

Transdermal Patches: State of the Art

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ABSTRACT

There is a considerable increase in preference for use of transdermal patches over conventional dosage forms owing to the advantages it possesses over them. Transdermal delivery of drugs has undergone rapid advancements through techniques like electroporation, microneedles, iontophoresis etc. This review is aimed at providing deep insight into transdermal technology and its types. An overview of the present market size of transdermal patches along with future prospects has been discussed. Transdermal products being manufactured by Indian pharmaceuticals also has been presented. Various components of transdermal patches being explored have been elaborated. After studying this review, it could be concluded that there are huge prospects for transdermal systems, and research aimed at the delivery of sparingly soluble drugs needs to be done to overcome limitations.

Keywords: Controlled release, Novel drug delivery system, Patch, Transdermal.

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INTRODUCTION

For thousands of years, the oral route of drug delivery has remained the route of choice for drug delivery to systemic circulation for therapeutic effectiveness due to the well-known advantages of patient compliance and ease of self-administration.^{1,2} But conventional dosage forms suffer certain limitations like non-specificity and inactivation while passing through the gastrointestinal tract and inability to provide the sustained effect.³ The transdermal route of drug delivery hence appears to be a good alternative approach instead of an oral route as it eliminates chances of drug loss by hepatic metabolism and even provides better patient compliance as opposed to other routes like parenteral route.^{4,5}

The topical route is not new to human beings as it has been in constant use for cosmetics and topical medications, but the word transdermal appeared in 1944 when Webster introduced it as a route of drug delivery.⁶ A transdermal patch is a self-contained dosage that is applied to intact skin and provides drug in a controlled manner.⁷

This review provides an insight into concepts of the transdermal drug delivery system. Recent advancements and marketed formulations of transdermal products also have been presented in this paper. Various components of the transdermal formulation, which are currently being used in innovation and marketed formulations have also been discussed along with evaluation parameters of transdermal formulations.

TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

It appears to be an effective mode of drug delivery to systemic circulation without pain by applying it on to intact skin. There has been a brisk increase in interest and research in the field of transdermal delivery due to following advantages:^{8,9}

- Minimization of fluctuation in peak plasma concentration as in case of the oral and parenteral route,
- No issue of hepatic first-pass metabolism (presystemic metabolism),
- Reduced dosing frequency and a dose of drug,
- Sustained effect,
- Bioavailability improvement

Owing to these benefits, TDDS market is expected to expand by 2025 up to \$95.57 billion.¹⁰ In 1979, scopolamine TDDS became the first of its kind to get United States Food and Drug Administration (USFDA) approval followed by nicotine patches in 1984.¹¹ But currently, only seventeen drug molecules have been approved by USFDA.¹²

However, transdermal delivery suffers some shortcomings like:

- It may cause irritation to the skin in certain cases,
- TDDS allows permeation of drugs having molecular weight 150–500 Daltons across skin,
- TDDS allows permeation of drug molecules with oil/water partition coefficient in the range of 10-1000,

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- It is suitable for drugs with a melting point less than 200°C,
- It is good for drugs with aqueous solubility greater than 1 mg/mL, and
- It is best suited for drugs with daily deliverable dose less than 10mg/mL.¹³

Still, the TDDS approach appears lucrative as advantages outweigh the shortcomings as even these limitations could be overcome by using advanced approaches of transdermal delivery like prodrug approach, iontophoresis, electroporation, microneedle approach.¹⁴⁻¹⁷

In 2008, Sparsha Pharma International Pvt. Ltd. became the first transdermal company in India to carry out research and development, and Manufacturing of transdermal products for global markets.¹⁸⁻²⁰ Table 1 shows some transdermal patch products being currently manufactured by Indian pharmaceuticals.

TYPES OF TRANSDERMAL DEVICES

Drug-in-adhesive patches

Such a dosage form consists of polymer with adhesive characteristics and serves as a depot of drug solution. Backing laminate, however, is placed above polymer lining that serves as a support for drug depot.²¹

Vapor Transdermal patches:

They are comprised of layers of polymer with adhesive properties having vapor release characters so that vapors are released upon exposure. Usually, such patches contain volatile oils.²² painless and non-invasive, to avoid gastro intestinal (GI

Membrane moderated transdermal reservoir patches:

In these types of systems, the release of drugs is dependent on the drug release rate controlling a porous polymeric membrane. A typical membrane moderated transdermal drug delivery device has a drug reservoir embedded in porous polymer and impermeable metallic or plastic layer acting as a backing membrane.²³

Microreservoir transdermal systems

Such devices employ principles of both matrix and reservoir type systems. The reservoir of drugs prepared by dissolving a drug in hydrophilic polymer solution is uniformly dispersed in a lipophilic polymer. The use of high shear force leads to the formation of many microscopic particles. The drug is released via zero-order kinetics in such systems providing uniform plasma drug concentrations.²⁴

Matrix system: Drug-in-adhesive

In such types of systems, the drug reservoir is made to be distributed evenly on polymer with adhesive characteristics. Such a drug-polymer matrix is then laid over impermeable backing membrane by solvent evaporation technique.²⁵

COMPONENTS OF TRANSDERMAL DRUG DELIVERY DEVICE

Polymer Matrix

Polymers that are used for transdermal drug delivery must possess following characteristics:

- Molecular mass, physical and chemical properties of polymer should be such that it allows passage of medicament at the required rate.
- Polymer should be chemically inert.
- Polymer must not decompose during shelf life of device.
- Polymer should allow the incorporation of a large amount of drugs into it.
- It should be cost effective²⁶

Most commonly used polymers include polypropylene, cellulose acetate nitrate, hydroxyl propyl methyl cellulose, eudragit, chitosan, alginate

Chitosan

It is a natural biodegradable polymer which is obtained by modification of chitin and can serve as polymer for transdermal patch preparation. Limitation of chitosan as a polymer for transdermal drug delivery device is that a high crosslinking ratio of a polymer may lead to decreased swelling characteristics and brittleness of the preparation.²⁷ Research-based on chitosan-based patch have been well documented.^{28,29}

Alginate

Alginate is a semi-synthetic polymer that can be used in transdermal drug delivery for matrix-type patches as illustrated for the first time by Demir and coworkers.³⁰

To overcome limitation of alginate to fabricate matrix type patches, a combination of alginate along with Polyvinyl alcohol or chitosan has also been studied.^{31,32}

Cellulose

Cellulose is a natural biopolymer found abundantly in nature, which is also biocompatible with most of the drugs. Past literature reports the application of bacterial cellulose for

Table 1: Marketed transdermal formulations in India

Drug	Strength	Company	Source
Fentanyl	12.5, 25, 50, 75 & 100 mcg/hr	Sparsha Pharma International Pvt. Ltd.	19
Buprenorphine	5, 10 & 20 mcg/hr		
Rivastigmine	9, 18, 27 & 36 mg		
Diclofenac diethylaminE	100 mg		
Tulobuterol	0.5, 1.0 & 2.0 mg		
Nicotine	21mg, 14mg and 7 mg	Rusan Pharma	20
Fentanyl	12.5 mg		

transdermal delivery.^{33,34} It has been reported that cellulose could enhance transdermal targeting.³⁵ Many researchers have successfully reported the use of semi-synthetic or modified cellulose for transdermal drug delivery. Use of cellulose acetate as transdermal polymer has been documented.³⁶ Ethyl cellulose and hydroxyl propyl methylcellulose also have been fabricated into transdermal patches.³⁷⁻⁴¹

Hyaluronic Acid

It is a biocompatible polymer that has been reported for the preparation of hydrogel patches.⁴² Hyaluronic acid-human growth hormone conjugate has been prepared for the transdermal delivery of drugs.⁴³

Polycaprolactone

Polycaprolactone is a biodegradable aliphatic polyester that is being used in transdermal devices due to its favorable rheological properties.⁴⁴ Polycaprolactone nanofiber assisted transdermal drug delivery has been documented in the literature.^{45,46} Recently research work for transdermal microneedle fabrication using polycaprolactone is gaining interest.⁴⁷

Polyvinyl Alcohol

Polyvinyl alcohol is another option for transdermal delivery of drugs owing to its favorable properties and non-toxicity.⁴⁸ Polyvinyl alcohol has been blended with different other biopolymers to attain desired permeation characteristics.⁴⁹⁻⁵¹ Poly vinyl alcohol even has been employed for the fabrication of the microneedle transdermal system.⁵²

Polyvinylpyrrolidone

It is a non-antigenic as well as a biocompatible synthetic polymer. It finds most of its applications in wound healing and hydrogel preparations.⁵³ Mixture of Polyvinyl alcohol and polyvinyl pyrrolidone have been reported for transdermal drug delivery.⁵⁴

Acrylic, Acrylate, Methacrylic, and Acrylamide based Polymers

These polymers are mostly being used for marketed transdermal devices and transdermal contraceptive device being a common example.⁵⁵ Acrylic patches are having hydroxyl groups shown increased flux as well as drug content.⁵⁶ It has been reported that Eudragit® RL exhibits good overall properties in a transdermal patch when tested in combination with tributyl citrate.⁵⁷

Pressure-sensitive Adhesives

Adhesive properties of the transdermal device play a vital role in the effectiveness of the delivery system. This component is responsible for bringing drugs into intimate contact with skin which occurs due to attractive interactions between adhesive and surface of skin.⁵⁸

Rate Controlling Membrane

This component of the transdermal system is meant for release of drug at a constant rate by varying the width and composition of polymer e.g., silicone rubber, ethylene vinyl acetate, polyurethane etc.⁵⁹

Release Liner

This component of the transdermal patch is intended to be taken off before applying it on to skin. Fluoropolymers and linear fluoroacrylates are often used as release liners.⁶⁰

Backing Laminate

This component is commonly composed of inert substance so that it doesn't interfere with the process of drug release and at the same time allowing passage of moisture and oxygen e.g. polyisobutylene, ethyl vinyl alcohol, etc.²²

Penetration Enhancers

These are substances that alter stratum corneum so that drugs could easily cross this barrier and get into blood circulation. Some compounds react with stratum corneum, while some of them enhance permeation characters of lipids in cells of stratum corneum. Commonly used permeation enhancers include terpenes, sulphoxide, fatty alcohols, surfactants, urea, terpenes.^{61,62}

Other Excipients

Except for the above-mentioned components, some other excipients are also included, like solvents for drug dispersion, eg. Methanol, dichloromethane, water, and acetone etc. Also, plasticizers are often added to enhance plasticity when used in a concentration of 5–20 %.^{63,64}

CHARACTERIZATION OF TRANSDERMAL PATCHES

Various tests have been reported in the literature with aim of evaluating transdermal patches as discussed below.

Drug-polymer Interaction studies

This parameter is used to evaluate any possible interaction between drug and polymer proposed to be used for transdermal drug delivery device preparation. This test uses differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) techniques.⁶⁵

Patch Thickness

This patch is determined to maintain uniformity in transdermal formulations. It is determined by measuring the thickness of patch at three places using micrometer.⁶⁶

Uniformity of Patch Weight

It is calculated by weighing ten different patches individually, and then the average weight and standard deviation were calculated. The acceptance criteria is that none of the weight should show a big deviation from mean weight.⁶⁷

Folding Endurance

It is determined to estimate the strength and flexibility of the patch. It is number of times a patch can be folded at any particular point without being broken.⁶⁸

Moisture Content

This parameter can be calculated by finding out the loss of moisture from the transdermal patch after keeping in a desiccator. The patch is weighed and kept in desiccators for 24 hours with Calcium chloride following which the final

weight of the transdermal patch is determined. It is expressed in percent terms.³⁶

$$\% \text{ Moisture content} = (\text{initial mass} - \text{final mass}) / \text{Initial mass} \times 100$$

Moisture uptake

This can be measured as the increase in weight of patch upon storage. It can be determined by initially weighing patch and keeping it in desiccator along Potassium chloride for one day with objective of maintaining 84 % relative humidity and then again weighing it for calculation using following equation:⁶⁹

$$\% \text{ Moisture uptake} = (\text{Final weight} - \text{initial weight}) / \text{Initial weight} \times 100$$

Evaluation of Water Vapor Permeability

It is measured using oven using the following equation:⁷

$$\text{Water vapor permeability} = \frac{\text{Amount of water vapor permeated in a patch (g/m}^2\text{/ 24 hr)}}{\text{Exposed surface area on patch (m}^2\text{)}}$$

Drug Content

To determine drug content, the transdermal patch is dissolved in solvent after breaking it and amount of drug present in filtrate is determined using specific analytical method.⁷⁰

Flatness Test

To determine this, a patch is cut into three longitudinal sections viz. from the centre, left and right and then the length is measured which will give flatness in terms of constriction as follows:⁷¹

$$\% \text{ Constriction} = (\text{Initial strip length} - \text{Final strip length}) \times 100$$

Stability Studies

To assure the stability, the patch is stored at 40 ± 0.5 °C with a relative humidity of $75 \pm 5\%$. During storage samples at an interval of 0, 30, 60, 90, and 180 days are analyzed for drug content to give idea about product stability.⁷²

Adhesiveness of Patch

It can be determined by tack test and peel force test.

Tack Test

Tack means property of substance or polymer to adhere to the surface upon application of some force. This property is a function of molecular mass and composition of polymer.⁷³

Peel Adhesion Test

This is expressed as the force required to take off an adhesive polymer from the substance. For measuring this, tape is put on backing layer, and the force needed peel off the tape upon pulling at 180° is noted.⁷⁴

Tensile Strength

It is determined by tensiometer and measuring the weight needed to break the patch. Average of three measurements is taken as tensile strength.⁷⁵

Swellability

This property of transdermal patch is measured by applying a known weight in a Petri plate with 50 mL phosphate buffer pH 7.4. Absorption of the sample occurs in time about 30

minutes. Change in weight of patch is expressed in terms of swellability:⁷⁶

$$\text{Swelling \%} = \frac{\text{weight of patch after time t} - \text{Weight of a patch at time zero}}{\text{Weight of patch at time zero}}$$

In vitro Drug Release

In vitro study of the release of drugs from transdermal is done by USP apparatus V (paddle over disc) or USP apparatus VII (reciprocating disc device). Also, diffusion cells like Franz diffusion cells are popularly used for in vitro drug release studies.⁷⁷

Mathematical models that describe the kinetics of drug release from a transdermal patch include Higuchi, first order, zero-order, and Peppas and Korsmeyer models are various models are found to express kinetics of drug release.⁷⁸

Ex vivo Permeation Studies

It is carried out in Franz diffusion cell with donor and acceptor compartments separated by animal biological membranes like pig ear skin or rat's skin usually having phosphate buffer pH 7.4 in acceptor compartment maintained at an ambient temperature of 37 ± 0.5 °C with appropriate provision for magnetic stirring.⁷⁹

Skin Irritancy Test

To evaluate possible irritation due to transdermal preparations, the patch is applied on a shaven skin of rat for 24 hours. Any possible change is reported in terms of edema and erythema.⁸⁰

CONCLUSION AND FUTURE PROSPECTS

From the above literature, it can be concluded that advantages of transdermal delivery makes it much more lucrative route of drug delivery, which has the potential to replace many conventional delivery systems wherever possible as is being explored. At the same time, its limitation to deliver big molecules needs further research and development. The market size of indicates that there is a vast scope for the transdermal market. The study components of transdermal patches reveal that although there are many polymers, penetration enhancers, and solvents available, an appropriate choice should be made during the optimization of these variables during formulation.

This study gives an idea about future prospects. Research can be carried out for transdermal delivery of molecules with low water solubility.

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