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Review Article

TRANSDERMAL PATCH: A DISCRETE DOSAGE FORM

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ABSTRACT

Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. Transdermal drugs are self-contained,discrete dosage form . Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs by the means of skin. Skin is an effective medium from which absorption of the drug takes place and enters the circulatory system. Various types of transdermal patches are used to incorporate the active ingredients into the circulatory system via skin. The patches have been proved effective because of its large advantages over other controlled drug delivery systems. This review article covers a brief outline of the principles of trasdermal permeation, various components of transdermal patch, approaches of transdermal patch, evaluation of transdermal system, when the transdermal patch are used and when their use should be avoid and some of the recent development in the field along with the future aspects in this field.

Keywords: Transdermal, Delivery, Patches, Evaluation of transdermal system.

INTRODUCTION

Drugs can be delivered across the skin to have an effect on the tissues adjacent to the site of application (topical delivery) or to have an effect after distribution through the circulatory system (systemic delivery). While there are many advantages to delivering drugs through the skin the barrier properties of the skin provide a significant challenge. By understanding the mechanisms by which compounds cross the skin it will be possible to devise means for improving drug delivery[1]. Some of the many factors that influence the rate of delivery of drugs across the skin include; the thermodynamic activity of the drug in the formulation; the interaction of the drug and the formulation with the skin; variations in skin with age, race, anatomical region and disease.

Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth or by oral route. Patients often forget to take their medicine, and even the most faithfully compliant get tired of swallowing pills, especially if they must take several each day. Additionally, bypassing the gastrointestinal (GI) tract would obviate the GI irritation that frequently occurs and avoid partial first-pass in activation by the liver. Further, steady absorption of drug over hours or days is usually preferable to the blood level spikes and troughs produced by oral dosage forms. These advantages are offered by the currently marketed transdermal products[1].

Transdermal patch or adhesive patch or skin patch used to deliver a controlled dose of a drug through the skin over a period of time. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), lidocaine to relieve the pain of shingles and many more drugs[2].

The first transdermal systems were simply pieces of plastic dipped into a drug that was dissolved in alcohol. The plastic had an adhesive around the edges. Although revolutionary in their day, they created a significant number of skin reactions, more often than not fell off, and had a number of other limitations. These problems gave a lasting negative impression of the whole sector[3].

The next generation — still in use today — uses a "drug in the adhesive" model. This is a significant improvement, as the skin irritation is diminished and in many cases eliminated. The adhesive serves two functions: It is the glue that keeps the patch attached to the skin, and it acts as the suspension that holds the drug. But it creates a major challenge: The concentration of the drug within the adhesive directly affects the "stickiness" of the adhesive. Thus, if there is a need for large quantities of drug, either the size of the patch must be increased or the patch needs to be reapplied more frequently. Basically, the patch would not stick, as it would be primarily made up of the drug[3].

Third generation patches have solved some of these issues by using an acrylic reservoir that holds the drug. Silicon adhesive is added to create a semisolid suspension of microscopic, concentrated drug cells[3].

Now, fourth generation transdermal systems involve the addition of an enhancer — a mechanism to increase the permeability of the skin — and in some of the technology, a mechanism to time the delivery and create bolus dosing. There are a number of enhancers to drug delivery. These include iontophoresis, ultrasound, chemicals including gels, microneedles, sonophoresis, lasers, and electroporatic methods[3].

FDA approved the first transdermal patch products in 1981. These delivery systems provided the controlled systemic absorption of scopolamine for the prevention of motion sickness (*Transderm-Scop*, ALZA Corp.) and nitroglycerine for the prevention of angina pectoris associated with coronary artery disease (Transderm-Nitro). Over the last two decades, more than 35 transdermal products have been approved generating sales of $3.2 billion in 2002, which is predicted to rise to $4.5 billion in 2008. More recently, such dosage forms have been developed and/or modified in order to enhance the driving force of drug diffusion (thermodynamic activity) and/or increase the permeability of the skin. These approaches include the use of penetration enhancers, supersaturated systems, prodrugs, liposomes and other vesicles[4].

The highest selling transdermal patch in the United States was the nicotine patch which releases nicotine to help with cessation of tobacco smoking. The nicotine patch, releases nicotine over sixteen hours, continuously suppressing the smoker's craving for a cigarette. The scopolamine patch is worn behind the ear and releases the alkaloid for three days, preventing motion sickness without the needto swallow tablets periodically. The fentanyl patch acts for seventy-two

hours, providing long-lasting pain relief. And an estrogen–progestin contraceptive patch needs to be applied only once a week, a boon for women who find it onerous to take one pill every day.

The first commercially available vapour patch to reduce smoking was approved in Europe in 2007. The first transdermal treatment of alzheimer's disease was done through rivastigmine patch[1,2].

PRINCIPLES OF TRANSDERMAL PERMEATION[5]

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration[2]. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows:

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary layer.
5. Effect on target organ.

Factors affecting permeability[7]

Physiological factors	Formulation factors	Physicochemical properties of enhancers
• Stratum corneum layer of the skin • Anatomic site of application on the body • Skin condition and disease • Age of the patient • Skin metabolism • Desquamation (peeling or flaking of the surface of the skin) • Skin irritation and sensitization • Race	• Physical chemistry of transport • Vehicles and membrane used • Penetration enhancers used • Method of application • Device used	• Partition coefficient of 1 or gearter is required • pH value should be moderate, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability • Concentration of penetrant higher than solubility, excess solid drug functions as a resorvior and helps in maintaining constant drug concentration for prolonged time.

BIOPHARMACEUTICAL PARAMETERS IN DRUG SELECTION FOR TRANSDERMAL PATCH[8]

- Dose should be low i.e <20mg/day.
- Half life should be 10 h or less.
- Molecular weight should be <400.
- Partition coffecient should be Log P(octanol-water) between 1.0 and 4.
- Skin permeability coefficient should be <0.5 X 10^{-3}cm/h.
- Drug should be non irritating and non sensitizing to the skin.
- Oral bioavailability should be low.
- Therapeutic index should be low.

BASIC COMPONENTS OF TDDS[5]

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents

Polymer matrix

Polymers are the backbone of a transdermal drug delivery system. Systems for transdermal delivery are fabricated as multilayered polymeric laminates in which a drug reservoir or a drug–polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane.

Polymer selection and design must be considered when striving to meet the diverse criteria for the fabrication of effective transdermal delivery systems. The main challenge is in the design of a polymer matrix, followed by optimization of the drugloaded matrix not only in terms of release properties, but also with respect to its adhesion–cohesion balance, physicochemical properties, and compatibility and stability with other componentsnof the system as well as with skin.

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, nitrile, acrylonitrile, neoprene, butylrubber *etc*.
- Synthetic Polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc*.

The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose are used as matrix formers for TDDS. Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membrane.

Drug

The most important criteria for TDDS is that the drug possesses the right physicochemical and pharmacokinetic properties. 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. For example, drugs like rivastigmine for alzheimer's and parkinson dementia, rotigotine for parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS.

Permeation enhancers

To increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug penetration enhancers interact with structural components of stratum corneum *i.e.,* proteins or lipids. The enhancement in absorption of oil soluble drugs is apparently due to the partial leaching of the epidermal lipids by the chemical enhancers, resulting in the improvement of the skin conditions for wetting and for transepidermal and transfollicular penetration. The miscibility and solution properties of the enhancers used could be responsible for the enhanced transdermal permeation of water-soluble drugs. Pharmaceutical scientists have made great efforts in transdermal permeation studies using various enhancers for several drug moieties.

Classification of penetration enhancers[6]

Terpenes(essential oils) :	E.g. Nerodilol, menthol, 1 8 cineol,limonene, carvone etc.
Pyrrolidones :	E.g. N-methyl-2-pyrrolidone(NMP), azone etc.
Fatty acids and esters:	E.g. Oleic acid, linoleic acid, lauric acid, capric acid etc.
Sulfoxides and similar compounds:	E.g. Dimethyl sulfoxide(DMSO), N,Ndimethyl formamide
Alcohols, Glycols, and Glycerides :	E.g. Ethanol, Propylene glycol, Octyl alcohol etc.
Micellaneous enhancers:	E.g. Phospholipids, Cyclodextrins, Amino acid derivatives, Enzymes etc.

The permeation of drugs across is also enhanced by physical means like pulsed DC iotophorosis i.e it passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier, sonophoresis i.e application of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules., electroporation i.e application of short, high-voltage electrical pulses to the skin for increasing the permeability of the skin for diffusion of drugs by 4 orders of magnitude, use of microprojections i.e transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. etc.

Pressure sensitive adhesive

A PSA maintains an intimate contact between patch and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, exert a strong holding force. For eg polyacrylates, polyisobutylene and silicon based adhesives. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. PSA should be physicochemically and biologically compatible and should not alter drug release. The PSA can be positioned on the face of the device(as in resorvior system) or in the back of the device and extending peripherally(as in case of matrix system).

Backing laminate

The primary function of the backing laminate is to provide support. Backing layer should be chemical resistant and excipient compatible because the prolonged contact between the backing layer and the excipients may cause the additives to leach out or may lead to diffusion of excipients, drug or penetration enhancer through the layer. They should a low moisture vapor transmission rate. They must have optimal elasticity, flexibility, and tensile strength. Examples of some backing materials are an aluminium vapor coated layer, a plastic film (polyethylene, polyvinyl chloride, polyester) and a heat seal layer.

Release liner

During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. The release liner is composed of a base layer which may be non-occlusive (*e.g*. paper fabric) or occlusive (*e.g*. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metallized laminate.

Other excipients

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

APPROACHES USED IN DEVELOPMENT OF TRANSDERMAL PATCH[9,5]

A. Membrane moderated systems

In this, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium e.g. silicon fluid. The rate controlling membrane can be micro porous or nonporous polymeric membrane e.g. ethylene vinyl acetate co-polymer on the external surface of the polymeric membrane, a skin layer of drug, compatible hypo allergic adhesive polymer may be applied to achieve an intimate contact of TDDS with skin surface.

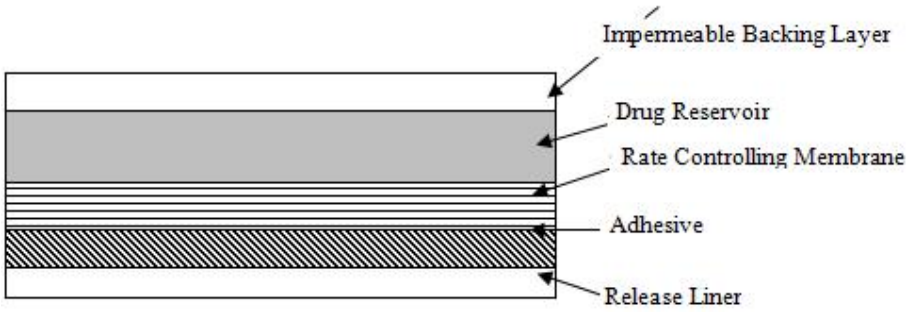

Fig. 1: Design of Membrane moderated transdermal patch

Marketed systems:
- Transderm-Nitro system for once a day.
- Transderm-Scop system- 3 days medication.
- Catapres- TTS – for weekly treatment

B. Adhesive diffusion controlled system

It is the simplest version of the membrane moderated drug delivery systems. In this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting onto a flat sheet of drug impermeable metallic plastic backing to form thin drug reservoir layer. On the top of the reservoir layer, layers of non-medicated rate controlling adhesive polymer of constant thickness are applied. Drug -in -adhesive patch may be single layer or multi layer. The multi layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane. Characteristics of drug in adhesive patch may account for improved patient compliance due to ease of remembering once weekly patch application, improved cosmetic acceptance and better adhesion.

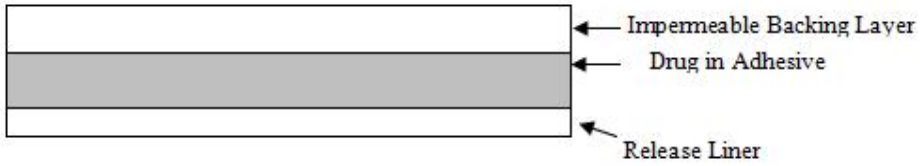

Fig. 2: Design of adhesive diffusion controlled transdermal patch

Marketed devices:

- Climara®
- Nicotrol®
- Deponit®

C. Matrix dispersion:

Here the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix and medicated polymer is then molded into disc with defined area and thickness. This is glued onto an occlusive base plate on the surface of the disc, the adhesive polymer is spread along the circumference to form a stripe of adhesive rim around the disc.

Advantages of matrix patches include absence of dose dumping, direct exposure of polymeric matrix to the skin and no interference of adhesive.

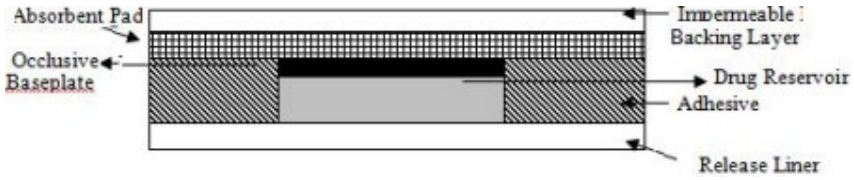

Fig. 3: Design of matrix dispersion transdermal patch

Marketed System :

- Nitro-Dur®

D. Micro-reservoir system:

These are considered as combination of reservoir and matrix dispersion type. In this the drug reservoir is formed by first suspending the drug solids in an aqueous solution of water soluble polymer and then dispersing the drug suspension homogenously in lipophilic polymer, by high shear mechanical force to form unleachable microscopic spheres of drug reservoir.

This dispersion is stabilized immediately by cross-linking the polymer chains which produces a medicated disc with constant surface area and thickness.

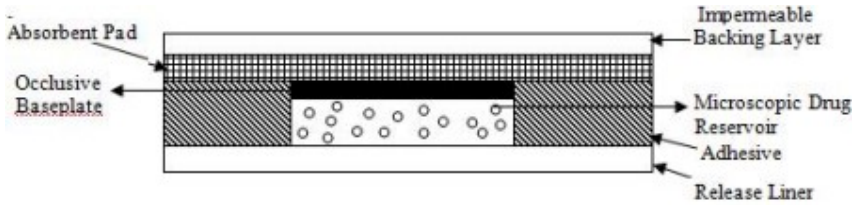

Fig. 4: Design of micro reservoir transversal patch

Marketed system

- Nitrodisc®

EVALUATION OF TRANSDERMAL PATCH[5]

Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types:

- Physicochemical evaluation
- In vitro evaluation
- In vivo evaluation

1. 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.

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.

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 transdermalpatches 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 percent moisture content is calculated using following formula.

$$\% \text{ Moisture content} = \frac{\text{Initial weight}}{\text{Final weight}} \text{x } 100$$

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 percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction } = \frac{I\,1 - I\,2}{I\,1} \times 100$$

% constriction = = x 100

I_2 = Final length of each strip

I_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.

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.

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

Tack properties:

It is 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.

Thumb tack test:

The force required to remove thumb from adhesive is a measure of tack.

Rolling ball test:

This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

Quick stick (Peel tack) test:

The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90 at the speed of 12 inch/min.

Probe tack test:

Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

2. (a) In vitro release studies[6]:

Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence their in vivo performance. The dissolution data is fitted to these models and the best fit is obtained to describe the release mechanism of the drug. There are various methods available for determination of drug release rate of TDDS.

The Paddle over Disc(USP apparatus 5/ PhEur 2.9.4.1):

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(USP apparatus 6 / PhEur 2.9.4.3)

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(USP apparatus 7)

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 (PhEur 2.9.4.2) may be used.

(b) In vitro permeation studies

The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages. 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 lipophillic 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.

3. In vivo studies

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during *in vitro* studies can be fully explored during *in vivo* studies. *In vivo* evaluation of TDDS can be carried out using:

- Animal models
- Human volunteers

Animal models

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.

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.

CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE USED [2]

Transdermal patch is used when:

(1)When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery. (2) Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia. (3) It can be used in combination with other enhancement strategies to produce synergistic effects.

RESEARCH ON TRANSDERMAL PATCHES OF MODEL DRUGS

Drugs	Workers	System	Work done	Refrence
Aceclofenac	Rakesh P Patel et al.	Matrix-type	transdermal therapeutic system containing drug Aceclofenac with different ratios of hydrophilic (hydroxyl propyl cellulose) and hydrophobic (ethyl cellulose) polymeric systems by the solvent evaporation technique	10
Dexamethasone	Biswajit Mukherjee et al.	Matrix-type	comparative studies between Povidone-Ethyl cellulose and Povidone-Eudragit Transdermal Dexamethasone matrix patches based on invitro skin permeation.	11
Terbutaline sulphate	Rathore RPS et al.	Matrix-type	matrix type patches of terbutaline sulphate were fabricated using ethyl cellulose and cellulose acetate polymer. The highest release rate was observed from CP3 and EP2 patches. The drug permeation from both the patches follows diffusion controlled drug permeation.	12
Ampicillin,	Janardhanan Bagyalakshmi et al.	Membrane -type	Formulation Development and In Vitro and In Vivo Evaluation of Membrane-Moderated Transdermal Systems of Ampicillin Sodium in Ethanol: pH 4.7 Buffer Solvent System	13
Aspirin	D.R.Krishna et al.	Matrix-type	Inhibition of platelet aggregation and reduction of serum lipid peroxides by matrix type asiprin transdermal patch	14
Ampicillin sodium	J.Bhagyalaksami et al.	Matrix-type	The efficiency of ampicillin sodium against e.coli using sodium alginate, chitosan, HPMC, CMC, cellulose acetate phthalate found that HPMC is best polymer having less colony forming units.	15
Atonolol and metoprolol	S.S.Aggarwal et al.	Matrix-type	Patch of atonolol and metoprolol was prepared by using HPMC, PVP, ethyl cellulose and cellulose acetate phthalate to improve bioavailability.	16
Carvedilol	Udhumansha Ubaidulla et al.	Matrix-type	transdermal therapeutic system containing carvedilol with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique.	17
Celecoxib	S Jayaprakash et al.		Preparation and evaluation of transdermal patch of celecoxib to achieve prolonged drug level.	18
Diltiazem	Sathurwar et al.	Matrix -type	Evaluation of Polymerized Rosin for the Formulation and Development of Transdermal Drug Delivery System by diltiazem patch	19
Fentanyl	Suneela Prodduturi et al.	Resorvior -type	Effect of Patch Age on Drug Release and Skin Permeation by Reservoir Based Fentanyl Transdermal patch	20
Chlorphenir-amine	Iman et al.	Drug in adhesive type	Formulated patch using different bioadhesives polymers such as PVP, cellulose acetate and ethyl cellulose with different plasticizers such as polyethylene	21

			glycol and evaluated	
Furosemide	Dhaval P. Patel et al.	Film-type	Development and Evaluation of Ethyl Cellulose-Based Transdermal Films of Furosemide for Improved *In Vitro* Skin Permeation	22
Glebenclamide	S.Shridevi et al.	Matrix-type	The drug embedded in a polymeric matrix of polymethyl methacrylate and ethylcellulose was evaluated for its hypoglycemic activity in normal and streptozotocin induced diabetic rats in comparison with its oral therapy.	23
Gliclazide	Anil kumar J shinde et al.	Matrik-type	Trandermal patch by film casting technique was prepared and evaluated	24
Haloperidol	Sadashivaiah et al.	Matrix-type	Design and in vitro evaluation of haloperidol lactate transdermal patch containing ethyl cellulose and povidone as film formers.	25
Indomethacin	Ting li et al.	Drug in adhesive	the formulation composition of a transdermal drug delivery system of indomethacin, MASCOS 10 (polyacrylic acid type) pressure sensitive adhesive was used to prepare a drug-in-adhesive type patch containing a variety of permeation enhancers (*i.e.* azone, *L*-menthol, 2-isopropyl-5-methylcyclohexyl heptanoate (M-HEP), isopropyl myristate (IPM), Tween-80 and oleic acid).	26
Insulin	Lina Nordquist et al.	Microneedle type	Novel microneedle patches for active Insulin delivery are efficient in maintaining glycaemic control by an initial comparison with subcutaneous administration	27
Ketoprofen	Shashikant D. Barhate et al.	Matrix type	Developed ketoprofen transdermal patches by mercury substrate method using polymer Eudragit RS100, Eudragit RL100, HPMC K100M, HPMC E5 and HPMC K4M. Propylene glycol and oleic acid used as a skin permeation enhancer and dibutyl phthalate and polyethylene glycol-400 used as a plasticizer and evaluated	28
Ketorolac	Shashikant D. Barhate et al.	Resorvior type	Effect of pH, alcohol and permeation enhancers on in vitro permeation of reservoir type ketorolc patch. Enhanced in vitro permeation was found by alcohols	29
Ibuprofen	Jianhua Zhang et al.	Drug in adhesive type	PDGW(polyvinyl pyrrolidone, D,L-lactic acid oligomers, glycerol and water) possesses excellent PSA properties and self-enhancement for drug percutaneous permeation, which can be used to develop new formulation of TDDS.	30
Lercanidine	Mamatha T et al.	Matrix-type	development of transdermal drug-delivery system (TDDS) of lercanidine and to determine the effect of penetration enhancer, limonene on drug permeation	31
Lidocaine	J.Fokuhl et al.	Matrix-type	the permeation behaviour of lidocaine from four different polymers made of growing raw materials	32

			with and without further additives was studied	
Losartan	V.Vijayan et al.	Resorvior-type	Transdermal patches of Losartan with hydrophilic(methyl cellulose and sodium carboxy methyl cellulose) and hydrophobic(HPMC and eudragit) polymers containing the drug reservoir were prepared by solvent evaporation method. Based on the kinetic studies, the patch containing both HPMC and Eudragit RS100 showed satisfactory drug release patterns.	33
Naltrexon	Satyanarayana Valiveti et al.	Matrix-type	In Vitro/in Vivo Correlation of Transdermal Naltrexone Prodrugs in Hairless Guinea Pigs	34
Nicorandil	V G Jamakandi et al.	Matrix-type	Formulation,characterization and in vitro evaluation of nicorandil patch prepared by different grades of HPMC	35
Nitrendipine	Ramesh Gannu et al.	Matrix-type	The matrix type TDDS of NTDP were prepared by solvent evaporation technique and evaluated. Ten formulations (composed of Eudragit RL 100 and Hydroxypropyl methyl cellulose in the ratios of 5:0, 4:1, 3:2, 2:3, 1:4 in formulations A1, A2, A3, A4, A5 and Eudragit RS 100 and Hydroxypropyl methyl cellulose in the same ratios in formulation B1, B2, B3, B4, B5 respectively) were prepared.	36
Papavarine	Samip S Shah et al.	Matrix-type	Formulaton and evaluation of transdermal patch of papaverine using ethylcellulose:PVP, PVP:PVA and eudragit RL-100:eudragit RS-100 with different ratios.	37
Sinomenine	Jianping wang et al.	Matrix-type	Development and evaluation of sinomenine transdermal patch	38
Parathyroid hormone	Peter E. Daddona et al.	Miconeedle-type	Pharmacokinetic and pharmacodynamic parathyroid hormone Coated microneedle patch for treatment of osteoporosis.	39
Propanolol	L. K. Omray et al.	Microresorvior-type	Microresorvior based patch of propanolol comprises of liquid crystals prepared by brij-35, cetosteryl alcohol and propanolol and evaluated for its anisotrophy, size and size distribution and drug entrapement efficiency.	40
Valsartan	Naohiro Nishida et al.	Drug-in-adhesive	Development and evaluation of a monolithic drug-in-adhesive patch for valsartan. A combination of isopropyl myristate(IPM)/diisooctyl sodium sulfosuccinate (AOT) most strongly enhanced the permeation of VAL.	41
Tramodol	Hussein O. Ammar	Matrix-type	Polymeric Matrix System for Prolonged Delivery of Tramadol Hydrochloride,	42

CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE NOT USED [2]

The use of transdermal patch is not suitable when:

(1)Cure for acute pain is required. (2) Where rapid dose titration is required. (3) Where requirement of dose is equal to or less than 30 mg/24 hrs.

IDEAL REQUIREMENT OF TRANSDERMAL PATCH[7]

- Shelf life up to 2 years
- Small size patch (i.e., less than 40 cm^2)
- Convenient dose frequency (i.e., once a day to once a week)
- Cosmetically acceptable (i.e., clear, white color)

RECENT ADVANCES IN THE FIELD OF TRANSDERMAL PATCHES

Many research works have been and are few are going on in this field. Few of the latest research done in the field of transdermal patches are stated below:

Patch technology for protein delivery [43]

Transdermal delivery of large proteins is a novel and exciting delivery method. There is no commercial technology currently available that incorporates proteins into transdermal patches. TransPharma uses its unique printed patch technologyfor transdermal delivery of proteins thereby complementing its ViaDermdelivery technology . Such printed patches contain accurate doses of proteins in adry state. It is postulated that the highly water soluble proteins are dissolved by the interstitial fluid that is secreted from the skin through the RF-MicroChannels, forming a highly concentrated protein solution in situ.The delivery of the dissolved molecules is then carried out, via the RF-Micro Channels, into the viable tissues of the skin, diffusing across a steep concentration gradient.

Pain-free diabetic monitoring using transdermal patches [2]

The first prototype patch measures about 1cm and is made using polymers and thin metallic films. The 5×5 sampling array can be clearly seen, as well as their metallic interconnections. When the seal is compromised, the interstitial fluid, and the biomolecules contained therein, becomes accessible on the skin surface. Utilizing micro-heating elements integrated into the structural layer of the patch closest to the skin surface, a high-temperature heat pulse can be applied locally, breaching the stratum corneum. During this ablation process, the skin surface experiences temperatures of 130°C for 30ms duration. The temperature diminishes rapidly from the skin surface and neither the living tissue nor the nerve endings are affected. This painless and bloodless process results in disruption of a 40–50μm diameter region of the dead skin layer, approximately the size of a hair follicle, allowing the interstitial fluid to interact with the patch's electrode sites.

Testosterone transdermal patch system in young women with spontaneous premature ovarian failure [44]

In premenopausal women, the daily testosterone production is approximately 300 μg, of which approximately half is derived from the ovaries and half from the adrenal glands. Young women with spontaneous premature ovarian failure (sPOF) may have lower androgen levels, compared with normal ovulatory women. Testosterone transdermal patch (TTP) was designed to deliver the normal ovarian production rate of testosterone. The addition of TTP to cyclic E2/MPA therapy in women with sPOF produced mean free testosterone levels that approximate the upper limit of normal.

Transdermal patch of oxybutynin used in overactive bladder [2]

The product is a transdermal patch containing Oxybutynin HCl and is approved in US under the brand name of Oxytrol and in Europe under the brand name of Kentera. OXYTROL is a thin, flexible and clear patch that is applied to the abdomen, hip or buttock twice weekly and provides continuous and consistent delivery of oxybutynin over a three to four day interval. OXYTROL offers OAB patient's continuous effective bladder control with some of the side effects, such as dry mouth and constipation encountered with and oral formulation. In most patients these side effects however are not a troublesome.

Nanotechnology gaining hold [3]

Another enhancer that is gaining advancement is microneedles. This technology combines the advantage of a needle and the transdermal patch. The devices are dime-sized pieces of polymer with hundreds of hollow microneedles between 100 and 1,000 micrometers long. These small needles penetrate the top layers of skin and allow the drug to pass through with ease. This technology can be combined with an electronically controlled micropump that delivers the drug at specific times or upon demand. Once approved by the FDA, these devices would allow the patient or physician to control the time and dose of the drug being delivered. These devices have the potential to place drugs precisely into the area where special immune cells reside, making these drugs capable of modulating the immune system, with relative ease.

Alza is using a slightly different variation on the use of needles. . The company has developed the patented Macroflux transdermal technology that uses microprojections to create superficial pathways through the dead skin barrier. The tips of the projections contain active drug — a quick bolus.

Pain relief [3]

Pain relief routinely benefits from transdermal patch technology. Most of the readers are aware of the Duragesic patch. There are several others now on the market. One is Lidoderm, a lidocaine 5 percent patch, which is used for post herpetic neuralgia. Other exciting advancements in pain control include the E-Trans fentanyl HCl patch. . This credit card-size patch is an active delivery device that has a self-contained battery that delivers pulses of fentanyl HCl, a strong narcotic. This mimics the use of intravenous self-controlled analgesic systems that are very expensive, cumbersome, and require considerable nursing care.

Molecular absorption enhancement technology [45]

Considerable research has been done on absorption enhancers, compounds that promote the passage of drugs through the stratum corneum. Terpene derivatives as well as certain phenols seem to improve transdermal absorption. For example, linalool, alpha terpineol, and carvacrol were studied in conjunction with haloperidol (a commonly prescribed neuroleptic drug). All three enhanced haloperidol absorption, but only linalool increased it to a therapeutic level. Limonene, menthone, and eugenol were found to enhance transdermal absorption of tamoxifen. Phloretin, a polyphenol, enhanced the absorption of lignocaine . In general, absorption enhancement research has been done with excised animal skin (pig or rabbit) or human skin obtained from cadavers or plastic surgery procedures.

FUTURE TECHNOLOGIES AND APPROACHES [46,43]:

- Thermal Poration is the formation of aqueous pathways across stratum corneum by the application of pulsed heat, this approach has been used to deliver conventional drugs and to extract intestinal fluid glucose from human subjects
- Jet injectors are receiving increased attention now days, which is opening doors for improved device design for controlled, needle free injection of drug solutions across the skin and into deeper tissue.
- Small needle is inserted a few millimeters into skin and drug solution is flowed through the needle into the skin at controlled rates using a micro-infusion pump that is contained within a large patch affixed to skin, morphine has been delivered to humans using this approach.
- During the past decade several theories have been put forward in addressing the combinations of chemicals and iontophoresis; chemicals and electroporation; chemicals and ultrasound; iontophoresis and ultrasound; electroporation and iontophoresis; and electroporation and ultrasound.
- TransPharma is focused on products for which our technology will provide clear benefits over existing therapies. Such benefits could include improving safety and compliance through the use of a drug patch or enhancing efficacy with the use of sustained release patch formulations, among others.
- The ViaDerm system may be applied to the delivery of local medications for topical applications in the fields of dermatology and cosmetics. The ViaDerm system may also allowenhanced immunisations, providing a nonpainful, safe and effective alternative to current intramuscular or subcutaneous vaccination methods.
- Altea Therapeutics is currently in clinical development of a transdermal patch designed to address a major unmet need by preventing 'off' periods and provide an improved therapeutic option for managing Parkinson's disease.

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. the use of the Transdermal Drug Delivery System has been limited. 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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