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TRANSDERMAL PATCHES IN NOVEL DRUG DELIVERY SYSTEM

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Abstract

The number of medications and the ways in which they can be administered have expanded dramatically over the years. One such advance has been the development of transdermal dermal patches in drug delivery. Skin is an effective medium from which absorption of the drug takes place and enters the circulatory system. The transdermal route has been recognized as one of the highly potential routes of systemic drug delivery and provides the advantage of avoidance of the first-pass effect, ease of use and withdrawal (in case of side effects and overdose), and better patient compliance. Various types of transdermal patches are used to incorporate the active ingredients into the circulatory system via skin. Transdermal dosage forms, though a costly alternative to conventional formulations, are becoming popular because of their unique advantages. Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal drug delivery system. Development of controlled release transdermal dosage form is a complex process involving extensive efforts. Transdermal drug delivery system is mainly fabricated for pain relief, inflammation, hormone replacement therapy, hypertension and smoking cessation. The objectives of present article were to focus on basic components of transdermal drug delivery system, importance, application and evaluation of transdermal patches.

Key words: Transdermal drug delivery system, Permeation enhancers, Design of transdermal patches, Evaluation of transdermal system.

Introduction

The most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks - namely poor bioavailability due to hepatic first pass metabolism and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. There is a need for the development of new drug delivery system to overcome such difficulties, which will improve the therapeutic efficacy and safety of drugs by more precise (i.e., site specific), spatial and temporal placement within the body thereby reducing both the size and number of doses⁽¹⁾. One of the most often utilized methods has been transdermal drug delivery system - meaning transport of therapeutic substances through the skin for systemic effect and local benefit. Closely related is percutaneous delivery, which is transport into target tissues, with an attempt to avoid systemic effects⁽²⁾. There are two important layers in skin Dermis and Epidermis. The outermost layer is Epidermis, is approximately 100 to 150 micrometers thick, has no blood flow and includes a layer within it known as the stratum corneum. This is the layer most important to transdermal delivery as its composition allows it to keep water within the body and foreign substances out. Beneath the epidermis, dermis contains the system of capillaries that transport blood throughout the body. The drug has to penetrate the stratum corneum to reach the blood stream. A process known as passive diffusion, which occurs too slowly for practical use, is the only means to transfer normal drugs across this layer. The transdermal drug delivery system is the method to circumvent to fabricate the drugs be both water-soluble and lipid soluble. The best mixture for transport is about fifty percent of the drug being each. This is because "Lipid-soluble substances readily pass through the intercellular lipid bi-layers of the cell membranes whereas water-soluble drugs are able to pass through aqueous pores and channel of the skin". Much more rapid and useful drug delivery is possible using drugs engineered in such manner⁽³⁾.

The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979, which administered scopolamine for motion sickness.

Advantages of Transdermal dermal drug delivery system

1. Longer duration of action resulting in a reduction in dosing frequency.
2. Increased convenience to administer drugs which would otherwise require frequent dosing.
3. Bypassing first pass hepatic metabolism and improved bioavailability.
4. More uniform plasma levels.
5. Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.
6. Flexibility of terminating the drug administration by simply removing the patch from the skin.
7. Improved patient compliance and comfort via non-invasive, painless and simple application.

Disadvantages of transdermal drug delivery system

1. Possibility that a local irritation at the site of application.
2. Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.

Basic components of transdermal drug delivery system (TDDS)

1. Polymer matrix.
2. Drug.
3. Permeation enhancers.
4. Pressure sensitive adhesive (PSA).
5. Backing laminate.
6. Release liner.
7. Other excipients like plasticizers and solvents.

1. Polymer matrix

Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status⁽⁴⁾.

The polymers utilized for TDDS can be classified as:

- **Natural polymers:** e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.
- **Synthetic elastomers:** e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, acrylonitrile, neoprene, butyl rubber etc.
- **Synthetic polymers:** e.g. polyvinylalcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.

2. Drug

Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non-compliance due to frequent dosing. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be non ionic, of low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1-3), a low melting point (less than 200°C) and are potent (dose in mg per day)⁽⁵⁾.

3. Permeation Enhancers

These are the chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate⁽⁶⁾. Permeation enhancers interact with structural components of stratum corneum i.e., proteins or lipids. E.g. oxazolidinones, urea, pyrrolidones, alcohol, glycol, glycerides, sulfoxides, ulfoxides etc.

4. Pressure sensitive adhesives (PSA)

A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tacky, and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue. Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDS⁽⁷⁾.

5. Backing Laminate

While designing a backing layer, the consideration of chemical resistance of the material is most important. An overemphasis on the chemical resistance may lead to stiffness and high occlusivity to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear⁽⁸⁾. E.g. polyethylene and polyester films.

6. Release Liner

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. E.g. paper fabric, polyethylene, polyvinylchloride, silicon or teflon, polyester foil and metalized laminates⁽⁹⁾.

7. Other excipients

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylphthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch⁽¹⁰⁾.

METHOD OF PREPARATION OF TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

Two methods are mainly used to prepare transdermal patches include

Solvent casting

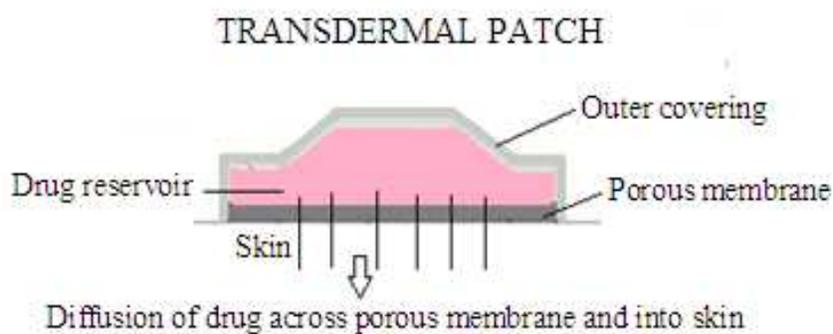
In this, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation, a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry.

Direct milling

In this, patches are manufactured without the use of solvents (solvent-free). Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described.

While there are only minor or even no differences in patch performance between patches fabricated by two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.

Figure 1: Release of drug in transdermal patches.



The application of the transdermal patch and the flow of the active drug from the patch to the circulatory system via skin occur through various mechanism consists of

1. Diffusion
2. Dissolution
3. Erosion

4. Osmotic pressure etc.

Types of transdermal patches

Four Major Transdermal Systems

1. Single-layer drug-in-adhesive
2. Multi-layer drug-in-adhesive
3. Drug reservoir-in-adhesive
4. Drug matrix-in-adhesive

Factors affecting transdermal bioavailability⁽¹¹⁾

Two major factors affect the bioavailability of the drug via transdermal routes:

- Physiological factors
- Formulation factors

Physiological factors include

(1) Stratum corneum layer of the skin; (2) Anatomic site of application on the body; (3) Skin condition and disease; (4) Age of the patient; (5) Skin metabolism; (6) Desquamation (peeling or flaking of the surface of the skin); (7) Skin irritation and sensitization; (8) Race.

Formulation factors include

(1) Physico-chemical properties of drug; (2) Vehicles and membrane used; (3) Penetration enhancers used; (4) Method of application; (5) Device used.

Evaluation of transdermal patches

These studies are predictive of transdermal dosage forms and can be classified into following types

- Physicochemical evaluation
- In-vitro evaluation
- In-vivo evaluation
- Stability studies

Upon the success of physicochemical and in-vitro studies, in-vivo evaluations and stability studies may be conducted.

Physicochemical evaluation

Thickness: The thickness of transdermal film is determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film⁽¹²⁾.

Uniformity of weight: Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution⁽¹³⁾.

Content uniformity test: 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Moisture content: The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percentage of moisture content is calculated using following formula.

$$\% \text{ Moisture content} = \frac{(\text{Initial weight} - \text{Final weight}) \times 100}{\text{Final weight}}$$

Moisture Uptake: Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. The percentage of moisture uptake is calculated as given below.

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

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percentage of constriction. Zero percent constriction is equivalent to cent percent flatness.

$$\% \text{ Constriction} = \frac{(l_1 - l_2) \times 100}{l_2}$$

Where,

l_2 = Final length of each strip

l_1 = Initial length of each strip

Folding Endurance: Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value⁽¹⁴⁾.

Tensile Strength: 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⁽¹⁵⁾.

$$\text{Tensile strength} = F/a.b (1+L/l)$$

Where,

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 another study, Tensile strength of the film is determined with the help of texture analyzer. The force and elongation were measured when the films break.

Microscopic studies: Distribution of drug and polymer in the film can be studied using scanning electron microscope.

Adhesive studies: The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesive properties of a TDDS can be characterized by considering the following factors

- **Peel Adhesion properties:** The force required to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a single coated tape, applied to substrate at 180° angle. The test is passed if there is no residue on the substrate.
- **Tack properties:** The ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer.

In-vitro evaluation

In-vitro release studies⁽¹⁶⁾

There are various methods available for determination of drug release rate of TDDS.

- **The Paddle over Disc:** This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C
- **The Cylinder modified USP Basket:** This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32 ±5°C.

- *The reciprocating disc:* In this method patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction cell method may be used.
- *Diffusion Cells e.g. Franz Diffusion Cell and its modification Keshary- Chien Cell:* In Diffusion Cell method transdermal system is placed in between receptor and donor compartment of the diffusion cell. The transdermal system faces the receptor compartment in which receptor fluid *i.e.*, buffer is placed. The agitation speed and temperature are kept constant. The whole assembly is kept on magnetic stirrer and solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals, the receptor fluid is removed for analysis and is replaced with an equal volume of fresh receptor fluid. The concentration of drug is determined spectrophotometrically.

The pH of the dissolution medium is 5 to 6, temperature is typically set at 32°C (reflecting physiological skin conditions), 100 rpm a typical agitation rate and also allows for testing an aliquot patch section. The latter may be an appropriate means of attaining sink conditions, provided that cutting a piece of the patch is validated to have no impact on the release mechanism.

In- vitro permeation studies

Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as Franz diffusion cell or Keshary-Chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophilic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount of drug permeated per centimeter square at each time interval is calculated. Design of system, patch size, surface area of skin, thickness of

skin and temperature etc. are some variables that may affect the release of drug. So permeation study involves preparation of skin, mounting of skin on permeation cell, setting of experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux *i.e.*, drug permeated per cm² per second.

In-vivo evaluation

In-vivo studies⁽¹⁷⁾

In- vivo evaluations are the true depiction of the drug performance. *In vivo* evaluation of TDDS can be carried out using Animal models & Human volunteers.

Animal models: Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Rhesus monkey is one of the most reliable models for *in vivo* evaluation of transdermal drug delivery in man.

Skin irritation studies: White albino rats, mice or white rabbits are used to study any hypersensitivity reaction on the skin. Example: Mutalik and Udupa (2005) carried out skin irritation test using mice.

Human models: The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc.

Stability studies

The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulations. The transdermal formulations are subjected to stability studies as per ICH guidelines.

Table-1: Marketed products of transdermal patches.

Brand Name	Drug	Manufacturer	Indications
Nicotinell	Nicotine	Novartis	Pharmacological smoking cessation
Matrifen	Fentanyl	Nycomed	Pain relief patch
Ortho Evra	Norelgestromin/ Ethinylestradiol	ORTHO-McNEIL	Postmenstrual syndrome
NuPatch 100	Diclofenac diethylamine	Zydus Cadila	Anti -inflammatory
Neupro	Rigotine	UCB and Schwarz Pharma	Early-stage idiopathic Parkinson's disease
Alora	Estradiol	TheraTech/ Proctol andGamble	Postmenstrual syndrome
Nicoderm	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Estraderm	Estradiol	Alza/Norvatis	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals	Postmenstrual syndrome
Androderm	Testosterone	TheraTech/	Hypogonadism in males

		GlaxoSmithKline	
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Transderm- Scop	Scopolamine	Alza/Norvatis	Motion sickness
Nuvelle TS	Estrogen/ Progesterone	Ethical Holdings/ Schering	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Catapres TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension
Fem Patch	Estradiol	Parke-Davis	Postmenstrual syndrome
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Climaderm	Estradiol	Ethical Holdings/ Wyeth- Ayerest	Postmenstrual syndrome
Duragesic	Fentanyl	Alza/Janssen Pharmaceutical	Moderate/severe pain
Estraderm	Estradiol	Alza/Norvatis	Postmenstrual syndrome

Fematrix	Estrogen	Ethical Holdings/ Solvay Healthcare Ltd.	Postmenstrual syndrome
Transderm- Nitro	Nitroglycerin	Alza/Norvatis	Angina pectoris
Testoderm TTS	Testosterone	Alza	Hypogonadism in males
Oxytrol	oxybutynin	Watson Pharma	Overactive bladder
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation

LATEST RESEARCH DONE IN THE FIELD OF TRANSDERMAL PATCHES ARE STATED BELOW

1. Pain-free diabetic monitoring using transdermal patches.
2. Testosterone transdermal patch system in young women with spontaneous premature ovarian failure.
3. Transdermal patch of oxybutynin used in overactive bladder.
4. Rotigotine transdermal patch is used for symptom control in Parkinson's disease.
5. Rivastigmine is a cholinesterase inhibitor approved in the United States for the symptomatic treatment of mild-to-moderate Alzheimer's disease and Parkinson's disease dementia.
6. Postmenopausal hormone therapy using oestrogen as transdermal patches.
7. Controlled-release products in human medicine (selected) for nicotine patches drug- in-adhesive prototype for smoking cessation therapy.
8. Transdermal nitroglycerin for vasospasm due to sub-arachnoid hemorrhage.
9. Transdermal preparation – Maxiderm for erectile dysfunction.
10. Transdermal testosterone for low libido in postmenopausal women.
11. Transdermal nanoparticles for immune enhancement in HIV.

12. ORTHO EVRA is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.

13. Transdermal lidoderm for post therapeutic neuralgia.

Adverse events ⁽¹⁸⁾

- In 2005, FDA announced that they were investigating reports of death and other serious adverse events related to narcotic overdose in patients using Duragesic, the fentanyl transdermal patch for pain control. Duragesic product label was subsequently updated to add safety information in June 2005.
- In 2007, Shire and Noven Pharmaceuticals, manufacturers of the Daytrana ADHD patch, announced a voluntary recall of several lots of the patch due to problems with separating the patch from its protective release liner. Since then, no further problems with either the patch or its protective packaging have been reported.
- In 2008, two manufacturers of the Fentanyl patch, ALZA Pharmaceuticals (a division of major medical manufacturer Johnson & Johnson) and Sandoz, subsequently issued a recall of their versions of the patch due to a manufacturing defect that allowed the gel containing the medication to leak out of its pouch too quickly, which could result in overdose and death.
- In 2009, the FDA announced a public health advisory warning of the risk of burns during MRI scans from transdermal drug patches with metallic backings. Patients should be advised to remove any medicated patch prior to an MRI scan and replace it with a new patch after the scan is complete.
- In 2009, an article in Europace journal detailed stories of skin burns that occurred with transdermal patches that contain metal (usually as a backing material) caused by shock therapy from external as well as internal cardioverter defibrillators (ICD).

Conclusion

A lot of progress has been done in the field of Transdermal Patches. Due to large advantages of the Transdermal Drug Delivery System, this system interests a lot of researchers. Many new researches are going on in

the present day to incorporate newer drugs via this system. Various devices which help in increasing the rate of absorption and penetration of the drug are also being studied. However, in the present time due to certain disadvantages like large drug molecules cannot be delivered, large dose cannot be given, the rate of absorption of the drug is less, skin irritation, and etc limited the use of the Transdermal Drug Delivery System in therapy. But, with the invention of the new devices and new drugs which can be incorporated via this system, it used is increasing rapidly in the present time.

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