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transdermal patch: review

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ABSTRACT:
Today, around 74% of medications are taken orally and are found to be less effective than expected, either as a result of bioavailability issues or drug degradation in the stomach's acidic pH.(TDDS) was developed to address these issues. While a large portion of the medicine is carried into the systemic blood circulation, transdermal drug delivery methods are dosage forms that entail drug transfer to the epidermal and dermal tissues of the skin for local therapeutic benefit. Systems for(TDDS), also called "patches."are dosage forms made to spread a therapeutically effective amount of medication across the skin of a patient. This review article gives a general overview of TDDS, as well as information on its benefits, drawbacks, numerous components, preparation techniques, transdermal patch types, factors affecting transdermal penetration, evaluation criteria, and novel TDDS methodologies.

I. INTRODUCTION[1-2]:

Recently, there has been a resurgence in interest in creating new methods for delivering current medicinal compounds. The creation of a novel delivery mechanism for already existing medicinal molecules significantly increases patient compliance, overall therapeutic benefit, and the efficacy and safety of the treatment.

Novel delivery systems can effectively deliver drugs with improved bioavailability by using the novel concepts of timed or pulsatile release, or gastro-resistant delivery, when properly designed and developed for a particular drug. For example, drugs that undergo partial or complete degradation before reaching the site of action could be delivered with improved bioavailability by using the novel concepts of timed or pulsatile release, or gastro-resistant delivery.

Drug compositions have improved during the past 20 years, as have new administration methods. We now understand more about how drugs move through tissues. The use of the skin as a channel for systemic medication delivery is relatively new, despite the fact that topical medicines or drug delivery systems have been utilised for centuries to treat localised skin problems. The advantage of transdermal medication delivery is that it is comparatively painless. In cases of access, the appeal of exploiting the skin as a portal for drug entry rests invast surface area, systemic access via underlying lymphatic and circulatory networks, and noninvasive drug delivery. Transdermal delivery, often known as skin absorption, is the practise of administering medications to the body . it was first usedin 1981, when Ciba-Geigy marketed Transderm V(present day marketed as Transderm Scop) toprevent the nausea and vomiting associated withmotion sickness.

TRANSDERMAL PATCH[1-4];

DEFINITION: A transdermal patch or skin 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 bloodstream.

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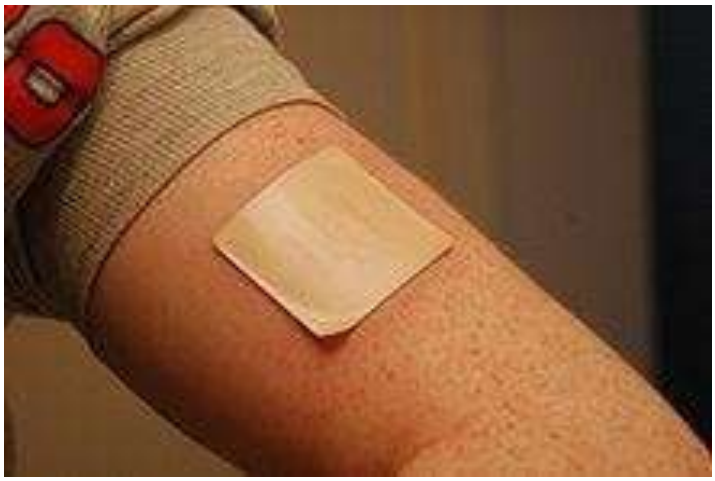

TRANSDERMAL PATCH

- **ADVANTAGE ANDDISADVANTAGEOF TRANSDERMAL PATCH[4-8]**

ADVANTAGES OF TRANSDERMAL PATCH

- They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administrationdrug.
- They can substitute for oral administration of medication when the route is unsuitable as with vomiting anddiarrhea.
- To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liner when takenorally.
- They are noninvasive, avoiding the inconvenience of parenteraltherapy.
- They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Transdermal clonidineday.
- The activity of drugs having a start half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlledrelease.
- Drug therapy may be terminated rapidly by removal of the application from the surface of theskin.

- **DISADVANTAGES OF TRANSDERMAL PATCH**

- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitatingdiscontinuation.
- Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin'simpermeability.
- Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.
- Long time adhere is difficult.

- Not practical, when the drug is extensively metabolized in the skin and when molecular
- size is great enough to prevent the moleculesfrom diffusing through the skin.

- Not suitable for a drug, which doesn't possess favourable, o/w partition coefficient
- The barrier functions of the skin of changesfrom one site to another on the same person,from person to person and with age.
- Transdermal delivery is neither practical noraffordable when required to deliver largedoses of drugs through skin

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CARE TAKEN WHILE APPLYING TRANSDERMAL PATCH[4-12]

Before applying the patch, the area of skin needs to be well cleaned. The patch should not be cut because doing so damages the drug delivery system. Before applying a new patch, it should be ensured that the old patch has been removed from the area. Anyone handling the patch has the potential to absorb the medicine, thus caution should be exercised when applying or removing it. Accurate patch application is required at the administration site.

- **FIRST-GENERATION TRANSDERMAL DELIVERY SYSTEMS[11-13]**.The majority of transdermal patches that have been used in clinical settings so far are from the first generation of transdermal delivery methods. The recent explosion of first-generation transdermal patches entering the market is the result of significant improvements in patch technology and widespread acceptability. However, as medications with beneficial qualities for such systems run out, this spike will start to taper off. Candidates for first-generation delivery must have low molecular weight, be lipophilic, and be effective at low dosages.
- **SECOND - GENERATION TRANSDERMAL DELIVERY SYSTEMS[14-15]**

The second generation of transdermal delivery systems acknowledges the necessity of improving skin permeability in order to broaden the application of transdermal medications. The perfect booster ought to

1. increase skin permeability by reversibly disrupting stratum corneum structure.
2. provide an added driving force for transport into the skin and, avoid injury to deeper, living tissues.

- **ANATOMY AND PHYSIOLOGY OFSKIN[12-20]**

Human skin comprises of three distinct but mutually dependent tissues: The stratified, vascular, cellular called as “epidermis” Underlying dermis of connective tissues, Hypodermis .

- **Epidermis**

Depending on cell size and the number of cell layers, the multilayered epidermis can range in thickness from 0.8mm on the palms and soles to 0.06 mm on the eyelids. Corneum stratum. This is the skin's outermost layer, commonly known as the horny layer. When fully hydrated, it grows to several times this thickness and is around 10 mm thick when dry. It has 10 to 25 layers of corneocytes, which are keratinized, dead cells. Although flexible, it is largely impermeable. The main defence against drug entry is the stratum corneum. It is possible to model the architecture of the horny layer as a wall-like structure. The keratinized cells in this model serve as protein "bricks" encased in lipid "mortar." Multiple bilayers are used to organise the lipids.

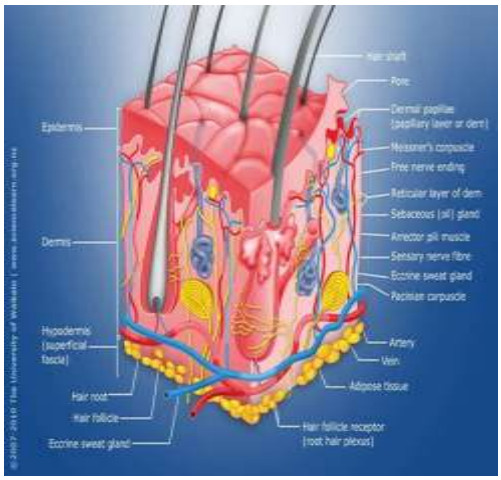

Fig.1 Structure of human skin

The lipid fraction contains enough amphiphilic material, including cholesterol and polar free fatty acids, to sustain a bilayer shape. Under the stratum corneum, there is viable epidermis that ranges in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. It is made up of different layers as it moves inward, including the stratum basal, stratum lucidum, stratum granulosum, and stratum spinosum. The epidermis is continuously renewed by cell division in the basal layer, and this proliferation makes up for the loss of dead horney cells from the skin's surface. The basal layer's outwardly migrating cells undergo morphological and histochemical changes as they undergo keratinization to form the stratum corneum's topmost layer.

- **Dermis**

The dermis is a 3 to 5 mm thick layer made up of a connective tissue matrix that houses nerves, blood vessels, and lymphatic vessels. The control of body temperature relies heavily on the cutaneous blood supply. While removing pollutants

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and waste, it also gives the skin nutrition and oxygen. Most molecules that penetrate the skin barrier sink in capillaries, which are located 0.2 mm from the skin's surface. Therefore, the blood supply maintains a very low dermal concentration of a drug, and the ensuing concentration gradient across the epidermis is crucial for transdermal permeation**.**

➢ **Hypodermis**

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer aids in temperature regulation, nutritional support, and mechanical protection. It connects major blood vessels and nerves to the skin and may house sensory pressure organs. Transdermal drug delivery requires drug penetration through all three layers and into systemic circulation, whereas topical drug delivery requires only stratum corneum penetration and drug retention in skin layers.

➢ **COMPONENTS OF TRANSDERMAL PATHCHES**[22-24]

• The Polymer Matrix

The polymer regulates the drug's release from the device. For a polymer to be utilised in transdermal patches, it must meet the following characteristics.

a)The polymer's molecular weight and chemical activity should be such that the specific medicine diffuses and is released through it appropriately.

b)The polymer needs to be stable.

c)The polymer should be harmless.

d)The polymer should be simple to produce.

e)The polymer should be cheap.

f) The polymer and its degradation product must not be poisonous or unfriendly to the host.

g)It contains a large amount of the active agent..

➢ **TYPES OF POLYMER**: -

a)Natural polymers: Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.

b)Synthetic Elastomers: Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.

c)Synthetic polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamiode, polyurea, epoxy.

➢ **DRUG**:

Direct contact between the drug solution and the release liner. Physiochemical characteristics:

a) The drug's molecular weight should be less than 1000 Daltons.

b) The medication needs to be able to bind to both lipophilic and hydrophilic phases.

- Biological characteristics:

a) The drug should be effective at doses of only a few mg per day.

b) The drug's half-life (t12) should be brief.

c) The medication must not cause an allergic reaction.

d)Under the near zero-order release profile of transdermal patches, drug tolerance must not form.

Different parts of transdermal patch

➢ **OTHER EXCIPIENTS**: -

- Adhesives: - The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device.
- It should be easily removed.
- Physical & chemical compatibility with the drug.
- Permeation of drug

➢ **FACTORS AFFECTING TRANSDERMAL BIOAVAILABILITY**[24-26]

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

- Physicochemical Factors: -
- Skin hydration:

In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectant is done in transdermal delivery.

- Temperature and pH:

The permeation of drug increase ten folds with

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temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

- Diffusion coefficient:

Penetration of drug depends on diffusion coefficient of drug. At a constant temperature, the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

- Drug concentration:

The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of will be more across the barrier.

- Partition coefficient:

Partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

- Molecular size and shape: Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

➢ **Biological Factors Skin condition**: Acids and alkalis, many solvents like chloroform, methanol damage the skin cells and promotes penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.

- Skin age:

The young skin is more permeable than older. Children's are More sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDS.

- Bloodflow:change in peripheral circulation can affect transdermal absorption. Regional skin sites Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration. Skin metabolism Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin

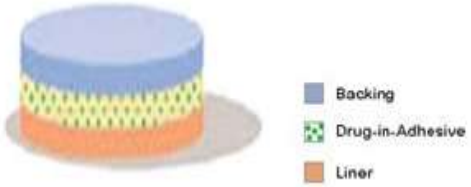
- Species differences:

The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration.

➢ **TYPES OF TRANSDERMALPATCHES**[8-12]

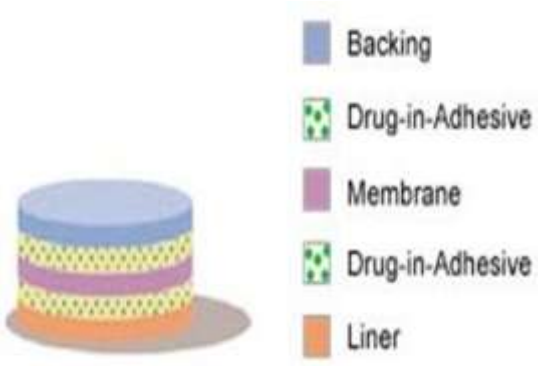
A. Single-layerDrug-in-Adhesive:

The drug is also present in the adhesive layer of this system. The adhesive layer in this type of patch is responsible for drug release as well as adhering the various layers together and the entire system to the skin. The adhesive layer is surrounded by a temporary liner and a backing.



B. Multi-layerDrug-in-Adhesive:

The single-layer system and the multi-layer drug-in adhesive patch are similar in that both adhesive layers are in charge of releasing the drug. But the multi-layer system differs in that it includes an additional layer of drug-in-adhesive that is typically separated from the others by a membrane (but not in all cases). This patch also has a long-lasting backing and a short-term liner layer.



C. Reservoir:

The reservoir transdermal system has a separate drug layer in contrast to the single-layer and multi-layer Drug-in adhesive systems. The adhesive layer serves as a physical barrier between the drug layer and a liquid compartment containing a drug solution or suspension. The backing layer also supports this patch. The rate of release in this

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kind of system is zero order.

D. **Matrix**:

The Matrix system has a drug layer that is partially overlaid by a semisolid matrix that contains a drug.

E. **Vapor Patch**:

The adhesive layer in this kind of patch not only holds the various layers together but also lets out steam. The essential oils released by the vapour patches, which are new on the market, can last up to 6 hours. The vapour patches, which mostly treat decongestion cases, release essential oils. There are also controller vapour patches on the market that enhance sleep quality.

There are also vapour patches on the market that help people smoke fewer cigarettes each month.

➢ **CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE USED**[32-45]:

Transdermal patch is used when:

- 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.
- 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

➢ **CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE NOT USED**:

The use of transdermal patch is not suitable when:

- Cure for acute pain is required.
- Where rapid dose titration is required.
- Where requirement of dose is equal to or less than 30 mg/24 hrs.

➢ **IDEAL PRODUCT REQUIREMENTS OF PATCHES**

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

❖ **EVALUATION TEST OF TRANSDERMAL PATCH**[28-40]:

➢ Drug Excipients Interaction Studies:

The drug and excipients should be compatible to produce a stable product, and it is mandatory to detect any possible physical and chemical interaction. Interaction studies are commonly carried out using thermal analysis, FT-IR studies, UV and chromatographic techniques by comparing their physiochemical characters such as assay, melting endotherms, characteristic wave numbers, and absorption maxima etc.

➢ Drug Content: A specified area of the patch is to be dissolved in a suitable solvent in specific volume. 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: The prepared patches are to be dried at 60°C for 4 hrs 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.

➢ Thickness of the Patch: The thickness of the drug loaded patch is measured in different points by using a digitalmicrometer and determines the average thickness andstandard deviation for the same to ensure the thickness ofthe prepared patch.

➢ Flatness Test: Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity

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in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

- Percentage moisture uptake = [Final weight- Initial weight/ initial weight] × 100.
- Moisture Loss: The prepared films are to be weighed individually and to be kept in a desiccator containing calcium chloride at 40oC. After 24 hrs the films are to be reweighed and determine the percentage of moisture loss from the below formula.
- % Moisture Loss = [Initial wt – Final wt/ Final wt] × 100

- **PATCHES AVAILABE IN MARKET[42-48]:**

Drug/product name	Utilization	Company	Year of FDA approval
Adlarity	Severe Alzheimer disease	Corium Biopharmaceuticalcompany	2022
Asenapine	Antipsychotic	Noven Pharmaceuticals	2019
Secuado	Atypical antipsychotic	GlobalData Healthcare	2019
5-HTP/Oxitriptan	Antidepressant,Sleep aid	Duchefa Farma B.V.	2014
Sumartriptane	Migraine	Teva Pharmaceutical Industries	2013
Rotigotine	Parkinson diesease	Vektor Pharma	2012
Buprenorphine/Butrans	Chronic pain	Purdue Pharma	2010
Capsaicin/Qutenza	Neuropathic pain	NeurogesX	2009
Menthol (Methyl Salicylate)	Muscle and joint pain	Hisamitsu Pharmaceutical	2008
Rivastigmine/Exelon	Dementia	Novartis Pharmaceuticals	2007
Diclofenac epolamine/Flector	Topical treatment acute pain	Lnstitute Biochimique SA	2007
Rotigotine/Neupro	Parkinson's disease	Schwarz BioSciences	2007
Selegiline/Emsam	Major depressive disorder	Somerset BioScience	2006
Methylphenidate/Daytrana	Attention deficit hyperactivity disorder	Noven Pharmaceuticals	2006
Ethinyl estradiol with norelgestromin/ Ortho Evra	Contraception	R.W.Johnson Pharmaceutical ResearchInstitute	2001
Lidocaine/ Lidoderm	Postherpetic neuralgia pain	Hind Health Care	1999
Lidocaine with epinephrine	Local dermal analgesia	IOMED	1995
Nitroglycerin/ Nitro-Dur	Angina pectoris	Schering	1995
Testosterone /testroderm	Testosteronedeficiency	ALZA	1993
Nicotine/Nicoderm CQ	Smoking cessation	Sonafi Aventis US	1991
Fentanyt/Duragesic	Chronic pain	Janssen Pharmaceutical	1990
Estradiol/Estraderm	Hormone replacement therapy	Novartis Pharmaceuticals	1986
Clonidine/Catapres-	Hypertension	Boehringer ingleheim	1984

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TIS			
Scopolamine/Transdermal Scop	Motion Sickness	Glaxosmithkline Consumer Health	1979

➢ **RECENT ADVANCES IN THE FIELD OF TRANSDERMAL PATCHES[42-51]:**

1. Patch technology for protein delivery
2. Pain-free diabetic monitoring using transdermal patches
3. Testosterone transdermal patch system in young women with spontaneous premature ovarian failure
4. Transdermal Patch of Oxybutynin used in overactive bladder (OAB).
5. Pain relief
6. Molecular absorption enhancement technology

II. CONCLUSION:

Regular doses of various medications can be administered painlessly, conveniently, and possibly effectively using transdermal drug delivery. Various medications can be administered. enhanced medication absorption Low cheap and simple to use with little issues and negative effects. Using the nicotine patch, for instance, millions of people are able to successfully quit smoking. Patients are also treated with nitroglycerin for angina, clonidine for hypertension, scopolamine for motion sickness, and estradiol for oestrogen insufficiency through the use of patches.

A medicinal product that is currently licenced for oral dosing can evade first pass metabolism by being delivered transdermally. The most popular method of transdermal medication administration uses skin patches.However,the transdermal technologies have limitations due to the relatively impermeable thick of outer stratum corneum layer. Researchers are trying to overcome this hurdle of poor permeability by physical and chemical means.

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