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Review on: Transdermal Drug Delivery Patches

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ABSTRACT:

For thousands of years, human civilizations have applied substances to the skin as cosmetic and medicinal agents. TDDS is one of the systems lying under the Category of controlled drug delivery in which the aim is to deliver the drugs through the skin in a predetermined and controlled rate. A Transdermal patch is a medicated adhesive patch that is placed on The skin to deliver a specific dose of medication through the skin and Into the blood stream. Transdermal patches are pharmaceutical preparation of varying sizes, containing one or more active ingredient to the systemic circulations. This review article covers brief outline advantages, disadvantages, anatomy and physiology of skin, basic components of transdermal patch, and types of transdermal patches , Evaluation of transdermal system, and application of TDDS.

KEYWORD: Transdermal drug delivery systems, NDDS, transdermal patches, methods and evaluation, Drug delivery.

INTRODUCTION

Transdermal drug delivery system is defined as the topically administered medications in the form of patches which when applied to the skin deliver the drug, through the skin at a predetermined and controlled rate. FDA approved the first Transdermal system Transder-SCOP in 1979. For the prevention of nausea and vomiting associated with trave, particularly by sea [1]. Transdermal drug delivery systems (TDDS), also known as patches are dosage forms designed to deliver a therapeutically effective amount of drug across a patients skin[2]. transdermal drug delivery system is controlled release systems. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin Throughout the past 2 decades, the transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms [3]. Transdermally delivered drugs avoid the risk and inconvenience of intravenous therapy, usually provide less chance of an overdose or underdose, allow easy termination, and permit both local and systemic treatment effects. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intra patient variation. In addition, because transdermal patches are user friendly, convenient, painless, and offer multi day dosing, it is generally accepted that they offer improved patient compliance. The growth rate for transdermal drug delivery systems is expected to increase 12% annually by 2007[4].

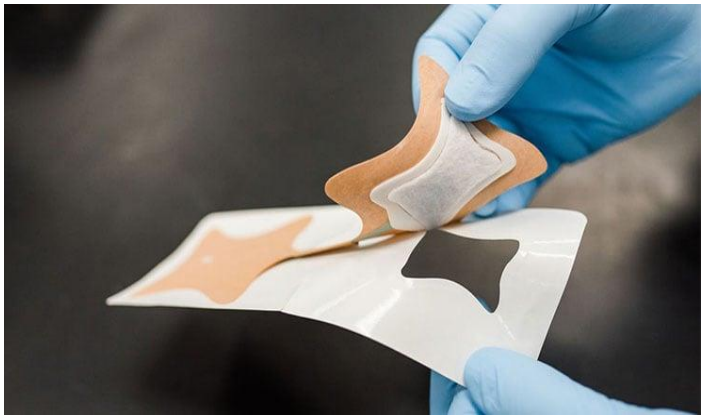

Fig. 1 Transdermal Patches

A. Advantages of Transdermal drug delivery systems [5, 6, 7]

1 To avoid the first pass effect eg. Transdermal Nitroglycerin. It is rapidly metabolized by the liner when taken orally.

2 They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.

3 Provides utilization of drugs with short biological half-lives, narrow therapeutic window .

4 Avoid inter and intra patient variation and enhance therapeutic efficacy.

5 Avoiding the fluctuation in drug levels.

6 Ability to deliver drug more selectively to a specific site .

7 Provide sutability for self- administration.

8 Transdermal patches are cost effective.

B. Disadvantages of Transdermal drug delivery system [8, 9,10]

1. Drugs with very low or high partition coefficient fail to reach blood circulation.
2. Long time adhere is difficult.
3. Not suitable for high drug doses.
4. Drugs that require high blood levels cannot be administered.
5. Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch

Formulation.

C. Anatomy and physiology of skin [11,12]

The skin is the largest organ of the body, accounting for about 15% of the total adult body weight. It performs many vital functions, including protection against external physical, chemical, and biologic assailants, as well as prevention of excess water loss from the body and a role in thermoregulation. The skin is continuous, with the mucous membranes lining the body's surface. However, the number of drugs available as marketed transdermal drug products is limited to those that display the correct Physicochemical and pharmacokinetic properties which facilitate their effective delivery across the skin. The structure of skin is given in Figure 1.

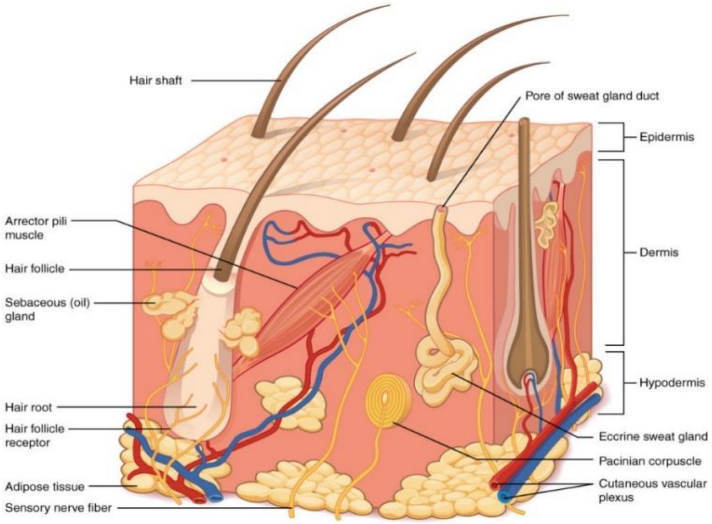

Fig.2 Structure of Skin

Taxonomical classification-

The skin is divided taxonomically into three scales, micro scale, meso scale and macro scale. The components of cell and layers of skin constitutes the micro scale as they can only be seen under the microscope and cannot be differentiated or identified with human eye. The meso scale comprises of skin features, hair, freckles, moles, scale comprises of skin features, hair, freckles, moles pores, skin surface and wrinkles as they can be seen with the naked eye and more clearly under the micro-scale if necessary. The macro scale comprises of body regions and body parts. The skin morphology and appearance appears different at different parts of the body[13].

Historical classification - The skin is divided histologically into the three layers namely ;

i. Epidermis

ii. Dermis,

iii. Hypodermis

Epidermis : Non-viable epidermis and viable epidermis together makes up the epidermis[14]. Stratum corneum is known as the non viable epidermis whereas the layer below the stratum corneum is called viable epidermis. The viable epidermis is made of various sub layers of epidermis which collectively is 50-100 µm thick and cells in this layer are held together by tonofibrils[15]. Blood capillaries and nerve fibers reach the epidermis by passing through the dermis and subcutaneous fat layer[16]. The main cell of the epidermis is the keratinocytes which make up 95% of the total cells present in the epidermis. The epidermis has the following sublayer as given in Table 1:

Table 1 Sub-layer of Epidermis

Stratum basale (basal cell layer)	It is the deepest sub-layer of the epidermis and is composed of a single layer of basal cells. Keratinocytes are produced in this sub-layer Stratum basale forms the boundary to the dermis. It holds approximately 8% of the water in the epidermis.
Stratum spinosum (prickle cell layer)	It refers to the 10 to 20 layers that lie on top of the basal cell layer. Basal cells, through the process of turn-over, make their shape somewhat flatter and form these layers. The thickness of this sublayer is from 50 to 150 µm.
Stratum granulosum (granular cell layer)	It is composed of 2 to 4 granular cell layers. The thickness of this layer is 3µm. In this sublayer, cornification or keratinization of keratinocytes begins.
Stratum lucidum (clear layer)	It can only be found in soles and palms. Its cells become flatter and more densely packed during turn-over[13].
Stratum corneum (horny layer)	The outermost layer of the skin, the stratum corneum, is responsible for the barrier function of the skin[17]. It is also known as non-viable epidermis[15].

Dermis: Once drug molecule is through the stratum corneum, it may pass through the deeper epidermal tissues and enter into the dermis. It is mainly made of fibrous tissues and is 1-2 mm thick. The dermis has a rich supply of blood vessels from where the drug gets absorbed into the general circulation. The skin surface of human is recognized to contain an average of 10-70 hair follicles and 200-250 sweat glands on every centimeter square of the skin area[18,19]. The dermis has following sub-layers as given in Table 2:

Table 2 Sub-layer of Dermis

Papillary layer	It is the upper sub-layer of the dermis that clearly segregates from the epidermis. Papillary layer is a loosely connected tissue and includes a large amount of nerve fibers, capillaries, water and cells (e.g. fibroblasts).
Reticular layer	It constitutes the lower part of the dermis and represents a continuous transition to the subcutaneous or hypodermis. Reticular layer has a denser and thicker network as compared to the papillary layer and includes fewer nerve fibers and capillaries[20].

Hypodermis: The hypodermis layer is also called as subcutaneous fat tissues. It supports the dermis and epidermis. This layer helps to regulate temperature and provides nutritional support. Subcutaneous fat tissue is third layer beneath the dermis. For transdermal drug delivery, drug has to penetrate through all these three layers and reach into the systemic circulation[20].

BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM

1. Drug reservoir / Polymer Matrix
2. Membrane
3. Drug
4. Permeation Enhancer
5. Backing Laminates
6. Pressure Sensitive Adhesives (PSA)
7. Release Liner
8. Other Excipients

POLYMER MATRIX[21]: Polymer should be chemically non-reactive. It should be non- toxic, should not decompose on storage and cost of polymer matrix should not be high. polymer matrix is the backbone of transdermal drug delivery system, which control the release of the drug. Main three types polymer namely; Natural polymer, Synthetic polymer, synthetic elastomer as given in table 3:

Table 3 Types of Polymer Matrix

Natural Polymer	Synthetics Polymers	Synthetics Elastomer
Cellulose derivatives, Zein, Gelatin, Waxes, Proteins, Gums, Natural rubber, Starch.	Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyvinylpyrrolidone, Polymethyl methacrylate, Epoxy, Polyurea, etc.	Polybutadiene, Hydrin rubber, polysiloxane, silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrene butadiene, Neoprene etc.

DRUG:

Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life. There are some examples of drugs that are suitable for transdermal drug delivery system like atenolol, metoprolol tartarate, captopril, nicardipine hydrochloride, verapamil hydrochloride, propranolol hydrochloride , clonidine , indapamide . The selection of drug for transdermal drug delivery depends upon physio-chemical factors and biological factors.

Physio-chemical properties:

1. Substances having a molecular weight of less than 1000 units are suitable[22].
2. Hydrogen bonding groups should be less than 2[7].
3. A saturated aqueous solution of the drug should have a pH value between 5.0 and 9.0 Drugs highly acidic or alkaline in solution are not suitable for TDD
4. The substance should have melting point less than 200 °C.
5. The drug should have some degree of solubility in both oil and water (ideally greater than 1 mg/ml)

Biological properties:

1. The drug should have short biological half life
2. The drug should not get irreversibly bound in the subcutaneous tissue
3. Drug should be very potent, i.e., it should be effective in few mg per day (ideally less than 25 mg/day)
4. The drug should be stable when in contact with the skin.

PERMEATION ENHANCER: Permeation enhancers is also called penetration enhancers. Substances exit which temporarily diminish the impermeability of skin are called permeation enhancer. The penetration enhancer should be pharmacologically inert, non- toxic, non -allergenic, non-irritating and ability to act specifically, reversibly and for predictable duration. These includes alcohol, azone, fatty acids , fatty acid esters, polyols,Terpene , sulfoxides like decyl-methyl sulfoxide, surfactants like benzalkonium chloride, organic acids, amides[23,24]

BACKING LAMINATES: Backing layer protect patch from outer environment. Backing materials must be flexible while possessing good tensile strength[25]. While designing a backing layer, the consideration of chemical resistance of the material is most important. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and high moisture vapour transmission rate[26]. The primary function of the backing laminate is to provide support. They should a low moisture vapor transmission rate. Some examples of backing materials are aluminum, polyvinyl chloride, polyethylene and polyester films

PRESSURE SENSITIVE ADHESIVES: The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device. They form inter atomic and inter molecular attractive forces at the interface, provided that the intimate contact is formed.

RELEASE LINER[27]: During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. Typically, a release liner is composed of a base layer that may be non occlusive (e.g. paper fabric) or occlusive (e.g. polyvinyl chloride) and release coating layer made up of silicon or Teflon . Other materials used for TDDS release liner include polyester foil and metalized laminate.

OTHER EXCIPIENT[22, 23,24] : In addition , plasticizers such as dibutyl phthalate, polyethylene glycol, triethyl citrate, propylene glycol are added to provide plasticity to the transdermal patch . This also chemically inert and compatible will all other ingredients in the formulation. Then various solvent such as acetone, methanol, chloroform, dicholoromethane and isopropanol are used to prepare drug reservoir

TYPES OF TDDS: Four major types transdermal drug delivery systems.

Single layer drug in adhesive: The adhesive layer of this system also contains the drug[7]. The single layer drug in adhesive system is characterized by the inclusion of the drug directly within the skin contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film[29].

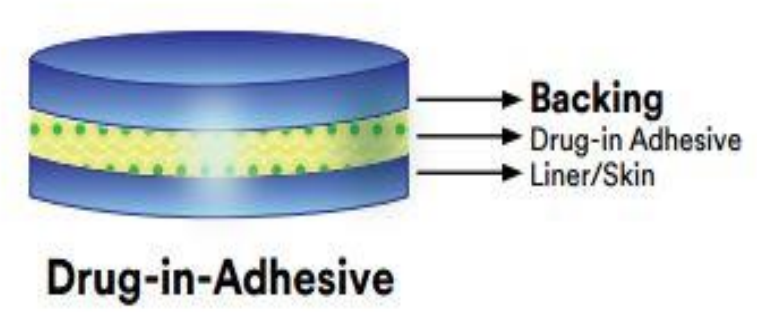

Fig. 3 Drug in Adhesive

Multi-layer drug in adhesive: The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multilayer encompasses either the addition of a membrane between two distinct drugs in adhesive layers or the addition of multiple drugs in adhesive layers under a single backing film[29].

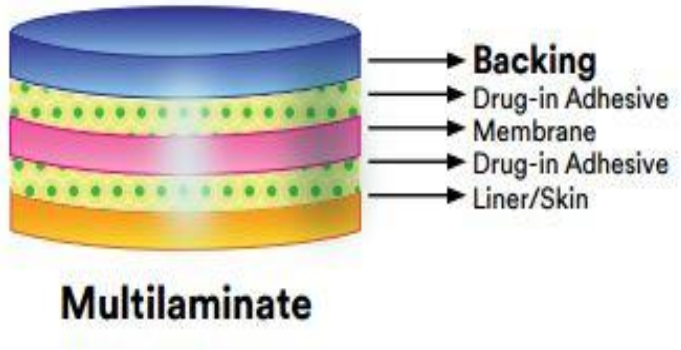

Fig. 4 Multi-layer drug in Adhesive

Reservoir System: Unlike the Single-layer and Multi-layer Drug-in adhesive systems the reservoir transdermal system has a separate drug layer[30]. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane In this type of system the rate of release is zero order.

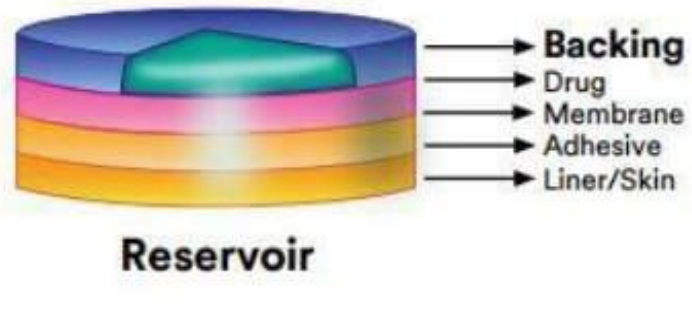

Fig. 5 Reservoir System

Matrix system: The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension The adhesive layer in this patch surrounds the drug layer partially overlaying it. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid.

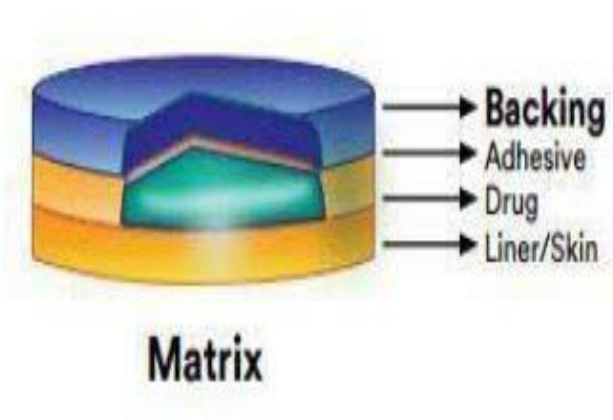

Fig. 6 Matrix System

EVALUTION OF TRANSDERMAL PATCH:

Physical Appearance: All the formulated patches were visually inspected for color, clarity, opaque, transparency, flexibility & smoothness.

Drug Content[31,32]: Take an accurately weighed portion of formulated patches is dissolved in a suitable solvent in which drug is soluble and then the solution is to be filtered through a filter medium and analyse the drug content with the suitable method (UV or HPLC technique). Each value represents average of three samples.

Weight Uniformity[32,33]: The prepared transdermal patches are to be dried at 60°C for 4hour before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Percentage moisture loss[34]: The prepared films are to be weighed individually and to be kept in a desiccator containing activated silica at 30 C. After 12hour the films are to be reweighed and determine the percentage of moisture loss.

Percentage moisture loss = [Initial wt – Final wt/ Final wt] × 100

Thickness of the Patch[35]: The thickness of patch is measured in different points of the formulated patches by different points of formulated patches by using digital micrometer/micrometer screw gauge/ travelling microscope/venire calipers. Determine the average thickness and standard deviation for the same to ensure the thickness of the prepared patch

Probe Tack Test[36]: In this test, the tip of a clean probe is contact with adhesive and bond is formed between probe and adhesive. Then the force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.

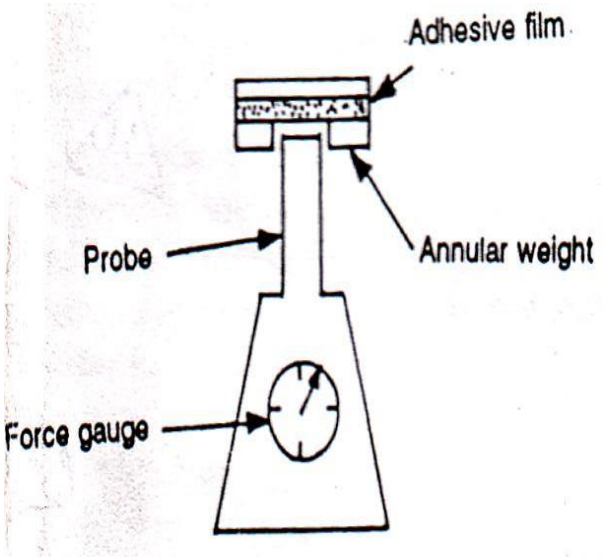

Fig. 7 Probe Tack

Rolling ball tack test[37]: In this test involves measurement of the distance that a stainless steel ball travels along an upward – facing adhesive. The less tacky the adhesive the for they will travel.

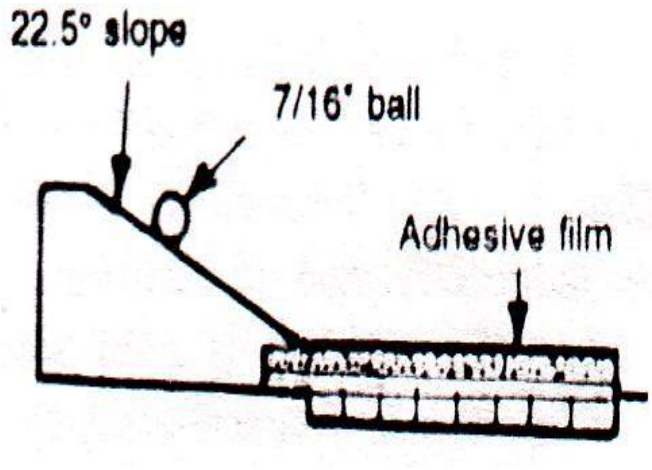

Fig. 8 Rolling Ball Tack

Flatness Test[38,39]: A transdermal patch should possess a smooth surface which not constrict with time. It can be studied by flatness test. In this test, one strip is cut from centre and two from each sides. The length of each strip is measured and variation in length is measured by percentage constriction. Zero percent constriction is equivalent to 100 percent flatness.

% construction = (initial length -final length)/initial lengthx100

Skin Irritation Test: Skin irritation testing is performed by using healthy rabbits. The formulated patches are applied on the dorsal surface of the skin rabbits. Before affixing the patch the hair is removed from the skin of the rabbits. After 24 hours the skin is to be observed.

Swellability[40]: The patches of 3.14 cm^2 was weighed and put in a petri dish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed.

The degree of swelling (S) was calculated using the formula,

$S (\%) = Wt – Wo/Wo \times 100$

where,

S is percent swelling

Wt is the weight of patch at time t

Wo is the weight of patch at time zero.

In vitro evaluation: The *in-vitro* evaluation study of fabricated transdermal patches of was carried out by using excised rat abdominal skin and Franz diffusion cell. The skin was sandwiched between donor and receptor compartments of the diffusion cell. A 2.2 cm diameter patch was placed in intimate contact with the stratum corneum side of the skin; the top side was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 12ml of normal saline. The cell contents were stirred with a magnetic stirrer and a temperature of 37 ± 5°C was maintained throughout the experiment. Samples of 1ml were withdrawn through the sampling port at different time intervals for a period of 24 h, simultaneously replacing equal volume by phosphate buffer pH 7.4 after each withdrawal. Then the samples were analyzed spectrophoto- metrically at 258 nm.

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.

APPLICATION OF TDDS[44]:

1. Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD)
2. It is used for treatment of Angina Pectoris, examples Nitroglycerine patches are sometimes prescribed for the treatment of Angina.
3. Transdermal patch of nicotine, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
4. Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.
5. Clonidine, the antihypertensive drug and ketoprofen, the non-steroidal anti-inflamatory drug are also available in the form of transdermal patches.

MARKETED PRODUCT OF TRANSDERMAL DRUF DELIVERY SYSTEM[41,42,43]

Table 4 Marketed Product of TDDS

S. No.	**Product**	**Active drug**	**Type of transdermal patch**	**Purpose**
1	Nicoderm CQ	Nicotine	Drug in adhesive	Smoking Cessation
2	Captropress TTS	Clonidine	Membrane	Hypertension
3	Climaderm	Estradiol	Matrix	Postmenstrual syndrome
4	Fematrix	Estrogen	Matrix	Postmenstrual syndrome
5	Transderm Nitro	Nitroglycerine	Reservoir	Angina pectoris
6	Fem patch	Estradiol	Matrix	Postmenstrual syndrome
7	Lidoderm	Lidocaine	Drug in adhesive	Anesthetic
8	Nu Patch 100	Diclofenac diethylamine	Drug in adhesive	Anti inflammatory

CONCLUSION :

The Transdermal Drug Delivery System has great advantages of avoiding hepatic first pass metabolism. It is a painless, convenient and potentially effective way to deliver regular doses of many medications. Dermal patches are the most common form of transdermal delivery of drugs. Due to large advantages of the Transdermal Drug Delivery System, this system interest a lot of researches Many new researches are going on in the present day to

incorporate newer drugs via this system. A better understanding of the interaction of enhancers with the stratum corneum and the development of structural activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity. 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 etc. the use of the Transdermal Drug Delivery System has been limited. This articles provides valuable information regarding Transdermal Drug Delivery Patches.

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