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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES: A RECENT ADVANCES

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ABSTRACT

The non-invasive method of delivering medications to the circulatory system via the skin layers is known as transdermal drug delivery. This review is emphasized on recent advances in the formulation and evaluation of transdermal patches which done through extensive literature survey i.e., Springer, Scopus, PubMed and Google Scholar.It includes drug reservoir, membrane, drug, permeation enhancer, pressure-sensitive adhesives, backing films, and plasticizers or solvents. Drug reaches the body through transappendageal route. It has various advantages over other conventional drug delivery pathways i.e., avoiding first-pass metabolism, extended drug release etc. Ionic medications cause issues in the formulation of transdermal patches. The formulated transdermal patches are characterized with various parameters i.e., Pre-formulation study, drug content, weight uniformity, percentage moisture uptake, thickness, flatness, Water Vapor Transmission Rate (WVTR) Studies, moisture loss, swellability, folding and tensile strength, in-vitro drug release, skin irritation, in vitro skin penetration. In conclusion, transdermal patches are very promising in the cure and management of numerous ailments with prolonged drug release and efficacy.

Keywords: Formulation, Evaluation, Transdermal Patches, Transappendageal Route, Review

INTRODUCTION

The non-invasive method of delivering medications to the circulatory system via the skin layers is known as transdermal drug delivery. There are several advantages of TDDS over oral and conventional injectable methods **[1]**. Adherence to medication therapy by patients can be improved with such a basic dose schedule **[2]**. Oral medication administration is the most widely used method **[3]**. Transdermal patches are designed to transfer a medication across the patient's skin in a therapeutically effective manner **[4]**.

Transdermal distribution not only enables controlled, continuous drug delivery, but it also removes the need for pulsed entry into the systemic circulation and permits continuous administration of medications with short half-life. The rate at which the liquid medication in the reservoir may penetrate the skin and reach the bloodstream is controlled by a unique barrier in a transdermal patch. Notable benefits of transdermal drug delivery include lowering hepatic first-pass metabolism, improving therapeutic potential and preserving the drug's constant plasma level **[5][6]**.

A certain quantity of therapy can be administered by means of the transdermal patch that enables drugs to enter the bloodstream through the skin. The patch can minimize systemic side effects and increase a treatment's therapeutic efficacy by controlling the drug's release. This is one benefit of using this route as opposed to oral, intravenous, and intramuscular medication delivery techniques **[7]**.

Materials frequently used to make patches are as below **[8][9]**:

1. **Drug reservoir**

The release of drug from the patch is regulated by the polymer in TDDS. As a result, the polymers employed in TDDS need to be chemically and biocompatible with medications and other system elements like PSA and penetration enhancers. In addition, polymers need to transport drugs reliably and efficiently. Polymers are classified as either natural or synthetic based on their source.

2. **Membrane**

In a multilayer patch, the membrane regulates the discharge of drugs from the reservoir. Drug and/or excipient availability in the skin is managed by the membrane's diffusion characteristics. Polyurethane, silicone rubber, and ethylene vinyl acetate are a few examples. Thus, this membrane controls the drug’s release.

3. **Drug**

The medicine to be utilized also affects the success of TDDS development. Transdermal patches, for instance, provide several benefits for medications i.e., high first-pass metabolism, shorter half-life that

result in non-adherence from frequent dosing.

4. Permeation enhancer

In order to achieve the intended therapeutic level, enhancers work to increase skin permeability. It must be non-toxic/non-allergic, colourless and doorless are the ideal characteristics.

5. Pressure-sensitive adhesives (PSA)

It is a substance that sticks to the substrate-leather in this case-when applied lightly and removes without leaving any residue. Polyacrylate, polyisobutylene etc. are PSA polymers that are frequently utilized in TDDS.

6. Backing film

The flexibility, appearance, and occlusion requirements of backing films are taken into consideration while selecting them. Since prolonged contact b/w the excipient and the backing layer may lead to separation of additives from the backing layer or excipient compatibility should also be considered.

7. Plasticizer/ solvent

Plasticizer i.e., polyethylene glycol, propylene glycol etc. are added to give the transdermal patches its flexibility.

Table 1: Diverse polymers utilized in the formulation of transdermal patch

Category	Polymers
Natural	1. Chitosan 2. Gelatine 3. Sodium alginate 4. Gum Arabic 5. Gum Tragacanth 6. Hyaluronic acid
Semi-synthetic Polymer	1. hydroxypropyl methylcellulose 2. Methylcellulose 3. Carboxymethyl cellulose
Synthetic Polymer	1. Polyvinyl alcohol 2. Polyvinyl chloride 3. Polyhydroxyethyl methacrylate 4. Polyethylene 5. Polypropylene glycol

Transdermal drugs delivery through skin pathways

When drugs are given topically, there are several ways they might enter and permeate the skin. Drugs can enter the body through the stratum corneumor appendages. It is commonly known that the main entry point into the stratum corneum is the intercellular route. The main cause of this is the heavily cross-linked cornified membrane that envelops the keratinocytes. For small hydrophilic molecules like water, transcellular transport cannot be completely ruled out. The appendage route, often referred to as the shunt route, includes the follicular duct and the duct of sweat glands. The contents of the sweat glands (eccrine) are mostly hydrophilic, in contrast to the lipophilic material found in the follicular duct. The sebum discharged into the

follicular duct opening is the main reason for this. Because of its large surface area, it is often accepted that intact stratum corneum serves as the main pathway for passive skin penetration **[10][11]**.

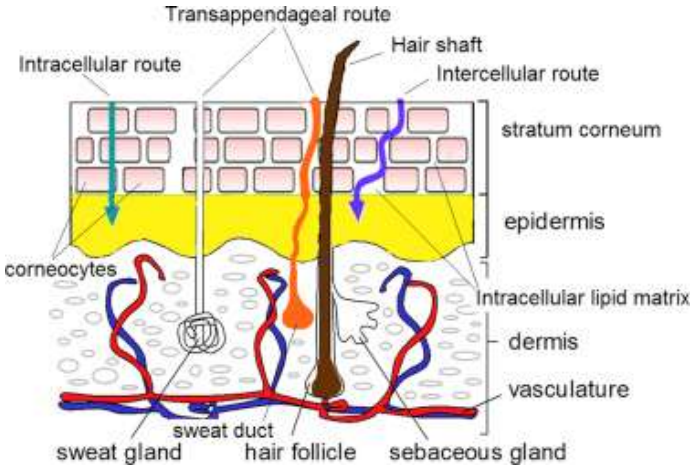

Figure 1: Transdermal drugs delivery through skin pathways

Types

Reservoir or matrix systems are the most common categories for patches that are sold commercially **[12][13]**.

1. The Matrix Method

Medications are evenly distributed in matrix of hydrophilic/ lipophilic polymers. Drug-consisting discs with appropriate thickness & surface area are coated with the drug-consisting polymer.

2. System of Reservoir

In this configuration, drug reservoir links the membrane and the backing layer. Thus, drug is released through the microporous membrane. The medication may exist as a gel, suspension/solution within the reservoir.

3. Micro-Reservoir System

It combines the reservoir with matrix system. In this, drug is dissolved in aqueous medium of lipophilic polymer then solution is spread-out in a lipophilic polymer to form millions of tiny reservoirs.

4. Adhesive Drug System

It is the most fundamental kind of membrane permeability control mechanism. Drug is kept in adhesive layer which joins the numerous layers altogether. The drug is kept on top of backing layer.

Preparation methods

- **Mercury Substrate**

Using this procedure, a predefined volume of polymer solution is utilized to dissolve the adequate amount of drug and plasticizer. Shake the previously mentioned solution for a long time to get a uniform dispersion. It should be set aside until air bubbles have been eliminated before it poured over a glass ring on the mercury surface (petri-dish). Over the petri-dish an inverted funnel kept

which regulates the rate at which the solvent evaporates. A desiccator is required for the storage of the dried films **[14–17]**.

- **Circular Teflon Mould**

This method uses solutions in an organic solvent that have different amounts of polymers. Drug is dissolved in organic solvent, plasticiser added to the drug-polymer solution. After stirring liquid, pour it into circular Teflon mould. It controls the pace of solvent vaporization through an inverted glass funnel placed within the teflonmold. After evaporation the films are kept ina desiccator **[18]**.

- **Glass Substrate method**

Adequateamount of plasticizer ispoured into the polymeric solutions and stirred for 10 minutes. Additionally, it is let aside for a time before being transferred into a clean, dry anumbrapetriplate to eliminate any trapped air. Over the petriplate, lay a glass funnel upside-down to control the pace of solvent evaporation. After being left overnight, the films are kept in desiccator **[19]**.

- **IPM Membranes method**

The drug is suspended in water and propylene glycol that contains carbomer 940 and then stirring the mixture for 12 hours using a magnetic stirrer. Triethanolamine must be added to the dispersion in order to neutralize it and make it viscous. If the medicine has very poor solubility in aqueous solution, a solution gel can be formed using buffer pH 7.4. The IPM membrane will incorporate the gel **[20]**.

- **EVAC Membranes Method**

The drug is suspended in propylene glycol, then added carbopol resin and 5% w/w NaOH. Drug is kept on to backing layer. The boundaries are sealed with heat and a rate-regulating membrane is placed over the gel **[21][22]**.

- **Aluminium-Backed Adhesive Film Method**

Unstable matrices can form in transdermal drug delivery systems when a loading dosage over 10 mg is applied. The aluminum-backed sticky film method is suitable. Chloroform is the preferred solvent for making adhesives and pharmaceuticals since it dissolves most of them. An adhesive material is added once the drug is dissolved in chloroform. Analuminium former is coated with aluminium foil and the ends are kept off using cork blocks **[23][24]**.

- **Asymmetric TPX Membrane Method**

The backing membrane can be made from heat-sealable polyester film of concave diameter of 1 cm. The drug is injected into concave membrane, adhesive is used to seal and then covered with an asymmetric TPX poly (4-methyl-1-pentene) membrane **[25]**.

Table 2: Ideal properties of transdermal patches [9][26]

Parameters	Properties
Dose	<20mg/kg
Half life	<10hrs
Molecular weight	<500D
Partition Coefficient (LogP)	B/w 1-3
Skin permeability coefficient	0.5×10^{3}cm/h
Lipophilicity	<1000
Solubility in water	>1mg/ml
Melting point	<200°C
pH	5-9
Skin Reaction	Non-irritating, non-sensitive

Advantages [27][28]

- First-pass metabolism can be avoided.
- It is possible to extend and forecast the duration of activity.
- The use of TDDS is advised to alleviate the difficulties associated with medication absorption in the gastrointestinal tract.
- If oral medicine is not appropriate, such as in patients who have diarrhea and vomiting, TDDS can be used in its stead.
- It is possible to sustain drug plasma concentration.
- Because TDDS is non-invasive, it can eliminate the inconvenience associated with parenteral treatment.
- It lessens the likelihood of volatility.
- It can be used to medications having a short therapeutic range and half-life.
- In the event of poisoning, drug therapy can be readily discontinued.
- It improves patient compliance by decreasing the frequency of medication delivery.

Disadvantages [29]

- It is challenging to provide a significant dose more than 10 mg each day.
- Ionic medications cause issues.
- Medications larger than 500 Dalton should not be used with TDDS.
- High concentrations of drugs can irritate the skin.
- obtaining a high plasma medication concentration is challenging.
- Patients experience discomfort during long-term adherence.
- Medications with high or very low partition coefficients are unable to enter the bloodstream.

Limitations [30]

- Transdermal patches are unable to provide ionic medications.
- It is impossible to produce high drug levels in the blood or plasma with transdermal patches.

- It is impossible to design patch formulations for medications with enormous molecular sizes.
- Transdermal patches cannot form if the medication or formulation irritates or inflames the skin.

The drawbacks of transdermal patches can be addressed with cutting-edge techniques known as electroporation, ultrasound, and iontophoresis.

Evaluation parameters

Preformulation study

The medication and excipients must get along, and any possible chemical and physical interactions must be identified, in order to produce a stable product. Drug-excipient compatibility, solubility, melting point, absorption maxima are studied in preformulation **[31][32]**.

Drug content

In a certain volume of a suitable solvent, a specific amount of the patch must dissolve. Before the drug content is ascertained using the proper technology (UV or HPLC), the mixture must next be filtered via a filter media. Each result is the mean of three samples **[33][34]**.

Weight uniformity

The generated patches need to be dried at 60°C for four hours before testing. A digital balance must be used to weigh the various areas of a predefined patch area. It is necessary to calculate the average weight and standard deviation of individual weight **[35]**.

Thickness

A digital micrometer is used to measure the drug-loaded patch's thickness at many locations in order to ensure the prepared patch's thickness. Next, the standard deviation and average thickness are computed for the same **[36]**.

Flatness test

In this, 3 longitudinal strips are cut from each film of diverse points including the center, left side, and right side. Each strip's length was measured, and the percentage of constriction (0% constriction = 100% flatness) was used to compute the length variation caused by non-uniformity in flatness **[37]**.

Moisture uptake

The weighted films must be kept in desiccators with saturated potassium chloride solution for a whole day at room temperature in order to maintain 84% relative humidity. To determine the proportion of moisture absorption, the films must be reweighed 24 hours later using the following formula **[38][39]**.

% moisture uptake= Final weight-Initial weight/ Initial weight× 100

Moisture loss

Weigh each produced film independently, then store them in a calcium chloride-filled desiccator at 40°C. To determine the percentage of moisture loss, the films must be reweighed 24 hours later using the following formula **[40]**.

% Moisture loss = Initial weight – Final weight/ Final weight × 100

Folding endurance

Cut an area-specific strip at the same position and fold it evenly and again until it breaks. It counts the no. of times the film is folded in the same direction without breaking **[41]**.

Tensile strength

The device's sensitivity was 1g. It consisted of two load cell grips. The lower one is set, whereas the higher one may be adjusted. Between these cell grips, a 4-by-1-centimeter test film is positioned, and force is gradually applied until the film breaks. It is ascertained by the dial reading in kilograms **[42]**.

Studies on drug release *in vitro*

The drug release from the produced patches can be evaluated using the paddle over disc method. An adhesive is to be used to fix dry films with a given thickness over a glass plate after they have been cut into a specific shape and weighed. After the apparatus was equilibrated to 32±0.5°C, the glass plate was submerged in 500ml of the phosphate buffer (pH 7.4) or dissolving medium. Next, the paddle was moved at a pace of 50 revolutions per minute and positioned 2.5 cm apart from the glass plate. Samples (5 ml) can be taken out at predetermined intervals for up to 24 hours, and high-performance liquid chromatography or a UV spectrophotometer can be used for analysis. The mean value may be computed, and the experiment needs to be run in triplicate **[43][44][45][46]**.

Study on skin irritation

It is necessary to clean the 50 cm2 dorsal area of the rabbit. Before applying representative formulations to the skin, the clean surface should be cleaned with rectified spirit and the hair should be shaved off. The patch should be removed after a full day, and the skin should be evaluated and categorized into five groups based on the extent of skin injury **[47][48]**.

Studies on in vitro skin penetration

A diffusion cell with diffusion medium inside is set on top of a magnetic stirrer with a tiny magnetic bead to ensure consistent diffusant dispersion. A heater with a thermostat was used to keep the cell's temperature at 32±0.5°C. With the epidermis facing upward into the donor compartment, the separated piece of rat skin should be positioned between the diffusion cell's compartments. It is necessary to regularly remove a certain volume of sample from the receptor compartment and replace it with an equivalent volume of fresh medium. Samples must first go through a filtering medium before being subjected to high performance liquid chromatography or spectrophotometric analysis. The flow may be easily calculated as the slope of the curve that plots the amount of medication penetrated (mg cm-2) against time in hours

[49][50] at steady-state values. The flow was divided by the initial drug load (mg cm-2) to get the permeability coefficients.

Stability Studies

Transdermal patches must be kept for 6 months at temp. (40±0.5°C) & RH (75±5%). The drug content of the samples, which were extracted at 0, 30, 60, 90, and 180 days was properly examined **[51][52][53][54]**.

Pharmaceutical applications of transdermal patches

Vaccination

Transdermal patches are being developed by researchers to administer vaccinations via the skin, perhaps providing a less painful and more convenient option than injections. The smallpox vaccination patch that uses microneedles is a prime example. IFN-γ secreting cells significantly increased, and levels were sustained for 12 weeks **[55]**. By employing a transdermal patch, the findings offer a novel method for safer, easier immunization with enhanced immunogenicity, which may allow for greater vaccination coverage **[56]**.

Gene Therapy

Transdermal patches have shown anti-tumor potential involving gene therapy. Thus, a transdermal patch might be a useful treatment option for subcutaneous malignancies **[57]**.

Insulin Delivery

It used to administer insulin into the bloodstream through the skin in order to treat diabetes. Because they are unable to use the insulin their bodies generate efficiently or create enough of it, diabetics may have elevated blood sugar levels. To far, a number of novel methods for delivering insulin have been documented, such as the utilization of liposomes **[58][59]**.

Cardiovascular Diseases

This study sought to ascertain the impact of systemic edema on critically ill patients' skin patch absorption of beta-blockers. Nevertheless, they discovered that after applying the bisoprolol skin patch, systemic edema of the lower limbs had no effect on blood levels or the medication's ability to reduce heart rate **[60][61]**.

Hormonal Deficiencies and Contraception

The first effort at transdermal hormone delivery dates back to 1938, when castrated male guinea pigs were given an ointment containing testosterone. The use of follicle-stimulating hormone and estrone topically to treat amenorrhea has been studied ever since. In 1984, the first reservoir for estradiol was released as a transdermal patch. After then, Menorest® was created with a transdermal matrix delivery technology. A superior pharmacokinetic profile, decreased variation in plasma estradiol and enhanced local tolerability following administration are all provided by the matrix transdermal delivery technology. When Menorest® 50 was in its steady state, its Cmax was 51 pg/mL. Climara, a fresh

iteration of the estradiol transdermal matrix patch, then emerged **[62]**. Early research on the effectiveness of transdermal patches of ethinylestradiol showed that medication compliance was statistically much higher than that of oral tablets **[63][64]**.

Infectious Diseases

New medication delivery techniques are made possible by developments in transdermal drug delivery techniques. Other medications, such vaccinations and antibiotics, are presently being tested for transdermal administration. For transdermal administration methods, tetracyclines have also been included to hydrogel-forming microarray patches. The Cmax of such a method was found to be 7.40μg/mL at 24 hours in a rat in vivo investigation, which contrasted with the oral tetracycline Cmax of 5.86 μg/mL at 1 hour **[65]**.

CONCLUSION

A useful drug delivery method with a number of benefits over other administration methods is transdermal patch technology. To maximize the effectiveness and safety of the delivery method, additional research and development is required.

A transdermal patch offers a number of advantages over conventional medicine delivery, such as enhanced bioavailability, avoiding first-pass metabolism, preventing unpleasant gastrointestinal side effects, drug retention in plasma, and improved patient compliance. The suitability of a patch for transdermal distribution is determined by its characteristics, in vitro release and penetration experiments, and the patch's composition of various polymers. The development of intelligent, high-loading/release, biodegradable, and 3D-printed patches is only one example of the notable advancements in transdermal patch technology in recent years. In conclusion, transdermal patches are very promising in the cure and management of numerous ailments with prolonged drug release and efficacy.

CONFLICT OF INTEREST

None.

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