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APPROACHES AND SIGNIFICANCE OF TRANSDERMAL DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT: Transdermal Drug Delivery System (TDDS) is the most innovative and Novel drug delivery systems by penetrating through the skin by increasing the scope of molecules that can be delivered. TDDS that traditionally uses a patch containing loaded drug substances pressed on to the skin is convenient, painless and non-invasive, to avoid gastro intestinal (GI) tract toxicity (peptic ulcer disease). Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation which often causes undesirable side effect. The number of medications and the ways in which they can be administered have expanded dramatically over the years. One such advancement is the development of transdermal patch delivery systems. Transdermal drug technology specialists are continuing to search for new methods that can effectively and painlessly deliver larger molecules in therapeutic quantities to overcome the difficulties associated with the oral route. Various products of TDDS are in use by applying approaches like micro needles, abrasion, micro scission, jet delivery, iontopher's, electroportation, ultrasound and radiofrequency. The present drug delivery is highly significant if compared to oral route for less side effect, better bioavailability and longer duration of action.

INTRODUCTION: For Thousands of years, human civilizations have applied substance to the skin as cosmetic and medicinal agents. However, it was not until the twentieth century that the skin came to be used as a drug delivery route.

In fact Merriam Webster dates the word "transdermal" to 1944 highlighting that it is a relatively recent concept in medical and pharmaceutical practice [1].

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TDDS deliver drugs through the skin as an alternative for more traditional route like oral, intravascular, subcutaneous and transmucosal[2]. A Transdermal Drug Delivery Systems (TDDS) or transdermal patch is defined as a flexible, multilaminated, pharmaceutical preparation of varying size containing one or more drug substances to be applied to the intact skin for systemic circulation to maintain the plasma level. This is normally formulated with pressure sensitive adhesive that assures the adhesion of the preparation to the skin [3]. Inception of transdermal patch systems paved the way for new medical therapies using existing drugs with the potential for fewer side effects for example estradiol patches, with a million users annually do not cause liver

damages, in contrast with oral formulation. As new medical therapy, Transdermal nicotine systems have helped millions of smokers quit smoking and likely increased their lifespan [4]. TDDS are ideally suited for diseases that demand chronic treatment. The chronic diseases like hypertension may be treated by the high cost of anti-hypertensive patches than conventional products [5]. TDDS not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic administration which often causes undesirable side effects [6].

Approaches Made in TDDS: Nearly 30-35 TDDS patch products are approved by the US-FDA for the last two decades. The First Commercially available prescription Patch was approved by the US-FDA in December 1979 which is used for the drug Scopolamine for the treatment of motion sickness. Various products of TDDS are in use by applying approaches like micro needles, abrasion, micro scission, jet delivery, iontophere's, electro-phortation, ultrasound and radiofrequency (**Table 1**).

TABLE 1: IMPORTANT TECHNOLOGIES USED IN THE TRANSDERMAL DRUG DELIVERY SYSTEM [15, 16]

Class	Type	Company Technology	Compounds in Development
Mechanical Energy	Micro Needles	Corium (Micro cor) Zosano Microflux 3M (MTS)	Fentanyl, Parathyroid Hormone Parathyroid Hormone, Influenza Vaccine, BA058(P.THr P analog)
		Nanopass Technologies	Allergy Vaccine
Electromagnetic spectral Energy	Abrasion Micro Scission Jet Delivery	Intercell (VE patch) Harvard MIT Glide Pharma	Pandemic Influenza Vaccine n/a Fentanyl, Octreotide
	Iontophoresis	Vyteris Incline Therapeutics (Ionsys) IOMED Travanti (Ionto patch)	Lidocaine (approved), Zelmitriptan, NASIDs Fentanyl (approved) Multiple Multiple
	Electroporation	Inovio	Cervical cancer, HPV, Influenza Vaccines
		Altea Therapeutics (passport)	Apo morphine, Insulin, Peptides
	Sonophoresis/ Ultrasound Radiofrequency	Echo therapeutics	Insulin, Erythropoietin, Heparin
		Transpharma (Vio Dor)	Parathyroid Hormone, GLP-1

With the technological advancement and various approaches TDDS has become popular and some of commercially available products are depicted in **Table 2**.

It is important for present study to review the structural and biochemical features of human skin and those characteristic which contribute to the barrier function and the rate of drug access into the body via skin. Anatomically, the skin has many histological layers but in general it is described in terms of three major tissue layers (**Fig. 1**).

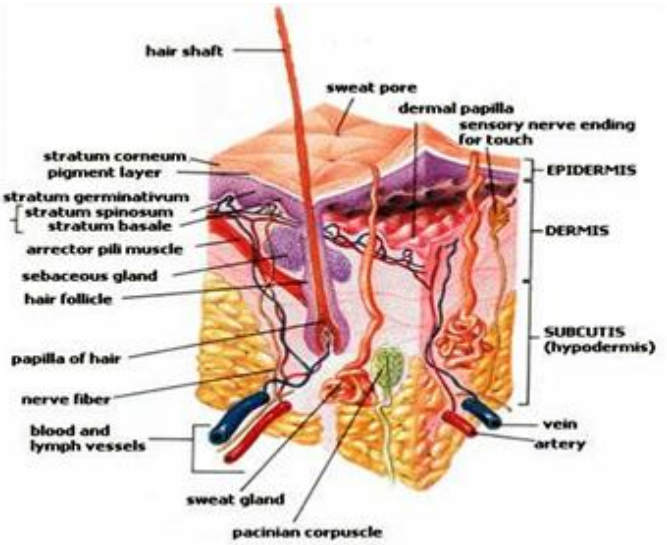

FIGURE 1: CROSS SECTION OF SKIN [7]

1. The epidermis layers, 2. The dermis, 3. The hypodermis. There are three main pathways by which drugs can cross the skin and reach the systemic circulation they are: Transcellular pathway, Intercellular route and Follicular route.

TABLE 2: SOME OF COMMERCIALLY AVAILABLE DRUGS IN THE MARKET

S. No.	GENERIC NAME OF DRUG	TRADE NAME OF THE DRUG IN THE MARKET	INDICATIONS
1.	Estradiol	1.Alore 2.Climaderm 3.Climara pro 4.CombiPatch 5.Estraderm 6.Esclim 7.Fempatch 8.Vivelle 9.Ortho-Evra(Ethynil estradiol)	Postmenstrual syndrome/Menopause
2.	Clonidine	1.Catapres-TTS	Hypertension
3.	Fentanyl/sisiontophore	1.Duragesic 2.Matrifen 3.Lonsys	Moderate/severe pain/Chronic pain/Acute Post-operative pain
4.	Nitroglycerin	1.Deponit 2.Minitran 3.Nitrodisc 4.Nitro-dur 5.Transderm Nitro 6.Nitroglycerine Generic	Angina Pectoris
5.	Dicloflenac diethylamine	Nupatch 100	Anti-inflammatory
6.	Scopolamine	Transderm Scop	Motion Sickness
7.	Nicotine	1.Nicoderm 2.Habitrol 3.Prostep 4.Nicotinell 5.Nicotrol 6.Nicoderm CQ	Smoking Cessation
8.	Testosterone	1.Androderm 2.Testoderm TT	Hypogonadism in Male/Testosterone deficiency
9.	Norelgestromin-estradiol Norelgostromin-Ethyinyl Estradiol	1.Ortho-Evra(Norlgestromin/Ethynil estrodiol 2.Combipatch(Estradiol-Norethidrone acetate) 3.Estradiol/Levonorgestrel	Birth Control/Postmenstrual syndrome Hormone replacement therapy/Menopause
10.	Estrogen/Progesterone	Nuvelle TS	Hormone replacement therapy
11.	Rotigotine	Neupro	Parkinson's disease(early-stage idiopathic)
12	Lidocaine	Lidoderm	Post-hepetic neuralgia pain
13.	Lidocaine/tetracaine Lidocaine/ultrsound	1.Synera 2.Sonoprep	Local dermal analgesia
14.	Methylphenidate	Daytrana	ADHD
15.	Selegiline	Emsam	Depression
16.	Rivastigmine	Exelon	Dementia
17.	Granisetron	Sancuso	Chemo-induced emesis
18.	Oxybutynin	Gelnique	Overactive bladder
19.	Buprenorphine	1.Butrans 2.Buvalor	Chronic pain Non-opioid analgesic

Significance of TDDS: TDDS has the advantage of easy to eliminate (simply to remove the patch) of drug delivery during toxicity or in case of any irritation occur at the site of applications. It causes avoidance of "hepatic first pass" metabolism of drugs. It maintains plasma concentration levels of drug within therapeutic range and it will decrease the side effects and it improves the bioavailability.

Drugs which would require frequent daily dosing for more uniform plasma levels may be more suitable to be administered as TDDS. This delivers a steady infusion of a drug over an extended period of time via non-invasive, painless and simple application.

This delivery is a good substitute for oral medication as in case of vomiting, diarrhea and GI tract associated problems like pH, enzymatic activity, drug food interaction or any disease of GI tract and free from the hazards and difficulty of IV infusion or IM injection.

The present delivery is suitable for self-administration and minimizes inter and intra patient variation. TDDS has the control of concentrations of drug with small therapeutic indices and provide predictable activity over extended duration of time with approximate zero-order kinetics. With the present example of drugs for TDDS, only small quantities of drug can be delivered through the stratum corneum, so relatively potent drugs with low dose are good choice for it.

TDDS patches are cost-effective and people prefer topical patches. If a transdermal delivery system is used in place of a needle, then medical waste can also be decreased, again decreasing healthcare costs. Some times TDDS used for peptide protein drugs, Hormone, vaccines and skin repair (cosmetics) products.

TDDS can be used for only narrow range of molecules with available technologies. Only small, relatively lipophillic molecules can pass through the lipid bilayers of the stratum corneum using traditional patch technology for larger and more complex molecules, new technologies (like nanotechnology) will be needed to deliver these drugs through the skin. Ionic drugs are not suitable candidate for TDDS.

The drug must have some desirable physicochemical properties for penetration through the skin. If the drug dose required for therapeutic value is more than 10mg/day the TDDS will be very difficult. The barrier function of the skin changes from one side to another on the same person, from person to person and with age. Clinical need is another area that has to be examined carefully before a decision is made to develop a TDDS product. Damage of the TDDS patch particularly a membrane or drug reservoir patch can result in poor control over the release rate.

These shortcomings may be overcome by using new TDDS technologies; these can be overcome to some extent by novel approaches such as iontophoresis, electroporation and ultrasound. TDDS Ionic drugs may be converted to non-ionic drugs for suitable TDDS.

Basic components of TDDS [9]: it becomes important to know components of TDDS. Basic components of TDDS are given in **fig. 2** and may be described as follows:

1. **Release Liner:** It protects the patch during the storage and external environment. The liner should be removed before its use.

2. **Drug:** The active drug solution in direct contact with release liner.

3. **Polymer Matrix/Drug Reservoir:** This is heart of TDDS, which control the release of the drug from the device.

4. **Adhesive and Peel Strip (PSA)**: Pressure Sensitive Adhesive the PSA serves to adhere the active compounds of the patch together along with adhering the patch to the skin.

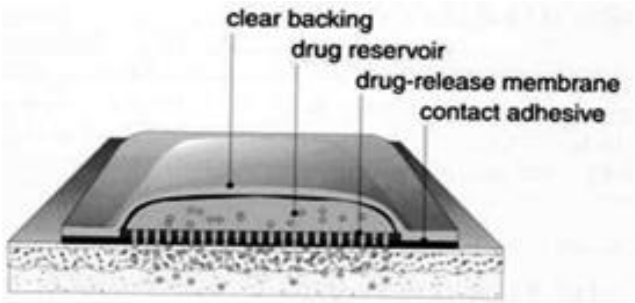

FIGURE 2: PARTS AND BASIC COMPOUNDS OF TDDS [14]

1. **Permeation Enhancer:** The chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate.

2. **Membrane:** It controls the release of the drug from the reservoir and multilayer patches.

3. **Backing laminate layer:** The film protects the patch from the external environment.

4. **Other excipients like Plasticizer and Solvent:** Various solvents like chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylpthalate, triethlcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

The application of the TDDS patches and the flow of the active compound drugs from the patch to the systematic circulation system (stratum corneum) via skin occur through various methods. For a systemically active drug to reach a target tissue, it has to possess some physicochemical properties which facilitate the absorption of the drug through the skin and enter the microcirculation [10].

TDDS may be used when the patient has intolerable side effects (including constipation) and who is unable to take oral medication. This might be useful in patients with are not able to self-medicate. It can be used in combination with other enhancement strategies to produce synergistic effect. TDDS may not be advised for cure of acute pain is required, where rapid and very high dose of titration is required.

TABLE 3: CHARACTERISTICS AND COMPARISONS OF DIFFERENT ROUTES OF DRUG DELIVERY SYSTEMS [15, 16]

Sl. No.	Route	Approx. surface Area	Physiological Properties	Enzymatic Barrier Properties	Unenhanced Bioavailability (%)	Technological Challenges
1.	Nasal	150cm^2	Mucus Ciliated Columnar Pseudo stratified Epithelium (10µm)	Medium	2-20	Small Surface Area Permeation
2.	Pulmonary	80-140cm^2	Bronchi and Bronchioles, Mucus, Ciliated columnar Pseudo stratified Epithelium (10-60µm), Alveoli; Squamous Epithelial Monolayer (<1µm)	Low	20-80	Precision of Delivery
3.	Buccal	100cm^2	Mucus, stratified, Partly Keratinized Epithelium(500-600µm), hydrated	Medium	0-5	Permeation
4.	TDDS	1.8m^2	Keratinized Stratified Epithelium (500-600µm)	Very Low	0-1	Large surface area (skin) Permeation
5.	Oral	>200m^2	Thick Mucus Layer Columnar Epithelial	High	0-1	Enzymatic Stability

The Comparison of oral route to TDDS from **Table 3** results in almost the same bioavailability for both route but very low enzymatic barrier properties for TDDS. The skin has approximately 1.8m^2 surface area (Table 3) which is exploited by technological improvement for better permeation on of drug to the blood. Ease to apply TDDS to any part of the skin makes this drug delivery popular and patient compliance.

Evaluation Parameters: The evaluation parameters of TDDS are classified in to six types:

1. Physicochemical evaluations include: Interaction studies, Thickness of the patch, Weight uniformity, Folding endurance, Percentage of Moisture content, Percentage Moisture uptake, Water vapor permeability (WVP) evaluation, Drug content determination, Uniformity of dosage unit test, Polari scope examination, Shear Adhesion test, Peel Adhesion test, Thumb tack test, Flatness test, Percentage Elongation break test, Rolling ball tack test, Quick Stick (peel-tack) test and Probe Tack test.

2. *In vitro* evaluations are *in vitro* drug release studies and *in vitro* skin permeation studies.

3. *In vivo* evaluations are comprised of Skin Irritation study, if Animal models (rat, rabbit, and monkey) and Human volunteers and Biophysical models.

4. Cutaneous toxicological evaluation are conducted by Contact dermatitis(contact irritant dermatitis 10-day primary irritation test, 21-day irritation test, Laser doper, Evaporation water loss measurement, contact allergic dermatitis) and Growth of Microorganism (Localized superficial infection)

5. Stability Studies.

6. Histopathology studies.

CONCLUSION: TDDS is a having many approaches to improve the bioavailability and increase the variety range of drugs. This is convenient route of administration for many clinical indications. The TDDS technology no longer is just an adhesive patches due to the latest advances in technology, it can be applied to the site of action without breaking the skin membrane. The TDDS route overcomes challenge associated with current popular drug delivery system and mostly suggested and accepted route of drug administration and its upcoming market is undoubtedly have promising future. The present review is highly illustrative in describing approaches and significance of TDDS.

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