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Transdermal Drug Delivery System: A Review

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ABSTRACT

Transdermal patches are designed to deliver a therapeutically effective amount of drug across the skin membrane. In order to deliver therapeutic agents through the skin for systemic effects, the great physicochemical, morphological and biological properties of the skin are taken into consideration. Transdermal drug delivery system offers controlled release of drug substance into patient's skin, it enables a mild blood level profile, resulting in reduced systemic side effects over the other dosage forms. Transdermal delivery is more convenient and painless technique for administration of drugs. It provides vanguard over injectables and oral route by increasing patient compliance and avoiding first pass metabolism respectively. The formation of transdermal drug delivery system (TDDS) has been one of the most innovative approaches of drug deliveries.

Keywords: Transdermal drug delivery system (TDDS), Transport mechanism, Permeation mechanism, Iontophoresis, Microneedles.

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INTRODUCTION [1,2,3,4,5,6]

"Transdermal drug delivery system is defined as the topically administered medications, which when applied to the skin deliver the drug, through the skin at a predetermined and controlled rate". Drugs are administered by various routes such as oral, parenteral, nasal, transdermal, rectal, intravaginal, ocular etc. Among all of them, oral route is most common and popular but this route of administration have some drawbacks like first pass metabolism, drug degradation in gastrointestinal tract due to pH, enzyme etc.

To overcome these drawback, a novel drug delivery system (Transdermal drug delivery system) was developed in which a polymer combined with a drug in such a way that drug is released from polymer matrix at a predetermined and controlled manner.

Special membrane used in transdermal patches to control the release rate at which the liquid drug contained patch reservoir can pass through the skin and into the blood circulation. Transdermal delivery not only provide controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives, and eliminates pulsed delivery into systemic circulation which is responsible for undesirable side effects. Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation effects.

The first transdermal system, Transderm SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel. Most transdermal patches are designed to release the active ingredient at a zero order rate for a period of several hours to days following application to the skin. This is especially advantageous for prophylactic therapy in chronic conditions. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy.

Advantages of Transdermal Drug Delivery System: [7,8,9,10,11]

- Transdermal drug delivery system avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and other orally administration of drug.
- Avoidance of first pass metabolism.
- Avoidance of gastrointestinal incompatibility.
- Minimizing undesirable side effects.
- Suitable for administration of drug having very short half-life and narrow therapeutic window.

Disadvantages of Transdermal Drug Delivery System: [12,13,14,15]

- Transdermal drug delivery system does not suitable for delivery of ionic drugs.
- Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's impermeability.
- It cannot deliver drugs in a pulsatile fashion.

ANATOMY AND PHYSIOLOGY OF SKIN: [18,19,20] **[Figure 1]**

Skin is the most extensive organ of the body covering an area of about 2m2 on in an average human adult. This multi-layered organ receives approximately one third of all blood circulating through the body. With thickness of only a millimeter, the skin separates the underlying blood circulation network from outside environment.

Human skin comprises of three distinct but mutually dependent tissues:

A. The stratified, vascular, cellular called as "epidermis"

B. Underlying dermis of connective tissues

C. Hypodermis.

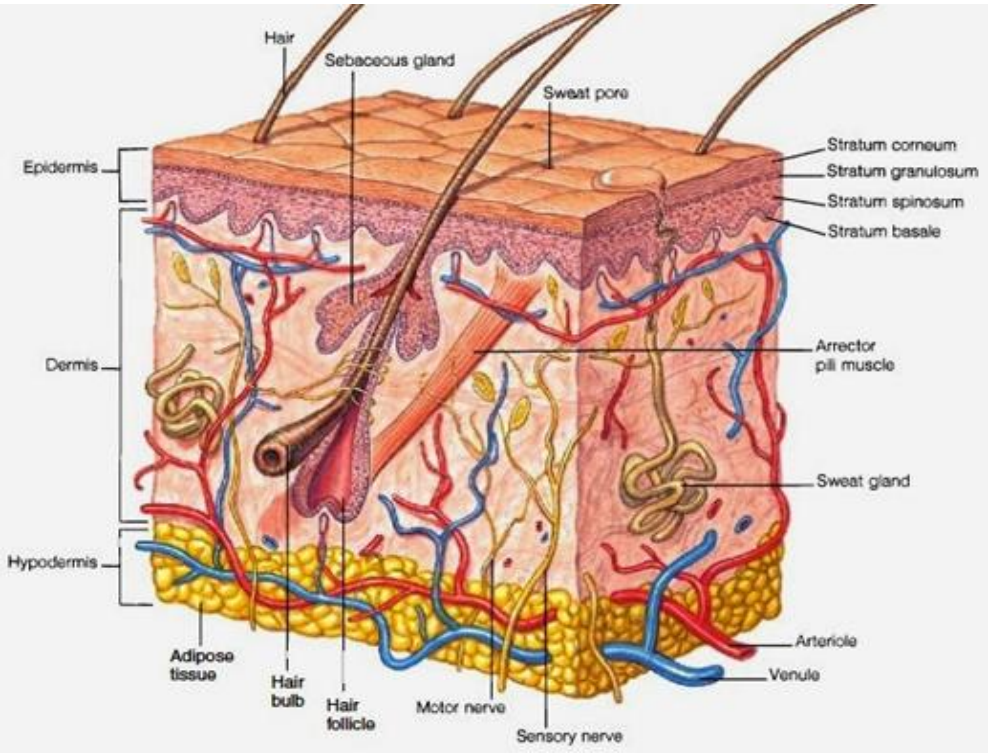

Figure 1: Structure of Human Skin

Route of Drug Permeation Through Skin: [19]

In the process of percutaneous permeation, a drug molecule may pass through the epidermis itself or may get diffuse through shunt pathway, mainly hair follicles, sebaceous glands and the sweat ducts. Therefore, there are two major routes of drug permeation.

TRANSCORNEAL PERMEATION:

Intra cellular permeation:

Drug molecule passes through the cells of the stratum corneum. Generally, hydrophilic drugs are passes through this route. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water.

Intercellular permeation:

Non-polar substances passes through the intercellular route. These molecules dissolve in and diffuse through the non- aqueous lipid matrix imbibed between the protein filaments.

Transappendageal Permeation:

This is also called as the shunt pathway. In this route, the drug molecule may transverse through the hair follicles, the sebaceous pathway or the aqueous pathway of the salty sweat glands. The transappendageal pathway is considered to be of minor importance because of its relatively smaller area (less than 0.1% of total surface). However this route may be of some importance for large polar compounds. The route through which permeation occurs is largely dependent on physico-chemical characteristics of penetrant, most importantantly being the relative ability to partition into each skin phase. The viable tissue layer and the capillaries are relatively permeable and the peripheral circulation is sufficiently rapid. Hence diffusion through the stratum corneum is the rate-limiting step. The stratum corneum acts like a passive diffusion medium. So for transdermal drug diffusion, the various skin tissue layers can be represented by a simple multilayer model as shown in Figure. **[Fig. 2]**

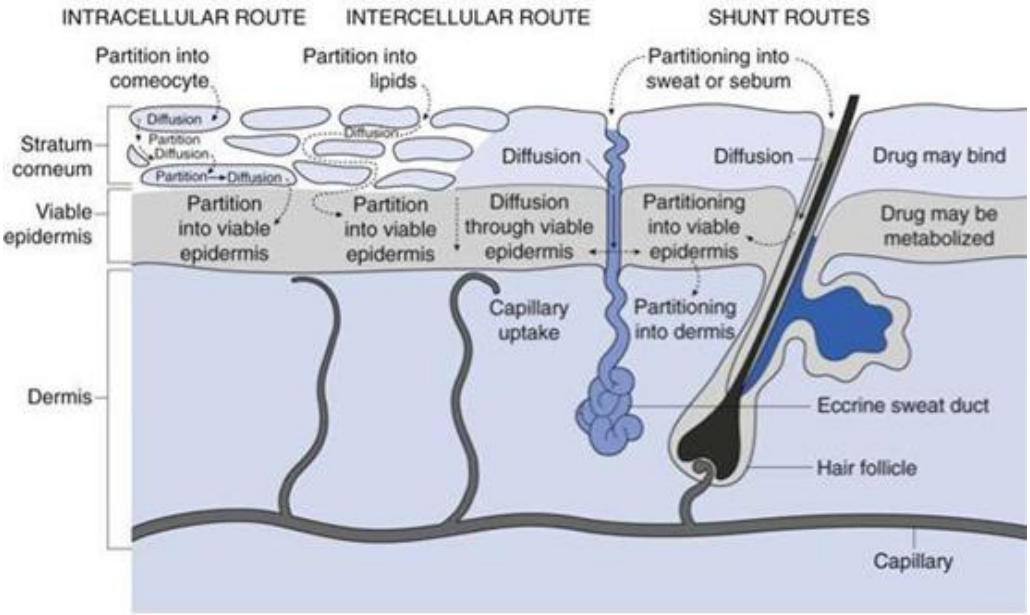

Figure 2: Route of drug permeation through skin

FACTORS AFFECTING TRANSDERMAL PERMEATION: [21,22]

The factors that affect the permeability of the skin are classified into following three categories:

A. Physicochemical properties of the penetrant molecule

B. Physicochemical properties of the delivery system

C. Physiological and pathological condition of the skin

Physicochemical properties of the penetrant molecule:

- Molecular size and shape
- Partition co-efficient
- Ph condition
- Ionization
- Drug concentration

Physicochemical properties of the drug delivery system:

- The affinity of the vehicle for the drug molecules
- Composition of drug delivery system
- Enhancement of transdermal permeation

Physiological and Pathological condition of the skin:

- Skin age
- Lipid film
- Skin hydration
- Skin temperature
- Cutaneous drug metabolism
- Species differences
- Pathological injury to the skin
- Blood flow
- Skin metabolism

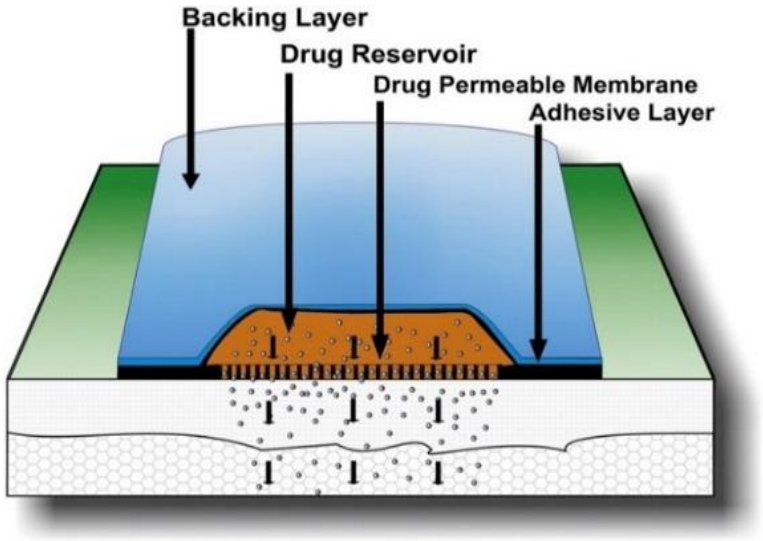

Figure 4: Basic components of TDDS

BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM: [23,24] [FIG. 4]

The components of transdermal drug delivery system include:

1. Drug substance
2. Polymer matrix
3. Penetration enhancers
4. Pressure sensitive adhesive
5. Backing membrane
6. Release linear

Drug substance: [Table 1]

Table 1: Table Showing Ideal Properties for Drug Candidate Used In Transdermal Drug Delivery System:

Parameter	Properties
Dose	Less than 20 mg/day
Molecular weight	Less than 1000 Dalton
Melting point	Less than 200°C
Half life	Less than 10 hours
Shelf life	Up to 2 years
Partition coefficient	1 to 4
Aqueous solubility	Greater than 1mg/mL
pH of the aqueous saturated solution	5-9
Skin permeability coefficient	Greater than 0.5×10-3cm/h
Skin reaction	Non irritating and non sensitizing
Oral bioavailability	Low

Polymer matrix: [Table 2]

Polymer is an integral and foremost important component of transdermal drug delivery system.

Table 2: Polymers Used for Transdermal Devices

Natural Polymers	Synthetic Polymers	Synthetic Elastomers
Cellulose derivatives	Poly vinyl alcohol	Hydrin rubber
Gelatin	Poly vinyl chloride	Silicone rubber
Waxes	Polyethylene	Polybutadiene
Proteins	Polypropylene	Nitrile
Gum	Polyamide	Acrylonitrile
Shellac	Polyurea	Neoprene
Natural rubber	Acetal copolymer	Chloroprene
Starch	Polystyrene	Polysiloxane
Chitosan	Epoxy	

PENETRATION ENHANCERS:

These are the compounds, which promote the penetration of topically applied drugs are commonly referred as absorption promoters, accelerants, or penetration enhancer.

Pressure sensitive adhesive:

A Pressure Sensitive Adhesive (PSA) is a material that helps in maintaining an intimate contact between transdermal system and the skin surface.

Backing membrane:

The primary function of the backing laminate is to provide support. They should be able to prevent drug from leaving the dosage form through the top. They must be impermeable to drugs and permeation enhancers. Eg.: Metallic plastic laminate, Vinyl polyethylene and Polyester films, Aluminium foil, Foam pad.

Release linear:

During storage the patch is covered by a protective liner that is removed and discarded before the application of the patch to the skin. It protect the patch during storage. A release coating layer is made up of silicon or Teflon.

APPROACHES IN THE DEVELOPMENT OF TRANSDERMAL THERAPEUTIC SYSTEM: [26,27] [FIG. 9]

Membrane permeation controlled system:

In this system the drug reservoir is totally embedded in a compartment molded between a drug-impermeable backing laminate and a rate controlling polymeric membrane The drug molecules are permitted to release across the rate controlling membrane simply by diffusion process through the pores. In the reservoir compartments the drug solids are dispersed

homogenously in a solid polymeric matrix (e.g. polyisobutylene) suspended in the unleachable viscous liquid medium (e.g. silicon fluid) to form a gel-like suspension, or dissolved in a releasable solvent (e.g. alkyl alcohol) to form a gel like in solution. The rate controlling membrane, can be either a microporous or non-porous polymeric membrane e.g. ethylene–vinyl acetate copolymer, having specific drug permeability. On the top surface of the polymeric membrane a thin layer of drug compatible adhesive polymer, e.g., silicone adhesives, can be applied, to provide intimate contact of the transdermal system with the skin surface. The release rate from this transdermal system can be tailored by varying the polymer composition, thickness of the rate controlling membrane , permeability coefficient and adhesive.

Examples of this system are TransdermScop (Scopolamine- 3 days protection) of motion sickness and TransdermNitro (Nitroglycerine-for once a day) medication of angina pectoris.

Matrix diffusion controlled system:

In this approach, the drug reservoirs are prepared by homogeneously dispersing drug particles in a hydrophilic or lipophilic polymer matrix or combination of both. The resultant medicated polymer is then molded into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in polymer matrix can be accomplished by either homogenously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of the polymer chains or homogenously blending drug solids with a rubbery polymer at an elevated temperature and/or under vacuum. The polymer disc which contains drug reservoir is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing. The adhesive polymer is then spread to form a strip of rim along the medicated disc. This matrix type of transdermal system is best example by the nitroglycerin releasing transdermal therapeutic system. The advantage of matrix dispersion type transdermal system is the absence of the dose dumping since the polymer cannot rupture.

Adhesive dispersion type system:

The system consists of drug-impermeable backing membrane, the drug reservoir which is prepared by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting or hot melting onto a flat sheet of drug-impermeable backing to form a thin drug reservoir layer. On the top of this, a layer of rate-controlling adhesive polymer(non-medicated) of constant thickness is spread to produce an adhesive diffusion-controlled drug delivery system with detachable release liner which in an ideal situation is removed and the patch is applied to the skin for a required period of time. Illustration of this type of system is exemplied by development and marketing of transdermal

therapeutic system of angina pectoris and Valsartan as angiotensin II type 1 selective blocker for one day medication.

Microreservoir type controlled system:

This system is basically hybrid of reservoir and matrix-dispersion type of drug delivery system. In this approach, drug reservoir is formed by suspending the drug in an aqueous solution of liquid polymer and then dispersing the drug suspension homogeneously in a lipophilic polymer e.g. silicone elastomers by high energy dispersion technique by shear mechanical force to form thousands of unreachable, and microscopic spheres of drug reservoirs. This technology has been utilized in the development of Nitro disc. Release of a drug from a micro reservoir-type system can follow either a partition-control or a matrix diffusion-control depending upon the relative magnitude of solubility of the drug in the liquid compartment and in the polymer matrix.

Example: Nitrodisc system for angina pectoris

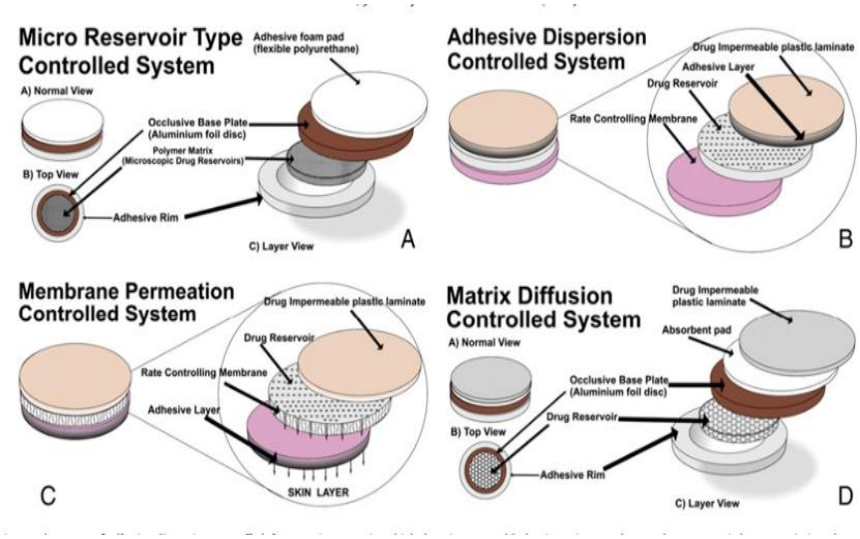

Figure 9: (A) Showing the presence of microscopic spheres of drug reservoir, (B) Development of adhesive dispersion controlled therapeutic system, (C) Diagrammatic representation of membrane permeation controlled system, (D) Representation of matrix type transdermal system

EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM: [25,26,27,28,29,30,31,32,33,34,35]

Evaluation studies are more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage form and can be classified into following types:

A) Physicochemical evaluation

A. *In vitro* evaluation

B. *In vivo* evaluation

A. Physicochemical Evaluation:

- Thickness of the patch
- Uniformity of weight
- Drug content
- Content uniformity
- Determination of surface pH
- Moisture content
- Moisture uptake
- Water vapour permeability (WVP) evaluation
- Flatness
- Folding Endurance

- **Adhesive properties:**

a) Shear adhesion test

b) Peel adhesion test

- **Tack properties**

a. Thumb tack test

b. Rolling ball tack test

c. Quick-stick (peel tack) test

d. Probe tack test

B. *In vitro* release studies:

- Paddle over disc apparatus (USP apparatus 5)
- Cylinder apparatus (USP apparatus 6)
- The reciprocating disc (USP apparatus 7)

***In vitro* permeation studies: [Figure 10]**

In vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Westar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin is thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into

the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed by spectrophotometry or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2).

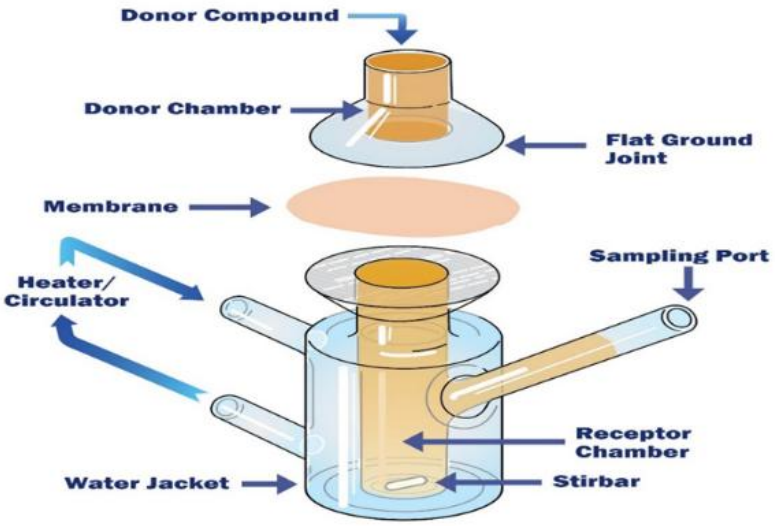

Figure 10: Franz Diffusion Cell

***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 and human volunteers.

a) Animal models

b) Human models

APPLICATIONS OF TRANSDERMAL PATCHES:

- Transdermal patch containing nicotine, which releases nicotine in controlled manner to help with cessation of tobacco smoking.
- Antihypertensive drug like clonidine and non-steroidal anti-inflammatory drugs are also available in the form of transdermal patches.
- Nitroglycerine patches are used in the treatment of angina pectoris.
- Transdermal agent for the Attention Deficit Hyperactivity Disorder (ADHD).
- Transdermal patch of the selegiline (MAO inhibitor) became the first transdermal delivery agent for major depressive disorder.

- Some transdermal patches for hormone delivery include the contraceptive patch.

Marketed Products of Transdermal Drug Delivery System: [39] [TABLE 3]

Table 3: Marketed Products of Transdermal Drug Delivery System

Brand Name	Drug	Manufacturer
Alora	Estradiol	TheraTech
Androderm	Testosterone	TheraTech/ GSK
Climaderm	Estradiol	Wyeth-Ayerest
Habitraol	Nicotine	Novartis
E-Trans	Fentanyl	Alza Corporation
Estraderm	Estradiol	Novartis
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals
TransdermScop^{R}	Scopolamine	Alza/Novartis
Neupro^{R}	Rigotine	UCB and Schwarz Pharma
NuPatch 100	Diclofenac diethylamine	Zydus Cadila
SonoDerm	Insulin	Imarx
Sono prep	Peptides	Sontra Medical corporation
Transderm nitro	Nitroglycerin	Novartis
Nicoderm	Nicotine	GlaxoSmithKline
Oxytrol	Oxybutynin	Watson Pharma
Matrifen^{R}	Fentanyl	Nycomed
Nicotinell^{R}	Nicotine	Novartis

CONCLUSION:

This article provides valuable information regarding the transdermal drug delivery systems and the details of evaluation process of TDDS is more useful reference for the research scientist. The study of transdermal drug delivery shows that it has great potentials, being able to use it for both hydrophilic and hydrophobic active substance into promising deliverable drugs. TDDS a realistic practical application as the next generation of drug delivery system and due to large advantages of it, many new researches are going on in the present day to incorporate newer drugs via the system.

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