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Transdermal Drug Delivery System: A Review

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ABSTRACT

Transdermal drug delivery system (TDDS) is an effective method for administering medications through the skin, allowing for a controlled and sustained release of the drug into the bloodstream. The clinical usage of first-generation transdermal delivery systems to administer tiny, lipophilic, low dose medications has continued to rise steadily. Currently 74% of medications are taken orally, and their effectiveness is shown to be deficient. The term "patches" refers to transdermal drug delivery systems (TDDS), which are dosage form intended to distribute a therapeutically effective quantity of medication across a patient's skin.

Keywords: Transdermal drug delivery system, patches, TDDS, Transdermal patch

1. INTRODUCTION

For millennia, humans have used topical applications for their healing properties, from herbal poultices to ointments. In contemporary medicine, various topical formulations have been created to effectively treat local conditions.[1-4] Transdermal delivery is increasingly recognized as a promising method for drug administration. Transdermal systems hold great promise for a wide range of therapies, including pain management, hormone therapies, and treatment of chronic conditions[5] In addition to enabling continuous administration of medications with brief biological half lives, transdermal distribution also prevents pulsed entrance into systemic circulation, which frequently results in undesired side effects. As a result, many innovative medications delivery methods, including transdermal, controlled release, and transmucosal delivery, were developed.[6] These days, a variety of transdermal medications are used to treat a range of illness such as nitroglycerine, clonidine, and hyoscin, which are used to treat cardiovascular disease, chronic pain and fentanyl.[7] The medicine is effectively absorbed through skin and gradually enters the bloodstream through this medium. Various transdermal medication delivery methods with varying release kinetics have seen developed.[8] Drugs used in transdermal patches (TDDS) are administered continuously, exhibiting their effects for a precise length. The transdermal patch approach is non-invasive and non-irritating, it is a compelling substitute method for more traditional methods when it comes to systemic drug administration.[9] Transdermal patches were created in the 1970s, and Scopolamine received its first FDA approval in 1981. The second patch to be approved contained nitroglycerine. There are a lot of transdermal patches on the market these days.[10-11] In contrast to conventional oral dosage forms, which cause a decline in plasma levels at the end of the dosing interval, this will improve bio availability, more uniform plasma peak levels, longer duration of action leading to a reduction in dosing frequency. Fewer side effects, and improved therapy.

1.2 Definition :

Adhesive patch that has medicated and applied to the skin to deliver a specified dosage of medication through the skin and into the bloodstream is called as Transdermal patch or skin patch.

2. Advantages :

 Quick drug notifications in an emergency and the ability to quickly eliminate drug effects by removing patches.

 By using transdermal medication delivery, gastrointestinal absorption and its potential for enzymatic and pH related inactivation can be avoided.

 Elimination of first pass metabolism.

 The absence of peaks in plasma concentration can lower the possibility of adverse effects, making relatively constant plasma level- requiring medications an excellent choice for Transdermal drug administration.

 Additionally, the patch allows for continuous dosage as opposed to the medication level peaks and valleys that come with oral medicine administration.

 Act as a substitute for oral route of administration.

 Particularly noteworthy is the convenience of patches that only need to be applied once a week: this kind of straightforward dosage schedule can help patients sick to their medication routine.

 Allow for the use of medications with brief biological half - lives and limited therapeutic windows.

 Reducing unfavorable side effects.

 Preventing gastrointestinal conflicts.

 Preventing variations in medication levels between and among patients.

 It is simple to stop therapy at any time.

 Due to the fact they are non-invasive, parenteral therapy's inconvenience is avoided.

 Assure suitability for independent management.

 The therapeutic delivery systems drug reservoir and controlled release mechanism prolong the effects of medications with short half lives.

 It has significant benefits for individuals who are unconscious or paralyzed.

 Transdermal patches are more effective method of delivering drugs that are heavily broken down by the liver, poorly absorbed from the gut, or broken down by the stomach.

 The cost of transdermal patches is reasonable.[12-17]

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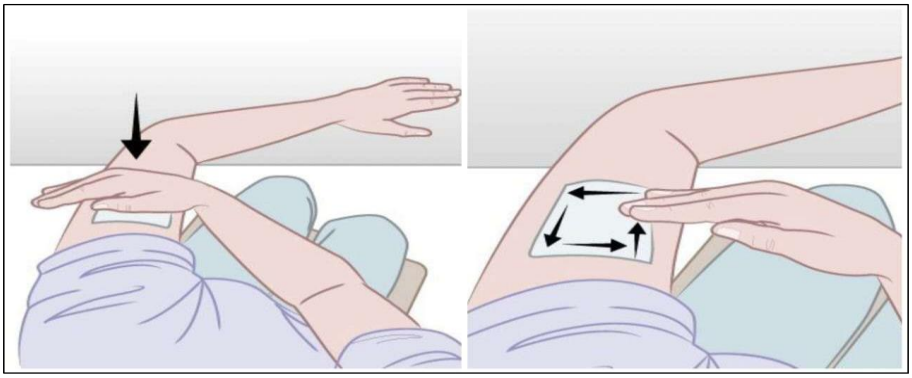


Figure 1 : Transdermal Patch application on skin

2.1 Disadvantage :

 Iconic medicines cannot be delivered by a transdermal drug delivery device.

 It is unable to produce elevated blood drug levels.

 It is incapable to develop for large molecular weight medicines,

 A log P (octanol/ water) of 1 to 3 is necessary for permeate to reach the underlying aqueous layer and transverse stratum corneum, indicating sufficient aqueous and lipid solubility.

 Chances of localized discomfort where application is made.

 It cannot develop if medication or drug formulation irritates the skin.

 Only strong medications are appropriate candidates for transdermal patches due to the skin's inherent impermeability, which places natural restrictions on drug entry.

 Long-term commitment is challenging.[13,15,17]

3. Preparation Method of Transdermal Patch :

The process of making TDDS was reduced by making changes to the previously published procedures. The solvent casting procedure was used to prepare the patches. A minimum amount of the solvent was added to a beaker containing the polymer (such as PVP/HPMC). Next, a mixture of two-thirds of the solvent and additional polymers, like PVA, was added, initially with stirring at a lower rpm and then at a faster speed. After adding and thoroughly mixing the plasticizer, the medication was added while still very agitated, and the volume was adjusted. After the films were placed into properly constructed and designed glass mold, they were dried at 40 degrees Celsius in an oven. Using a sharp knife, the films were cut off by inserting them along their edges.

1) Asymmetric TPX membrane method: - A heat sealable polyester film with a concave of 1 cm diameter can be utilized as the backing membrane to create a prototype patch. The drug sample is dispensed into a concave membrane, sealed with an adhesive, and coated with an asymmetric TPX {poly-(4-methyl-1-pentene)} membrane.[5]

2) Mercury Substrate Method : This approach involves dissolving the medication in a polymer solution with plasticizer. To ensure a uniform dispersion, the aforementioned solution should be agitated for ten to fifteen minutes. Then, it should be poured over a leveled mercury surface and covered with an inverted funnel to prevent solvent evaporation.

3) Aluminium backed adhesive film method : If the loading dose for a transdermal drug delivery system is more than 10 mg, unstable matrices may be produced. The adhesive film approach with aluminum backing is appropriate. Since most medications and adhesives dissolve in chloroform, it is the solvent of choice for making the same. Adhesive substance is added to the drug solution and dissolved once the drug is dissolved in chloroform. Aluminum foil is used to line a specially constructed aluminum former, and cork blocks that fit firmly are used to blank off the ends.

4) Free film method : Casting on the surface of mercury creates a free film of cellulose acetate.

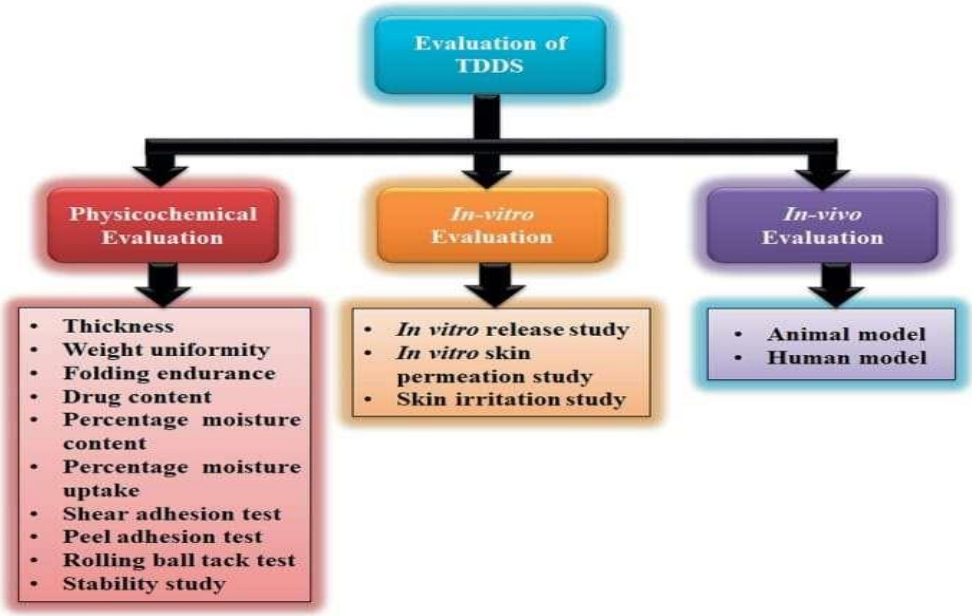
Chloroform is to be used to make a 2% w/w polymer solution. Plasticizers must be added at a 40% weight-to-weight concentration of the polymer. A glass ring was filled with five milliliters of polymer solution and set over the mercury surface in a glass petri dish. Covering the petri dish with an inverted funnel regulates the solvent's rate of evaporation. When the solvent has completely evaporated, the mercury surface is observed to determine the creation of the film. Before being used, the dried film will be removed and kept in a desiccator between the wax paper sheets. It is possible to create free films with varying thicknesses by altering the volume of polymer solution.

5) Circular Teflon mould method : An organic solvent contains solutions with different ratios of polymers Half as much of the same organic solvent is used to dissolve the calculated amount of medication. The second half of the organic solvent is used to dissolve enhancers at varying concentrations before adding them, The drug polymer solution is plasticized with the addition of Di-N butyl phthalate. After 12 hours of stirring, the entire mixture is put into a circular Teflon mould. To regulate solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s, the molds are set on a flat surface and covered with an inverted funnel. For tewnty-four hours, the solvent is left to evaporate. After drying, the films are kept in a desiccator with silica gel for a further twenty-four hours at 25+0.5 degree Celsius.

6) "IPM membranes " method : Using a magnetic stirrer, the medication is dissolved in a solution of water and propylene glycol that contains carbomer 940 polymer, and the combination is then agitated for 12 hours. Triethanolamine is to be added to dispersion in order to neutralize it and make it viscous. If the drug is very poorly soluble in aqueous solution, solution gel can be obtained by using buffer pH 7.4. The IPM membrane will incorporate the gel that has produced.

7) "EVAC membranes" method : Polyethylene (PE), ethylene vinyl acetate co polymer (EVAC) membranes, and 1% Carbapol reservoir gel can all be utilized as rate control membranes to prepare the goal transdermal therapeutic system. Gel is made with propylene glycol if the medication is not suitable in water. Propylene glycol is used to dissolve the drug, carbopol resin then added to the mixture and neutralized by 5% w/w sodium hydroxide solution. The medication (in gel form) is applied to a backing layer sheet that covers the designated area. To create a leak proof device, a rate regulating membrane is placed over the gel and the borders are sealed with heat.

8) Preparation of TDDS by using pro-liposome : The film deposition technique is used in the carrier approach to prepare the pro-liposome. An optimal dosage of lecithin in a ratio of 0:1:2:0 can be obtained from the previous reference medication. The process for making the pro-liposome. Involves placing 5 mg of mannitol powder in a 100 ml round-bottom flask, keeping it at a temperature between 60 and 70 ^{0}C rotating the flask at 80 to 90 rpm, and vacuum - drying the mannitol for 30 minutes. The water bath's temperature is brought down to 20-30 ^{0}C after drying. Appropriate organic solvent mixture is used to dissolve the drug and lecithin. An aliquot of 0.5 ml of the organic solution is added to a round bottomed flask at 37 ^{0}C, and another 0.5 ml of the solution is to be added once the solution has completely dried.[18-24]



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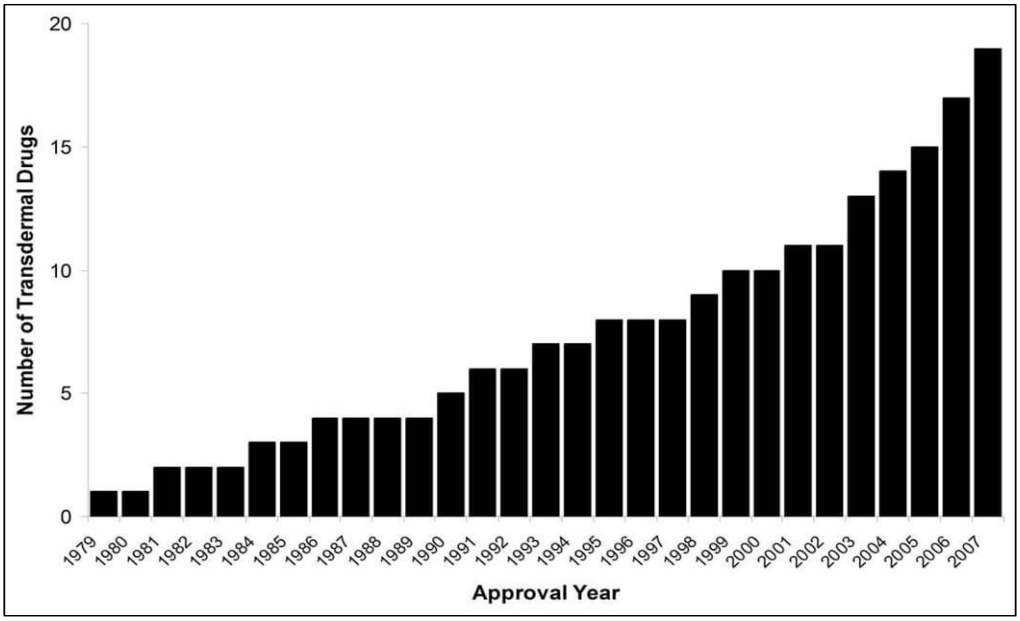


Figure 2 : Number of Transdermal drugs that the FDA has approved since the drugs initial approval in 1979. As of now, the United States has approved 19 different drug combinations as well as individual drug combinations as well as Individual drug (see Table 1). Data were obtained from the FDA Orange Book [25]

4. Mechanism of Action of Transdermal Patch

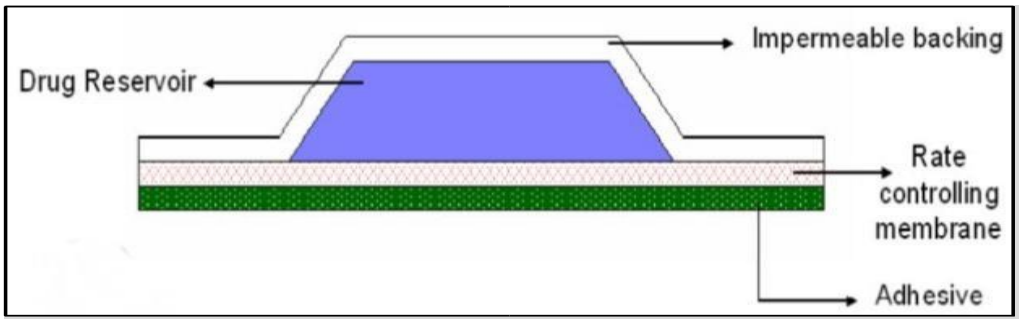
There are several ways to apply the transdermal patch and transfer the active medication ingredient from the patch to the skin and circulatory system.

Iontophoresis

Drug administration over the barrier is facilitated by iontophoresis, which applies a few milliamperes of current to a few square centimeters of skin through the electrode in contact with the formulation. mostly used in conjunction with pilocarpine administration to cause perspiration as a diagnostic test for cystic fibrosis. For a quick onset of anesthesia, iontophoretic delivery of lidocaine seems to be a promising method.

Electroporation

One technique for applying brief, high-voltage electrical pulses to the skin is called Electroporation. The skin's permeability for drug diffusion is raised by four orders of magnitude following Electroporation. It is thought that the electrical pulses create temporary aqueous holes in the stratum corneum, which allow for the transfer of drugs. Using closely spaced electrodes to limit the electric field within the nerve-free stratum corneum, electrical pulses can be applied safely and painlessly.



Use of microscopic projection

Transdermal drug delivery was facilitated by transdermal patches with tiny protrusions known as micro-needles. Needles are grouped in arrays with lengths varying from around 10 to 100 µm. The arrays cause microscopic punctures in the skin when rubbed against it, large enough to transfer macromolecules but small enough that the patient is not aware of the puncture or discomfort. To promote quick absorption, the medication is surface coated on the micro needles. They are employed in the creation of cutaneous tetanus and influenza vaccinations. Transdermal patches can also be applied by a number of additional techniques, including photomechanical waves, magnetosphere, and thermal poration. These techniques, however, are still in their infancy and necessitate more thorough research.

Application by ultrasound

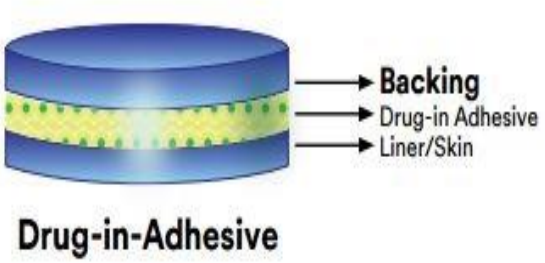
It has been demonstrated that using ultrasound, especially low frequency ultrasound, improves the transdermal delivery of a variety of medications, including macromolecules. Another name for it is sonophoresis. Katz and colleagues documented the application of low-frequency sonophoresis in the topical administration of EMLA cream.[27]

5. Advance Development of TDDS :

The predominant method for passive transdermal distribution of drugs is now adhesive technology; adhesives and excipients are the subject of two research topics in formulation science. The main goals of adhesive research are to tailor the adhesive to enhance medication stability and solubility, decrease lag time, boost rate of distribution, and improve skin adherence during the use period. Customizing the adhesive chemistry enables the transdermal formulator to maximize the efficacy of the transdermal patch polymer, as there isn't a single adhesive that works for all drugs and formulation chemistries. TDDS is a realistically applied next generation drug delivery technology.[28]

6. Types of Transdermal Patches :

1. **Single Layer Drug in Adhesive :** The medication is also included in this system's sticky layer. In this kind of patch, the adhesive layer is in charge of both releasing the medication and holding the numerous layers and the complete system to the skin together. A backing and a temporary liner encircle the adhesive layer. [29]



2. **Multi-layer Drug in Adhesive :**

The medicine is released by both adhesive layers in a Multi-layer drug-in-adhesive patch, which is comparable to a single-layer approach. The Multi-layer method differs in that it incorporates an additional drug-in-adhesive layer, typically (though not always) divided by a membrane. In addition, this patch features a permanent backing and a temporary liner layer.[30]

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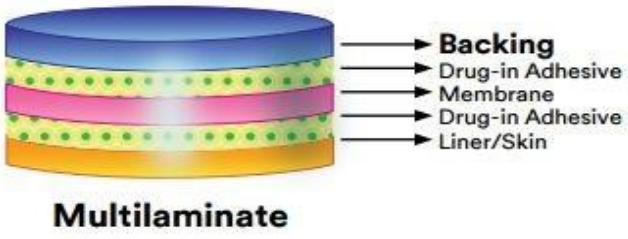
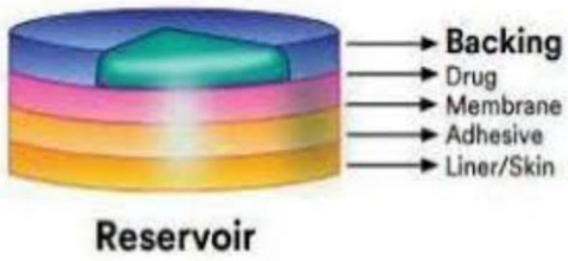
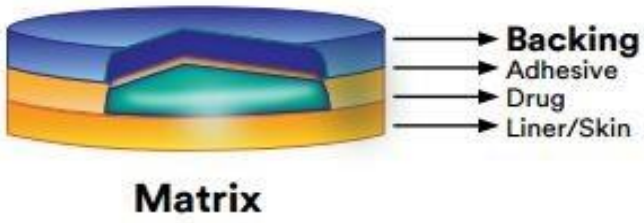


3. **Reservoir :** The reservoir transdermal system differs from the single-layer and Multi-layer drug-in adhesive systems in that it has a distinct drug layer, which is a liquid compartment with a drug solution or suspension that is isolated by the adhesive layer. The backing layer also supports the patch, and the rate of release in this kind of system is zero order. [31]



4. **Matrix :**

The drug layer of the matrix system is a semi-solid matrix that contains a drug suspension or solution. In this patch, the medication layer is partially covered by the adhesive layer. [32]



5. **Vapour Patch :**

In this form of patch the adhesive layer not only helps to adhere the various layers together but also to emit vapour. The essential oils are released by the recently released vapour patches for a maximum of six hours. Mostly utilized for decongestant, the vapor patches release essential oils. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that lessen the quantity of cigarettes that one smokes in a month are also available on the market.[33]

7. Evaluation Parameters :

1) **Thickness of the Patch :**

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch. [34]

2) **Percentage Moisture Content :**

Each prepared film must be weighed separately and stored in a desiccator. keeping fused calcium chloride for a whole day at room temperature. The films must be reweighed after a day in order to calculate the moisture content as a percentage using the formula below. [Initial weight-Final weight/Final weight] x 100 is the percentage moisture content.[34]

3) **Drug Content :**

A certain volume of a patch must be dissolved in an appropriate solvent. After that, the solution must be filtered through a filter medium, and the drug content must be examined using the appropriate technology (either the UV or HPLC method). shown by each value.[35]

4) **Shear Adhesion test :**

The purpose of this test is to determine an adhesive polymer's cohesive strength. The molecular weight, degree of cross linking, type, composition, and quantity of tackifier used can all have an impact. A stainless steel plate is covered with adhesive-coated tape, and to make the tape pull parallel to the plate, a predetermined weight is suspended from it. The time it takes to remove the tape from the plate is used to calculate the shear adhesion strength. The shear strength increases as the removal time increases.[34]

5) **Thumb tack test :**

It is a qualitative test used to determine the adhesive's tack properties. The relative tack quality can be found by merely pressing the thumb against the adhesive.

6) **Folding endurance :**

It is necessary to cut a strip of a certain area equally and fold it repeatedly until it breaks. The value of folding endurance was determined by how many times the film could be folded in the same spot without breaking.[34]

7) **Skin Irritation study :**

Healthy rabbits weighing between 1.2 and 1.5 kg on average can be used for skin irritation and sensitization testing. The rabbit's dorsal surface (50 cm2) should be washed, the hair should be shaved off, the surface should be cleaned with rectified spirit, and the representative formulations can be applied to the skin. After 24 hours, the patch is to be taken off, and the skin will be examined and categorized into 5 grades according to the extent of the skin damage.[34]

8) **Prob Tack test :**

In this test, adhesive is applied to the tip of a clean probe with a specified surface roughness, and a bond is formed between the probe and adhesive. It is mechanically broken by the probe's subsequent removal. Tack, which is measured in grams, is the force needed to remove the probe from the adhesive at a set rate.[36]

9) **Polariscope examination :**

The purpose of this test is to use a Polariscope to study the drug crystals from the patch. To determine if the drug is present in the patch in crystalline or amorphous form, a certain surface area of the piece must be maintained on the object slide and examined for drug crystals.[34]

10) **Rolling Ball tack test :**

This test evaluates a polymer's talk-related softness. In this test, a 7/16-inch-diameter stainless steel ball is dropped upon an incline such that it rolls downward and makes contact with horizontal, upward-facing adhesive. Tack, which is measured in inches, is determined by how far the ball moves along the adhesive.[36]

11) **Stability Studies :**

According to ICH recommendations, stability tests must be carried out by keeping the TDDS samples for six months at 40±0.5°C and 75±5% relative humidity. The samples were taken out at 0, 30, 60, 90, and 180 days, and their drug content was appropriately analyzed.[37]

8. Conclusion :

This Article Provides Valuable Information For the benefit of the research scientists working on TDDS, this article offers useful information about transdermal drug delivery systems and the specifics of its evaluation procedure. The aforementioned demonstrates the immense potential of TDDS, which can be used to create promising deliverable pharmaceuticals with both hydrophobic and hydrophilic active substances. More knowledge of the various biological interaction pathways and polymer is needed to optimize this drug delivery technology. TDDS is a viable real-world use case for the next drug delivery technology.

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