at time zero

j. Folding endurance
It is necessary to cut a strip of a particular area evenly and fold it repeatedly until it breaks.
The number of times the film could be fold at the same place without breaking gave the value of the folding endurance.

k. Polariscope examination
The purpose of this test is to use a Polariscope to examine the drug crystals from the patch.
To determine whether the drug is present in the patch in crystalline form or amorphous form, a specific surface area of the object should be kept on the object slide and checked for drug crystals.

l. Percentage elongation break test
By noting the length just before the break point, the percentage elongation break is to be calculated. The formula below can be used to calculate the percentage elongation.
Elongation percentage = \[ \frac{L1-L2}{L2} \times 100 \]

Where, L1 is the final length of each strip and L2 is the initial length of each strip.

**m. Tensile strength**

Using a universal strength testing machine, the tensile strength of the film was determined. The device had a 1 g sensitivity. There were two load cell grips in it. The upper one is movable, while the lower one is fixed. Between these cell grips, a test film (4 x 1 cm2) is fixed, and force is gradually applied until the film breaks.

The tensile strength of the film is taken directly from the dial reading in kg. Tensile strength is expressed as follows

Tensile strength = \[ \frac{\text{Tensile load at break}}{\text{Cross section area}} \] \[^{[30]}\]

**Steps for apply\[^{[31]}\]**

**A. DO**

- Follow the “five rights” of drug administration.
- Ensure discretion, wash your hands, and describe the process
- Don gloves. Remove the old patch if necessary, and dispose of it in accordance with facility policy.
- Choose a new location for the patch on a flat area like the upper arm, back, flank, or chest. Choose a site on your patient's back if he is very young or confused so that he can’t remove the patch. Rotate sites throughout therapy. Make sure the skin is intact, no irritated, and no irradiated. If you can, stay away from hairy areas and trim any extra hair. Use only clear water to clean the area if necessary, before application, and allow the skin to completely dry.
- Peel half of the patch’s protective liner off before removing the patch from its pouch.
- Place the adhesive side on the skin, and then peel off the other half of the liner. Make sure the skin patch adheres to the skin, particularly at the edges, by pressing firmly on it for at least 30 seconds with the palm of your hand.
- Remove your gloves and perform hand hygiene

**B. DON’T**

- Don’t remove a medication patch from its packaging until you are prepared to use it.
- If the seal on a drug patch has been altered, cut, or in any other way damaged, do not use it.
• Avoid using any products that could irritate or change the skin, such as alcohol, soaps, oils, lotions, and other similar substances.
• Avoid using heating pads or other direct external heat sources near the application site.

Applications[^32]

• 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

CONCLUSION

In clinical practice, topical and transdermal drug delivery systems have demonstrated important benefits for drug delivery to the body's action site, which has decreased systemic side effects. Growth of the patch based wound healing products in the market increases because of their significant advantages convenient for patients. And Physicians should improve their knowledge of patch based wound healing products medications (patch) to adequately weigh the clinical implications related to their use, and be able to discuss with patients their possible benefits.

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