A Review On Delivering Drugs Through The Skin: A Thorough Exploration Of Transdermal Systems

[1]Kishor C. Badgujar, [2]Balaprasad P. Borade, [3]Mr. Kalpeshkumar Wagh, [4]Ms Shital Rajput, [5]Mr. Kalpesh More

Department of Pharmaceutics
Kisan Vidya Prasarak Sanstha`s Institute Of Pharmaceutical Education
Boradi, Dhule-425428

***Abstract*- Transdermal drug delivery systems have come a long way from their inception, evolving into a critical component of modern medicine. This review provides a comprehensive exploration of the various aspects surrounding transdermal drug delivery. It begins with an introduction, defining and delving into the historical development of transdermal patches. The advantages of this drug delivery method, including painless administration, sustained release, and avoidance of first-pass metabolism, are discussed, along with the inherent limitations, such as restrictions on drug types, skin permeability issues, and size constraints. The mechanisms of transdermal delivery, encompassing passive diffusion and active transport, are detailed, shedding light on the key factors affecting skin permeability and drug absorption rates. Transdermal patch design, incorporating different types and materials, is explained, along with drug selection criteria and formulation considerations. The importance of adhesive technology in ensuring patch adherence, skin compatibility, and wearability is highlighted.**

***Keywords:* Transdermal delivery, skin penetration, Permeation enhancer, Mechanisms of Transdermal system, Application of Transdermal systems.**

Introduction:

A transdermal drug delivery system is designed to allow the passage of medicinal substances from the surface of the skin, through its various layers, and into the systemic circulation[1] TDDS has become one of the most researched routes of non-invasive drug delivery to the body. Through the skin, as opposed to conventionally used direct routes of administration, which use injections with a needle. TDDS has significantly influenced the administration of various agents, particularly in pain management, hormone therapy, and the treatment of cardiovascular and central nervous system diseases [2, 3].

Dermal (topical) administration of the drug is used to define a localized effect on pathological sites in the skin with minimal systemic absorption. However, transdermal drug delivery systems (TDDS) are defined as self-contained dosage forms that deliver the active agent(s) through the skin at a controlled rate into the systemic circulation over an extended period of time. The first Food and Drug Administration (FDA, 1979) approved TDDS was a three-day patch for scopolamine (Transderm-Scop) for the treatment of motion sickness. A decade later, nicotine patches were the first transdermal blockbuster, raising awareness of transdermal application among healthcare professionals and the general public. There are currently more than 19 TDDSs for many active ingredients including estradiol (Estraderm), nitroglycerin (Transderm-Nitro), fentanyl (Duragesic), clonidine (Catapres-TTS), lidocaine (Lidoderm), and testosterone (Testoderm). In addition, fixed-dose combination patches containing more than one active ingredient have been developed for contraception and hormone replacement, eg, estradiol with norethidrone (Combipatch), and iontophoretic (fentanyl HCl/Ionsys) and ultrasound (lidocaine/SonoPrep) delivery systems for analgesia.[4]

TDDS does not involve gastrointestinal passage, there is no loss of drug due to first-pass metabolism, and drugs can be administered without interference with pH, enzymes, or gut bacteria. Another advantage of TDDS is dose reduction compared to oral dosage forms for the same drug [14] In addition, TDDS has improved bioavailability, more uniform plasma levels, and longer duration of action, resulting in lower dosing frequency, fewer side effects, and improved therapy due to plasma level maintenance until the end of the dosing interval, in contrast to the decline in plasma levels with conventional oral dosage forms.[5-6].

The following characteristics should be present in an ideal drug candidate for transdermal drug Delivery [7]:

- The molecular weight should be <500Da;
- Log partition coefficient (log P) should lie within a range of 1-3
- The drug molecule should be potent with a therapeutic dose of less than 10 mg

- The aqueous solubility should be greater than 100 ug/mL.

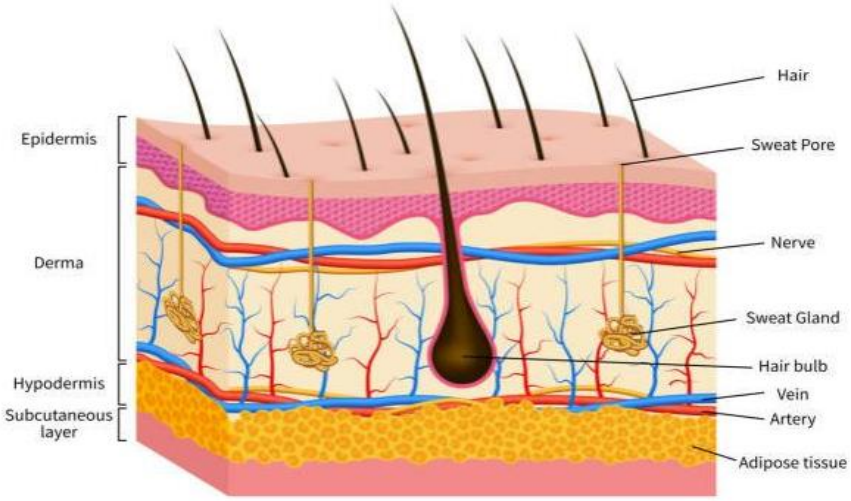

Fig. No.:01 Anatomy of Skin

The Anatomy and Physiology of Skin [8]:

With a surface area of 1.7 m^2, the skin is the largest organ of the body accounting for nearly 16 percent of an average person's total body mass. The primary function of the skin is to protect the body from microorganisms, Ultra-violet radiation permeation, chemicals, allergens, and water loss.

Layers of Epidermis:

The layers of the epidermis include the stratum basal (the deepest portion of the epidermis), stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum (the most superficial portion of the epidermis).

Dermis

The dermis is connected to the epidermis at the level of the basement membrane and consists of two layers, of connective tissue, the papillary and reticular layers which merge together without clear demarcation. The papillary layer is the upper layer, thinner, composed of loose connective tissue and contacts epidermis. The reticular layer is the deeper layer, thicker, less cellular, and consists of dense connective tissue/ bundles of collagen fibres. The dermis houses the sweat glands, hair, hair follicles, muscles, sensory neurons, and blood vessels.

Hypodermis

The hypodermis is deep to the dermis and is also called subcutaneous fascia. It is the deepest layer of skin and contains adipose lobules along with some skin appendages like the hair follicles, sensory neurons, and blood vessels

HISTORY OF TDDS:

Although the term TDDS was coined recently, the knowledge and history of transdermal drug application is well known since ancient times. For several years, several cultures of ointments, pastes, plasters and complex medical procedures have been known in the treatment of various diseases. [9] Mustard plaster can be considered as an example, which has been used for a long time as a home remedy for severe chest congestion. Briefly in this process, powdered mustard seed (Brassica nigra) was mixed with warm water and the resulting paste was spread on a strip of flannel and applied to the patient's chest using a cloth bandage wrapped around the body to hold the patch in place. . Moisture and body heat activated an enzyme (myrosin) in the mustard that hydrolyzed the glycoside (sinigrin), causing the release of the pungent active ingredient allyl isothiocyanate (CH_2=$CHCH_2NCS$). The most notable prototype of modern transdermal medication was Stronger Mercurial Ointment, used to treat syphilis.[10].

Taking into account the global economic situation, despite the small number of drugs that are currently delivered by this route, it is estimated that the worldwide sales of transdermal products are 3 billion USD, divided between the USA 56%, Europe 32% and Japan 7% Overall, there has been a huge increase in research and development that has allowed remarkable progress to be made in the formulation and clinical development of transdermal products for cardiovascular diseases or neurological problems such as Parkinson's disease, Alzheimer's disease, depression, anxiety, attention deficit hyperactivity disorder (ADHD) or cancer, for example, skin cancer or sexual dysfunction in women, postmenopausal bone loss and urinary incontinence [11-13].

The mammoth price tag, long time, and uncertainty about returns have stifled the discovery of newer drugs, so the concept of new uses for drugs or finding newer and more convenient routes of drug administration has come into the picture. The application of controlled release drug delivery concepts and techniques helped construct these new drug delivery systems that not only extended the effective life of an existing drug but also minimized the scope and expense of testing required for FDA approval. This new approach led to advances in transdermal patches in the 1970s, which produced the first patch approved by the US FDA in 1979, called Transderm-SCOP. [14]

Initially in 1877, Fleischer stated that the skin was completely impermeable. This was a bold and extreme claim that could not stand for long 13 With a large number of collective studies and after almost 80 years, new ideas began to emerge. Research has been done to determine what causes the skin to have barrier properties that prevent molecular permeation. In 1924, Rein suggested that the layer of cells connecting the stratum corneum (SC), the outermost layer of the skin, with the epidermis, represents the main resistance to transdermal transport. Blank modified this hypothesis after removing sequential SC layers from the skin surface and showed that the rate of water loss from the skin increased dramatically after SC removal. [15]

Advantages and Disadvantages of TDDS [16-18]:

Advantages:

- More loading capacity for some drugs
- Less water in the dispersion
- Prevent or minimize the drug expulsion during storage
- Control and targeted drug release
- Feasibilities of loading both lipophilic and hydrophilic drugs
- Use of biodegradable and biocompatible lipids
- Avoid organic solvents
- More affordable (less expensive than polymeric/surfactant based carriers
- Easier to qualify, validate and gain regulatory approval
- Better physical stability
- Ease of preparation and scale-up
- Improve benefit/risk ratio
- Increase of skin hydration and elasticity
- Small size ensures close contact with the stratum corneum
- Enhanced stability of drugs

Disadvantages:

- Cytotoxic effects related to the nature of lipid matrix and concentration
- Irritation and sensitizing action of surfactants
- Stability of Lipid
- Application and efficiency in case of protein and peptide drugs and gene therapy
- Delivery systems still need to be exploited

Limitations of TDDS [19]

- Possibility of local irritation at the site of action application and the frequency Skin irritation or contact dermatitis due to drug or exipients
- Skin's low permeability limits the number of drugs that can be delivered in this manner

Mechanisms of Transdermal drug delivery systems:

Transdermal chemical penetration enhancers with active ingredients and Mechanisms of action:

Sr No	CPEs	Drug Used	Mechanism of action
1	Dimethyl sulphoxide	Hydrocortisone[20]. Testosterone[21]. Naloxone[22]	• Disrupt the lipid bilayer of the SC • Denature the proteins of the SC • Change the intercellular keratin conformation of the SC
2	Azone	Ketoprofen[23]. Dimethyl fumarate[24]. Fluorouracil[25].	• Disrupt the lipid bilayer of the SC
3	Pyrrolidone	Ketoprofen[23]. Lidocaine	• Change the intercellular keratin conformation of the SC

Table	hydrochloride[26]. Bupranolol[27].	• Change the solubility properties of the SC

No.01: Mechanisms of Transdermal drug delivery systems

Transdermal Patch Design

1. **Matrix Patches [28]:** Designed to optimize drug delivery, the API is contained within the application area and does not come into contact with the adhesive, allowing for higher potential drug loading. In addition, our occlusive pad increases the rate of penetration compared to gels or creams.
2. **Reservoir Patch [29]:** Medicines in the reservoir patch are stored in their own liquid layer, separate from the adhesive. When applied to the skin, the drug slowly leaves the liquid layer through a rate-controlling membrane. Medicines then reach the skin through the glue. The top layer contains the other side of the liquid drug layer.
3. **Single-Layer Drug-in-Adhesive [29]:** The entire patch is composed of a single layer of adhesive that contains a dose of medicine. When applied, this layer adheres to the skin and simultaneously releases the drug.
4. **Multi-Layer Drug-in-Adhesive [29]:** Similar to single-layer, but contains more than one layer of drug in the adhesive. It is usually used for longer term patches. Each layer begins to diffuse through the next as the layers closest to the skin complete drug delivery.
5. **Vapour Patch [29]:** The adhesive layer of the vapour patch also serves as a vector for vapour release. Steam patches can last up to six hours and are most commonly used as decongestants or sleep aids.

Drug Selection and Formulation:

Selection Criteria for TDDS [30]:

Sr No	Parameter	Properties
1	Dose	<20ng/Day
2	Half-life in hr	10 or less
3	Molecular weight	<400
4	Partition Coefficient	Between - 1.0 To 4
5	Skin Permeability Coefficient	> 0.5×10^{-3} cm/h

Table No.02 Selection Criteria for TDDS

Formulation of TDDS [31]:

A transdermal therapeutic system is essentially a multilaminate structure that is composed of following constituents:

1. **Drug :**

The most important requirement of a drug to be administered transdermally is demonstrated by the need for controlled administration, such as a short half-life, adverse effect associated with another route, or complex oral or I.V. dosing regimen. Drug parameter required for an ideal drug candidate for transdermal drug delivery.

2. **Polymer matrix :**

Advances in transdermal drug delivery technology have been rapid due to the sophistication of polymer science, which now allows polymers to be incorporated into the transdermal system (TDS) in adequate amounts. Polymers useful for transdermal devices.

- Gelatin
- Gum tragacanth
- polyethylene
- Methyl and ethyl cellulose
- Polyhydroxyethyl methacrylate (PHMA)
- Polyvinyl chloride (PVC)

3. **Penetration enhancer :**

A commonly investigated approach to promote skin penetration of poorly penetrating drug molecules is to incorporate a chemical penetration enhancer into TDDS.

There are mainly three approaches for the penetration enhancement:

- **Chemical approach :**

a. Synthesis of lipophilic analogs;
b. Delipidization of stratum corneum;
c. Co-administration of skin permeation enhancers.

- **Biochemical approach :**

a. Synthesis of bio-convertible pro-drugs
b. Co-administration of skin metabolism inhibitors.

- **Physical approach**

a. Iontophoresis
b. Sonophoresis: Ultrasonic energy
c. Thermal energy;
d. Stripping of stratum corneum
e. Hydration of stratum corneum

4. Adhesive layer

The adhesive must have sufficient properties to firmly attach the system to the skin surface and hold it in place for the required time, even in the presence of water. After removing the patch, it must be possible to wash off all adhesive residues with soap and water. The adhesive must have sufficient properties to firmly attach the system to the skin surface and hold it in place for the required time, even in the presence of water. After removing the patch, it must be possible to wash off all adhesive residues with soap and water.

1. Peel: The resistance against the breakage of the adhesive bond.
2. Track: The ability of a polymer to adhere to a substrate with little contact Pressure.
3. Creep: The viscous relaxation of the adhesive bond upon shear.

5 Backing layer :

The backing layer must be impermeable to the drug and permeation enhancers. The back membrane serves to hold the entire system together while protecting the drug reservoir from exposure to the atmosphere, which could result in breakage or loss of the drug through evaporation.

6 Release liner :

The peel strip prevents the loss of drug that has migrated into the adhesive layer during storage and protects the finished device from contamination. Typical materials commonly used are polyester films and other metallized laminates.

Application of Transdermal Patches [32-34]:

❖ The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking,

❖ Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans).

❖ Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).

❖ Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.

❖ The anti-hypertensive drug Clonidine is available in transdermal patch form.

❖ Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.

❖ Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).

Future Trend and Research:

Single-frequency SP of drugs:

Sonophoretic drug delivery relies on the generation of microjets from acoustic cavitation to increase skin permeability and allow transport of molecules through small channels. Considerable past and current research in the field of sonophoretic drug delivery has focused on better understanding the underlying mechanisms, optimizing transport and successful transdermal delivery of a wider range of drugs. [35] Several studies have been conducted in the field of ultrasound-mediated transdermal delivery using a variety of therapeutic compounds, and of these studies, many have explored the potential for transdermal delivery of insulin due to the high prevalence, cost, and inconvenience of diabetic treatment. [36]

Dual-frequency SP:

To increase percutaneous transport with single-frequency SP would typically require an increase in duration or intensity of ultrasound treatment, but recent studies have found that dual-frequency SP is able to enhance transdermal transport minimizing thermal effects. The predominant observed configuration for the dual-frequency SP placed the low-frequency transducer perpendicular to the surface, with the high-frequency transducer arranged at 90° to the low-frequency transducer. A study by Schoell hammer et. al. investigated the potential of dual-frequency ultrasound to improve skin permeability through cavitation activity. Their research consisted of two parts and used low ultrasound frequencies of 20, 40 and 60 kHz combined with high frequencies of 1 and 3 MHz[37].

Conclusion:

In conclusion, transdermal drug delivery systems represent a pivotal and continually evolving aspect of modern medicine. The journey from the early concept of transdermal patches to the current state of advanced drug delivery mechanisms has been marked by significant advancements. The advantages of transdermal drug delivery, such as painless administration, sustained release, and circumvention of first-pass metabolism, continue to drive its utility across various therapeutic areas. Nevertheless, limitations persist, including constraints on drug types that can be effectively administered through the skin, challenges related to skin permeability, and size restrictions on patch design. Understanding the mechanisms of drug absorption through the skin is crucial, with passive diffusion and active transport mechanisms playing essential roles. Researchers must consider factors that affect skin permeability and drug absorption rates to optimize delivery.

Transdermal patch design, including various types and materials, has seen innovative developments. Selecting suitable drugs and formulating them correctly for transdermal delivery is a nuanced process involving considerations of solubility and release kinetics. The adhesive technology employed in these patches is vital for patient adherence and comfort. Achieving skin compatibility and wearability is essential for the success of transdermal products. The clinical applications of transdermal drug delivery are vast, spanning from pain management to hormone replacement therapy and smoking cessation. Successful case studies illustrate its effectiveness in real-world scenarios.

Regulatory compliance and safety considerations are paramount. Understanding FDA regulations and addressing issues related to skin irritation, allergies, and patch removal are essential for patient safety. Looking forward, the future of transdermal drug delivery is promising. Emerging technologies and ongoing research hold the potential for breakthroughs that can revolutionize the field. These advancements will likely have a profound impact on healthcare by offering new treatment options and improving patient adherence. In the marketplace, transdermal drug delivery continues to grow. Monitoring current trends and recognizing key players is crucial in understanding the industry's dynamics. In summary, transdermal drug delivery systems have emerged as a vital component of modern medicine, offering numerous benefits and addressing various challenges. With the continual advancements and a deep commitment to research and development, the future of transdermal drug delivery promises to shape the healthcare landscape positively.

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