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A Brief Review On Transdermal Composite Film: A Novel Approach To Topical Drug Delivery System

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ABSTRACT :

Transdermal drug delivery systems (TDDS) provide regulated release of a contained medication into the bloodstream by means of skin layer penetration. It is simple to implement and remove these systems as needed. The skin is a useful medium via which drugs are absorbed. The active components are incorporated into the skin through a variety of transdermal patch forms. The patches' significant benefits over alternative controlled drug delivery methods have demonstrated their efficacy. The introduction of transdermal drug delivery systems, skin anatomy, transdermal permeation principles, transdermal patch components, transdermal patch approaches, drug release kinetics from transdermal patches, and transdermal patch advantages and disadvantages are all covered in this review article.

Keywords:- Transdermal patch, Topical drug delivery system, Composite film, Permeation Enhancers

Introduction :

Drugs have been administered to patients utilizing a variety of pharmaceutical dose forms in order to treat both acute and chronic conditions. It is well recognized that this dose form offers a rapid medication release. However, a number of technological developments in recent times have led to the development of novel medication delivery methods. The rate of medication release can be regulated using these methods. Oral administration is currently the most popular method of drug delivery. Although this method has many advantages, such as easy administration and poor bioavailability due to hepatic metabolism, it also has significant disadvantages, such as a tendency to produce rapid blood level spikes, both high and low, which requires high and/or frequent dosing, which can be expensive and inconvenient[1]. In order to address these challenges, a novel drug delivery system must be developed. This system will increase the therapeutic efficacy and safety of the medicine by making it more exact (i.e., site specific). An accurate and timely location inside the body, hence lowering the dosage's size and quantity. To transport innovative, genetically designed pharmaceuticals (peptides, proteins) to their site of action without significantly increasing immunogenicity or biological inactivation, new drug delivery systems are also necessary. Transdermal delivery, or the introduction of medicinal chemicals through the skin for a systemic impact, has been one of the most often used methods. Per cutaneous delivery is closely associated with attempting to prevent adverse effects by transporting the medication into the target tissue[2]. Transdermal delivery is a non-invasive approach that results in minimal to no pain or infection risk for the patient.

Transdermal drug delivery system used for medicines with short biological half-lives are continuously added, eliminating pulsed entry—which frequently results in unfavorable side effects—into the systemic circulation.[3] A skin patch uses a unique barrier to regulate how quickly the liquid medication inside the patch's reservoir can permeate the skin and enter the bloodstream. It is possible to regulate the rate at which a medicine is delivered from a transdermal device into the bloodstream in addition to its predictable pharmacokinetic profile. As a result, prolonged medication levels can be maintained without the severe peak and trough swings associated with oral administration. With transdermal devices, medication can be administered locally, and therapy can be stopped right away by just taking off the patch. The markets for non-medication patches include those for heat and cold patches, nutritional patches, skin care patches (which is divided into two main subcategories: therapeutic and cosmetic), weight loss patches, aromatherapy patches, and sun exposure measurement patches.

1.1 Common Application for Transdermal Patches

- Nicotine patches
- Fentanyl for excruciating pain
- Vitamin B12
- Nitroglycerine for angina

- Scopolamine for motion sickness
- Anti-hypertensive; Anti-depressant
- Attention Deficit Hyperactivity Disorder (ADHD)

1.2 Composite Film or Transdermal Patch

A transdermal drug delivery system is a topically applied patch that delivers medication at a predetermined and controlled rate for systemic effects. An alternative method of delivering medication is offered by a transdermal drug delivery device, which can have an active or passive design. Pharmaceuticals can now be administered across the skin barrier thanks to these devices. Transdermal patches operate quite simple in theory.[4] A comparatively large amount of medication is put to the inside of a patch, which is worn on the skin for a long time. The medication reaches the bloodstream through the skin directly through a diffusion mechanism. The medication will continue to diffuse into the blood for a considerable amount of time, maintaining the constant concentration of drug in the blood flow, because there is a high concentration on the patch and a low concentration in the blood.[5] The benefits of transdermal medication delivery over traditional drug delivery are numerous and can be covered in the sections that follow.

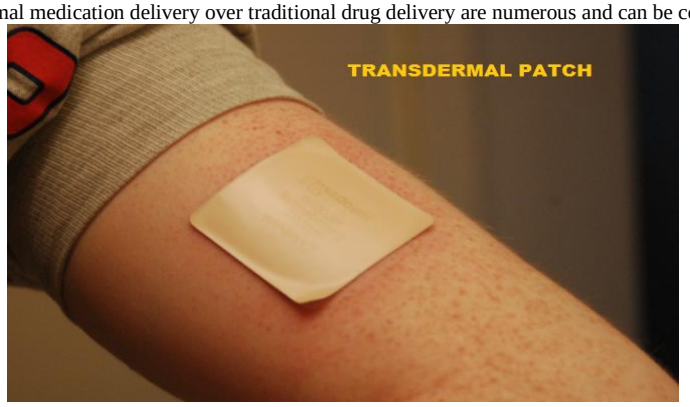

Fig:- 1. Transdermal patch

1.3 Advantages of topical route and transdermal film [6-10]

1. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
2. They can substitute for oral administration of medication when that route is unsuitable, as with vomiting and diarrhea.
3. They avoid the first-pass effect, that is, the initial pass of drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.
4. Because they are noninvasive, parenteral therapy's inconvenience is avoided.
5. They improve compliance compared to other dosage forms that need to be taken more frequently since they offer prolonged therapy with just one application.
6. The therapeutic delivery system's drug reservoir and regulated release prolong the effects of medicines with short half-lives.

1.4 Drawbacks of transdermal patch [6-10]

1. Because the skin's natural barriers to drug entrance are imposed by its impermeability, transdermal administration is only appropriate for relatively potent tiny, lipophilic medicines.
2. A few patients experience contact dermatitis at the application site from one or more system components, which calls for stopping the treatment.
3. Drugs needing high blood levels cannot be administered using this delivery method.
4. Transdermal delivery could not be a cost-effective option.
5. Depending on the type of patch and the surroundings, adhesiveness may change.

Basic principle of drug permeation

In the past, skin was thought of as an impermeable barrier for protection, however further studies demonstrated the usefulness of skin as a systemic delivery route.[2]Because the skin's surface and underlying capillary network are separated by merely a few millimeters of tissue, the skin is the body's most intensive and easily accessible organ. The following are the different stages that go into getting a medication from a patch into the systemic circulation

1. Drug diffusion to the rate-controlling membrane from the drug reservoir.
2. Drug diffusion into the stratum corneum from the rate-limiting membrane.
3. Permeation via living epidermis and sorption by stratum corneum.
4. Drug absorption via the dermal papillary layer's capillary network.

5. Impact on the intended organ

Skin structure and physiology[11-12]

Human skin is made up of three different tissues that are interdependent.

A) The connective tissue's stratified, vascular, and cellular epidermis
B) The dermis beneath it
C) The hypodermis.

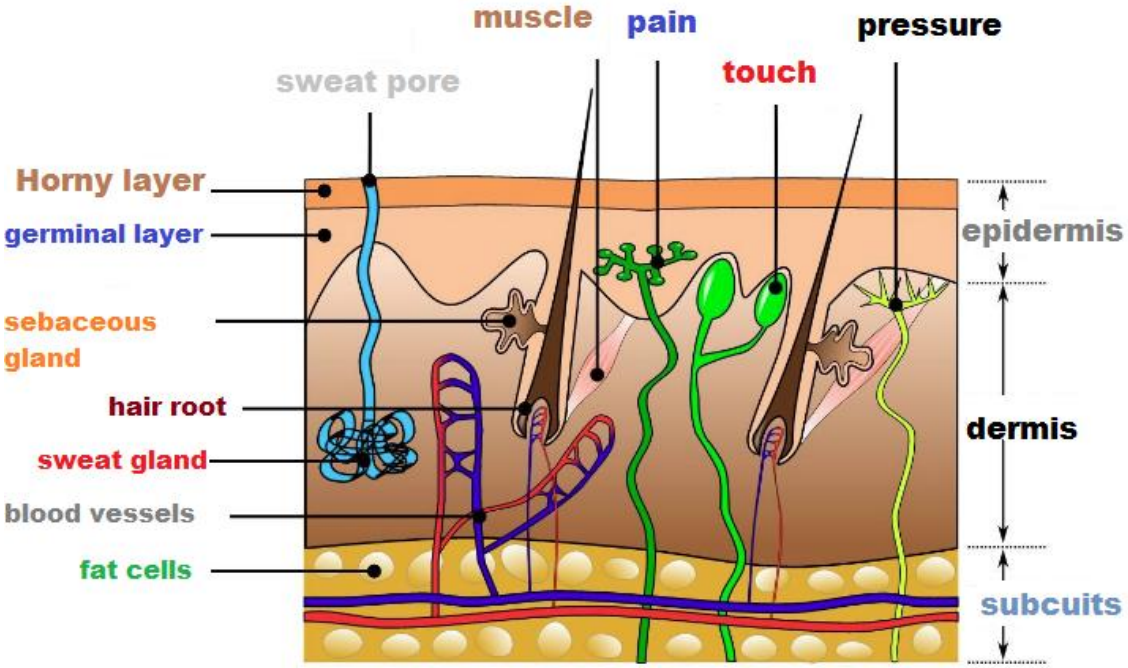

Fig:- 2 Structure of skin

Epidermis

The thickness of the multilayered envelop of the epidermis varies from 0.8 mm on the palms and soles to 0.06 mm on the eyelids, depending on the size and number of cell layers. A significant portion of the skin is covered by the stratum corneum and the remaining epidermis, also known as the viable epidermis. Since the epidermis lacks blood vessels, waste materials and nutrients must permeate through the dermo-epidermal layer to preserve tissue integrity. The epidermis contains four histologically distinct layers which, from the inside to the outside, are as follows:-

- Stratum Germinativum (Growing Layer)
- Malpighion Layer (Pigment Layer)
- Stratum Spinosum (Prickly Cell Layer)
- Stratum Granulosum (Granular Layer)
- Stratum Lucidum, and Stratum Corneum (Horny Layer)

Dermis

The dermis is a layer of connective tissue that is 3 to 5 mm thick and is made up of nerves, lymph vessels, and blood vessels. The cutaneous blood supply plays a crucial role in controlling body temperature. In addition, it eliminates waste materials and pollutants from the skin while supplying it with nutrients and oxygen. The majority of molecules that penetrate the skin barrier find a place to sink thanks to capillaries, which extend to within 0.2 mm of the skin's surface. Because of this, the blood supply maintains permeate's dermal concentration at an extremely low level. The ensuing concentration differential across the epidermis provides the vital force of transdermal permeation.

Hypodermis: The Layer of Subcutaneous Fat

The dermis and epidermis are supported by the hypodermis, or subcutaneous fat tissue. It acts as a place to store fat. This layer offers protection from mechanics, nutrients, and aids in temperature regulation. Principal blood arteries, nerves, and maybe sensory pressure organs are carried to the skin by it. In order for a medicine to be delivered transdermally, it must pass through all three of these layers and enter the systemic circulation; however, for topical distribution, only the stratum corneum must pass through before the drug is retained in the skin's layers.

4. Skin Functions[8,10]

- Protection against the infiltration of microorganisms, substances, physical agents (such UV light and moderate trauma), and dehydration.
- Sensory nerves cause reflex action in response to stimuli.
- Control body temperature: Maintain a body temperature range of 0.5 to 0.75 degrees Celsius, or around 36.8 to 98.4 degrees Fahrenheit.
- Creation of vitamin D: In the presence of UV light from the sun, a fatty molecule found in the skin called 7-dehydrocholesterol is transformed into vitamin D.
- Absorption absorbs harmful substances like mercury as well as several low molecular weight drugs.

Basic fundamentals of drug permeation through skin[8]

The skin was thought to be impermeable—apart from gases—until the last century. 21ST century revealed the permeability to lipid-soluble medications like electrolytes. Furthermore, it was discovered that the skin's layers are not all equally permeable—that is, the epidermis is less permeable than the dermis. Following a significant debate, all questions regarding the permeability of stratum corneum were answered, and it was proposed that the stratum corneum significantly inhibits permeation using isotope tracers.

Different pathways for drug permeation[1.8]

Transcellular or intracellular

Transport of chemicals over a cell's epithelial membrane is referred to as a transcellular route. These consist of the endocytosis and transcytosis of macromolecules, the passive transport of small molecules, and the active transport of polar and ionic substances.

Paracellular

The term "paracellular pathway" refers to the movement of chemicals within or between cells. There are tight connections or other comparable conditions between the cells. A permeant's major route is mostly determined by its partition coefficient (log k). Drugs that are hydrophilic partition more preferentially into the intracellular domains, while lipophilic permeants (o/w log k >2) go via the intercellular layer to cross the stratum corneum. Most permeants enter the stratum corneum using both entrance points.

Factors affecting transdermal drug delivery system[8]

There are two types of factors which directly affects the drug permeation

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. Them intact skin is better barrier but the above mentioned conditions affect penetration.
Skin age – The young skin is more permeable than older. Children are more sensitive for skin
absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDSs.
Blood supply – Changes in peripheral circulation can affect transdermal absorption.
Localized skin location Site-specific differences include differences in appendage density, stratum corneum type, and skin thickness. These elements have a major impact on penetration.

Sr. No.	Skin Region	Thickness (µm)	Permeation (mg/cm2/hr)
1	Abdomen	15	0.34
2	Volar forearm	16	0.31
3	Back	10.5	0.29
4	Forehead	13	0.35
5	Scrotum	15	1.90
6	Back of Hand	49	0.56
8	palm	400	1.14
9	planter	600	3.90

Table -1.Regional variation in water permeability of stratum Corneum

Skin metabolism: The skin breaks down chemicals that cause cancer, hormones, steroids, and some medications. Therefore, the effectiveness of a medicine absorbed through the skin is determined by skin metabolism.
Variations between species - The thickness of skin, density of appendages, and keratinization of skin differ amongst species, which influences the penetration.

Factors related to physiochemistry

Skin hydration: When skin comes into contact with water, its permeability greatly increases. The most crucial element boosting skin penetration is hydration. Humectants are therefore used in transdermal delivery.

Temperature and pH: Changes in temperature cause a ten-fold increase in medication penetration. With a drop in temperature, the diffusion coefficient falls. The dissociation of weak acids and weak bases is contingent upon the pH and pKa or pKb values. The amount of drug in the skin is determined by the percentage of unionized drug. Consequently, two critical variables influencing medication penetration are pH and temperature.
Diffusion coefficient: The drug's penetration is dependent on its diffusion coefficient. The features of the drug, the diffusion medium, and their interactions all affect the drug's diffusion coefficient at a constant temperature.

Drug concentration: The concentration gradient across the barrier is proportional to the flux, and a higher concentration gradient results from a higher drug concentration across the barrier.

Partition coefficient: For a desirable course of action, the ideal K partition coefficient is needed. High K drugs are not yet ready to leave the lipid layer of the skin. Drugs with low K content won't penetrate either.

Factors affecting permeability[13]

A. Physiological factors

- Anatomic site of application on the body
- Skin condition and disease
- Age of the patient
- Skin metabolism
- Desquamation (peeling or flaking of the surface of the skin)
- Skin irritation and sensitization
- Race

B. Formulative factors

- Transport's physical chemistry
- The vehicles and membranes employed
- The penetration enhancers used
- The application technique
- The device used

C. Enhancers' physicochemical characteristics

- A gearter or partition coefficient of one is necessary.
- The pH level should be moderate since variations in pH can vary the ratio of charged to uncharged species and their transdermal permeability, which can impact the flow of ionizable medicines.
- A penetrant concentration greater than its solubility; surplus solid drug serves as a reserve and aids in sustaining a steady drug concentration over an extended period of time.

Techniques for development of transdermal film[14,15]

There are 4 types of methods

8.1 TDD systems with a polymer membrane partition control

The drug reservoir in these kinds of devices is sandwiched between a rate-controlling polymeric membrane and a drug-impermeable backing laminate.

8.2 Diffusion-controlled TDD devices based on polymer matrix

In this approach, the drug particles are homogeneously dispersed in a hydrophilic or lipophilic polymer matrix to form the drug reservoir. The resulting medicated polymer is then molded into medicated disks with predetermined thickness and surface area. The drug reservoir with polymer disk is thereafter installed in a compartment made of a drug-impermeable plastic backing on an occlusive base plate. Adhesive polymer is put around the edge of the patch to create an adhesive strip rather than directly onto the medicated disk's surface.

8.3 Gradient-controlled TDD devices for drug reservoirs

Drug loading levels in polymer matrix drug dispersion-type TDD systems can be adjusted incrementally to create a drug reservoir gradient that follows the diffusional path between the several sticky layers. This kind of drug reservoir gradient-controlled TDD systems' drug release can be stated as

$$\frac{dq}{dt} = \frac{k_{a/r} \cdot D_s}{h_a(t)} A(h_a)$$

for example, the nitroglycerine-containing Deponit system for angina pectoris.

8.4 Dissolution-controlled TDD systems utilizing microreservoirs

A combination of matrix dispersion and reservoir-style drug delivery devices, comprising a deep reservoir created by initially suspending the drug particles in an a lipophilic polymer by applying a high shear mechanical force to an aqueous solution of a water-miscible drug solubilizer, such as propylene glycol, and evenly spreading the drug suspension with regulated aqueous solubility to create thousands of un leachable microscopic drug reservoirs.

Transdermal patch or composite film[16]

An adhesive patch that has been medicated and applied to the skin to deliver a specified dosage of medication through the skin and into the bloodstream is called a transdermal patch. Transdermal drug delivery has an advantage over other forms of medication delivery (oral, topical, intravenous, or intramuscular). The patch allows for a controlled release of medication into the patient, typically via the body's heat melting thin layers of medication embedded in the adhesive or through a porous membrane covering a reservoir of medication.

9.1 Components of Transdermal patch[8]

- Polymer matrix and drug storage
- API Substance
- Enhancers of penetration
- PSA, or pressure-sensitive adhesive
- Laminates for backing
- Discharge to release the lining
- Additional excipients, such as solvents and plasticizers

Polymer matrix

The foundation of a transdermal medication delivery system is polymers. Transdermal delivery systems are made up of multilayered polymeric laminates in which a drug reservoir or drug polymer matrix is sandwiched between two polymeric layers: an inner polymeric layer that serves as a rate-controlling membrane and/or adhesive, and an outer polymeric layer that is impervious to drugs and stops drug loss through the backing surface. In order to fabricate transdermal delivery systems that effectively meet the various criteria, careful consideration must be given to the selection and design of polymers.

Drug substances

The primary need for TDDS is that the medication has the appropriate pharmacokinetic and physicochemical characteristics. Drugs with a limited therapeutic window, high first-pass metabolism, or short half lives that result in non-compliance from repeated dosage can all benefit greatly from transdermal patches. Methylphenidate for attention deficit hyperactivity disorder, rivastigmine for Parkinson's and Alzheimer's dementia, selegiline for depression, and rotigotine for Parkinson's disease are a few examples of medications that have recently been approved as TDDS.

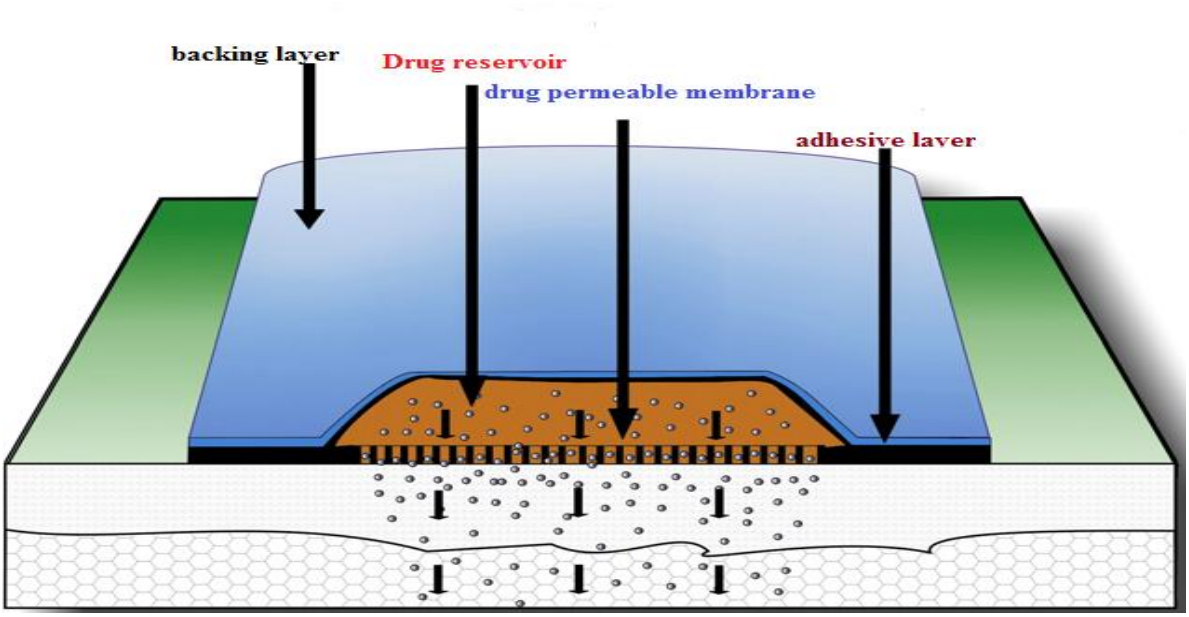

Fig-3: Components of Transdermal patch

Penetration Enhancers

Penetration enhancers interact with proteins or lipids in the stratum corneum to increase permeability, which in turn allows for higher therapeutic levels of the drug.

The improvement in oil-soluble medication absorption is appears that this is because the chemical enhancers partially leached the epidermal lipids, improving the skin's ability to be wet as well as penetrate through the epidermis and follicles. The increased transdermal penetration of water-soluble medications may be due to the miscibility and solution qualities of the employed enhancers. Researchers in the pharmaceutical industry have worked very hard on transdermal penetration studies with a variety of enhancers for different drug moieties.

PSA or pressure-sensitive adhesive

A PSA keeps the patch in close proximity to the skin's surface. It should be aggressively and persistently tacky, adhere with just finger pressure, and provide a strong holding force. Polyacrylates, polyisobutylene, and silicon-based adhesives are a few examples. The medication formulation and patch design are two of the many considerations that go into choosing an adhesive. PSA shouldn't change the release of drugs and should be compatible with biology and physicochemistry. The PSA can be mounted either in the rear of the device and extending outward (as in the case of the matrix system) or on the face of the device (as in the reservo system).

Laminated backing

The backing laminate's main purpose is to offer support. Because prolonged contact between the backing layer and the excipients may cause additives to leak out or may result in the diffusion of excipients, drugs, or penetration enhancer through the layer, the backing layer should be chemically resistant and compatible with the excipients. Their rate of moisture vapor transmission ought to be minimal. They need to be as elastic, flexible, and tensile strong as possible. Some examples of backing materials are a heat seal layer, a plastic film made of polyester, polyvinyl chloride, or aluminum, and an aluminum vapor coated layer.

Release liner

A release liner stops contamination and drug loss during storage when it migrates into the adhesive layer. As a result, it is thought of as a component of the main packaging material for the drug rather than the dosage form. The release liner is made up of a silicon-based release coating layer and a base layer that can be either occlusive (such as polyethylene or polyvinyl chloride) or non-occlusive (such as paper fabric). Polyester foil is one of the additional materials used for the TDDS release liner.

Other excipients

To produce the drug reservoir, a variety of solvents are utilized, including dichloromethane, acetone, methanol, and chloroform. Furthermore, plasticizers including polyethylene glycol, triethyl citrate, and dibutyl phthalate and propylene glycol are added to provide plasticity to the transdermal patch.

Transdermal patch evaluation[17]

1. Research on interactions
2. Patch thickness
3. Uniformity of weight
4. Sturdy folding ability
5. Moisture content as a percentage and
6. Moisture uptake as a percentage
7. Evaluation of water vapour permeability (WVP)
8. Medication composition
9. Dosage unit test uniformity
10. Examining the periscope
11. Tests for Shear Adhesion
12. Peel Adhesion,
13. Thumb Tack,
14. Flatness
15. The break test for percentage elongation
16. The rolling ball tack test
17. The peel-tack (quick stick) test
18. Test for Probe Tack
19. Research on drug release in vitro
20. Studies on in vitro skin penetration
21. A research on skin irritation

Clinical considerations in general while using TDDS

Please inform the patient of the following general instructions. It is important to let the patient know how important it is to use the suggested site and to switch up where they visit. Rotating areas is crucial to preventing skin irritation and restoring the skin's natural permeability. TDDSs should be used to clean, dry skin that is largely hair-free and is not damaged, callused, greasy, irritable, or inflammatory. Drug penetration can be accelerated beyond the ondansetron period by damp or moist skin. Oily skin may make a patch less tenacious. In the event that hair is present at the location, it should be gently trimmed rather than wet shaven or treated with a depilatory agent, as these actions may destroy stratum corneum and alter the rate and degree of drug penetration.

- Applying skin lotion at the application location is discouraged since it can change the drug's partition coefficient and dehydrate the skin.
- Cutting should not physically change TDDSs because doing so compromises the system's integrity.
- Carefully remove the protective backing so as not to come into contact with your fingertips. Using the heel of your hand, press the TDDS firmly against the skin spot for approximately 10 seconds.

CONCLUSION

The field of transdermal medication delivery systems, particularly transdermal patches, has made significant strides. Many academics are interested in this method since transdermal medication delivery systems have so many advantages. Many fresh studies are being conducted these days in an effort to include newer medications via this method. Despite years of research, chemical enhancers have only modestly increased the transdermal transport of small molecules and have only marginally improved the transport of macromolecules under conditions that may be therapeutically effective. Additionally, other tools that speed up the drug's penetration and absorption are being researched. Transdermal medication delivery is not widely used. However, because to the development of new medications and gadgets that can be integrated via this system, its use is currently growing quickly.

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CONFLICT OF INTERESTED

The authors declare no conflicts of interest

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