INTRODUCTION

Transdermal drug delivery system (TDDS), also known as “patches”, are the dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin. The adhesive of the transdermal drug delivery system is very crucial to the safety, efficacy and quality of the product. Recently, it has been recognized that the skin can also serve as the port of administration for systemically active drugs. The drugs applied topically are first absorbed into the blood stream and then are transported to the target tissues. Now, it is becoming evident that the benefits of intra venous infusion can be closely duplicated by using skin as the port of drug administration to provide continuous transdermal drug infusion into the systemic circulation. One of the objectives of TDDS is the maintenance of blood concentration of drug at therapeutic level by means of controlled permeation throughout the skin during a long period of time and using only one administration. The drug input can be terminated at any point of time by just removing the patch. Rate of drug release from the TDDS is normally much greater than the amount that the skin can possibly absorb. Hence, even if there is a variation in skin permeability, a constant rate of drug input into the circulation is achieved. This article provides an overview of type of transdermal systems, role of adhesion, possible adhesion failures and the measurement of adhesion. In vitro techniques like peel adhesion, tack and shear strength are discussed. Adhesion needs to be a critical parameter for designing a transdermal drug delivery system in order to provide good quality and efficacy to the patient. This review also covers a brief outline of various components of a patch, their advantages, when the patch should be used and when their use should be avoided.

Components of a transdermal patch

- Liner- protects the patch during storage. The liner is removed prior to use and it should be chemically inert.
- Drug- drug solution is in direct contact with the release liner.
- Adhesive- to adhere the components of the patch together along with adhering the patch to the skin surface e.g. Poly-isobutylene, acrylics, silicones etc.
- Membrane- controls the release of the drug from the reservoir and multilayer patches. It is diffusion properties are used to control availability of drug or excipients to skin.
- Backing- protects the patch from outer environment and gives appearance, flexibility to the patch. e.g. Polyester films, polyethylene films, poly-olefins films etc.
- Penetration enhancer- modulates the skin permeability in some fashion. e.g. Propylene glycol, methyl laurate, ethyl oleate, carvone, lauric acid etc.

ADHESION AS A CRITICAL PARAMETER

Transdermal drug delivery system is the system in which the delivery of the active ingredients of the drug occurs by the means of skin. Transdermal drug delivery system is the method that can effectively and painlessly deliver large molecules in therapeutic ranges to overcome the difficulties that are associated with oral and other routes. In transdermal drug delivery system, skin is the medium from where the drug is being absorbed and finally the drug reaches the circulatory system. These transdermal patches have been proved to be more effective because of their large advantages over other controlled drug delivery systems. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a time-released dose of medication through the skin to treat systemic conditions. Transdermal therapeutic system (TTS) has been available commercially since the early 1980’s. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. The major aim of transdermal drug delivery system is to provide a controlled and continuous delivery of drugs via skin to the systemic circulation. It overcomes various side effects like painful delivery of drugs and first pass metabolism of drugs occurred with other routes of drug delivery systems. Hence, this system has been a great field of interest in the recent time. The drug is delivered to the skin with the help of a patch which adheres to the skin. The main advantage of this system is that there is a controlled release of the active medicament and the medication is painless. Absorption of drug through the skin is affected by a number of factors such as skin sites, skin thickness, skin temperature, body temperature, blood flow, lipid concentration, number of hair follicles, skin cleansing, hydration status, sweat gland function, ethnic group, pH of skin surface and integrity of the stratum corneum. A transdermal patch has several components like liners, adherents, drug reservoirs, drug release membrane etc. It has become a highly research field because of its great advantages. A transdermal patch or a 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 blood stream. The first prescription patch was approved by U.S. Food and Drug Administration in 1979, which administered Scopolamine for motion sickness.

Transdermal patch design

In almost all transdermal patch designs, the drug is stored in a reservoir that is enclosed on one side with an impermeable backing and has an adhesive that contacts the skin on the other side. Some designs employ drug dissolved in a liquid or gel-based reservoir, which can simplify formulations and permit the use of liquid chemical enhancers, such as ethanol. These designs characteristically are composed of four layers: an impermeable backing membrane; a drug reservoir; a semi permeable membrane that may serve as a rate-limiting barrier; and an adhesive layer. Other designs incorporate the
drug into a solid matrix, which simplifies manufacturing. Matrix system can have three layers, by eliminating the semi-permeable membrane, or just two layers, by incorporating the drug directly into the adhesive.

**Drug selection criteria**
- The drug should have a molecular weight less than approximately 1000 Daltons.
- The drug should have affinity for lipophilic and hydrophilic patches.
- The drug should have a low melting point.
- The drug should be effective in a low daily dose.
- The half life of the drug should be short.
- The drug should not induce an allergic response.
- The tolerance to the drug should not develop under nearly zero-order release profile of trans dermal system.

**Conditions in which transdermal patches are used**
A transdermal patch is used when:
- The patient has intolerable side effects and is requesting another method of drug delivery.
- The pain control might be improved by reliable administration.
- It can be used with other enhancement strategies to produce synergistic effects.

**Care taken while applying a patch**
- The part of skin where the patch has to be applied must be properly cleaned.
- The patch should not be cut because doing this will destroy the drug delivery system.
- New patch should be applied only after removing the previous one.
- The patch should be applied accurately on to the administration site.
- Care must be taken while applying or removing a patch because uneven handling of the patch may cause absorption of drug before the application of the patch.

**Mechanism of Action of a Transdermal Patch**
The application of the patch and the flow of the active drug from patch to blood stream via skin occur through various methods.

**Iontophoresis**
By passing a few milliamperes of current to a few square centimeters of skin through the electrodes placed in contact with the formulation, the drug delivery across the barrier is facilitated. For rapid onset of anesthesia the iontophoretic delivery of lidocaine is a promising approach. Pilocarpine is also given by this method in some cases. Iontophoresis has been studied for more than a century by typically applying a continuous low-voltage current. While there can be increased skin permeability, iontophoresis provides an electrical driving force for transport across stratum corneum. Charged drugs are moved via electrophoresis, while weakly charged and uncharged compounds can be moved by electro-osmotic flow of water generated by the preferential movement of mobile cations instead of fixed anions in the stratum corneum. Iontophoresis does not change the skin barrier itself; it is mostly applicable to small molecules that carry a charge and some macromolecules up to a few thousand daltons. The strongest asset of iontophoresis is that the rate of drug delivery scales with electric current, which can be readily controlled by a microprocessor or, in some cases, the patient. In this way, drug delivery can be turned on and off and even modulated over time to enable complex delivery profiles. However, the maximum current- and therefore the maximum delivery rate- are limited by skin irritation and pain caused by the general inability of iontophoresis to localize its effects to the stratum corneum.

**Electroporation**
In this technique, short, high voltage pulses are applied on to the skin. By this, the diffusion permeability of the skin is increased by four orders of magnitude. These electrical pulses form transient aqueous pores in the stratum corneum and the drug can easily transport through these pores. By using closely spaced electrodes the applied electric field can be constrained within the nerve-free stratum corneum and the electrical pulses can be administered painlessly. Hence this method is safe. Electroporation is well known as a method to reversibly disrupt cell membranes for gene transfection and other applications. Electroporation is also found to disrupt lipid bilayer structures in the skin. As the stratum corneum has greater electrical resistance than the deeper tissues, the electric field applied during electroporation is initially concentrated in the stratum corneum. Upon electroporation of stratum corneum lipid bilayer, its electrical resistance drops down and this field is then distributed into the deeper tissues, which contain sensory and motor neurons. The associated pain and muscle stimulation can be avoided by using closely spaced microelectrodes that constrain the electric field within the stratum corneum.

**Sonophoresis**
Sonophoresis is the enhancement of migration of drug molecules through the skin by ultrasonic energy. In this technique we use ultrasound, particularly low frequency ultrasound waves. Acoustic waves of particular frequency reduce the resistance offered by the stratum corneum. This technique increases transdermal transport of various drugs including macromolecules. reported on the use of low frequency sonophoresis for topical delivery of EMLA cream. Some of the drugs given by this method are Dexamethasone, Ibuprofen, Hydrocortisone, Indomethacin, Phenyl butazone etc. Ultrasound was first widely recognized as a skin permeation enhancer when physical therapists discovered that massaging anti-inflammatory agents into the skin using ultrasonic heating probes increased efficacy. The pressure gradient and oscillations associated with ultrasound act as a driving force to move drugs into the skin. It appears that the effect is to disrupt stratum corneum lipid structure and thereby increase skin permeability. Associated tissue heating that is not targeted to the stratum corneum can damage deeper tissues.
Use of microscopic projections
Transdermal patches with microscopic projections called micro needles are used to facilitate the transdermal drug transport. Needles ranging from 10 - 100 µm in length are arranged in arrays. When pressed into the skin, these arrays make microscopic punctures that are large enough to deliver macromolecules and small enough that the patient does not feel pain. The drug is coated on the surface of the micro needles to help in rapid absorption. This method is mainly used for cutaneous vaccines for tetanus and influenza.

Micro needles
- Increase skin permeability by creating micron-scale pathways in the skin.
- Can actively drive drugs into the skin either as coated or encapsulated cargo introduced during micro needle insertion.
- Target their effects to the stratum corneum, although micro needles typically pierce across the epidermis and into the superficial dermis too.

Thermal Ablation
Thermal ablation selectively heats the skin surface to generate micron scale perforations in stratum corneum. Heating the skin surface to hundreds of degree for microseconds to milliseconds localizes heat transfer to the skin surface without allowing the heat to propagate to the viable tissues below. Most recent studies suggest that temperature well above the boiling point of water is needed for this purpose. Skin heating is achieved by ohmic micro heaters and radiofrequency ablation.

Microdermabrasion
Final way to remove stratum corneum barrier employs abrasion by microdermabrasion or by simple sandpaper. This abrasive mechanism which is related to sand blasting on the microscopic scale has been shown to increase skin permeability to drugs like lidocaine, 5-fluorouracil, which suggests possible applications in TDDS.

Recent Techniques Used in TDDS
Poroplastic membrane
The poroplastic membrane is an open cell ultra microporous form of cellulose triacetate. It holds the saturated drug solution by capillary action. The main advantage of this type of system is that their diffusive permeability can be varied over a wide range.

Use of hydrophilic gel matrix over the polymeric transdermal system
The matrix is an “open cell molecular sponge”. The plasticizer contains the drug in a soluble or suspended state in a micro space. It also contains a mixture of hydrogen bonding liquids like water, glycerin, polyethylene glycol, polypropylene glycol etc.

Types of Transdermal Patches
Single - layer drug - in- adhesive
In this type of system, drug is present in the adhesive layer. The adhesive layer serves to adhere the various layers together and also helps in adhesion of entire system with the skin. This adhesive layer is also responsible for the release of drug from this system. The adhesive layer is surrounded by a temporary liner and a backing layer.

Multi - layer drug - in adhesive
This patch is similar to single-layer system that in both adhesive layers is responsible for the release of the active drug. This multi-layer system is different however, that it adds another layer of drug in adhesive, usually separated by a membrane. This patch also has a temporary liner and a permanent backing layer.

Reservoir
This system is different from previous two systems. Reservoir system has a separate drug layer. The drug is present in the form of solution or suspension separated by the adhesive layer. The rate of release of drug from reservoir type of system is zero order.

Matrix system
The matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. Drug layer is surrounded by the adhesive layer. Nitroglycerin releasing system is an example of matrix type of system. Main advantage of this system is that the dose dumping cannot occur with this system.

Vapor patch
In this patch, the adhesive layer not only serves to adhere various layers together but also to release vapors. Vapor patches are also used to improve the quality of sleep. Such patches are known as controller patches. Vapor patches are also used to decrease the quantity of cigarettes that a person smokes in a month.

Rising Interest in Transdermal Vaccines
TDDS offers compelling opportunities to improve vaccine administration. Vaccine delivery via skin is more attractive because it targets the potent epidermal langerhans and dermal dendritic cells that may generate a strong immune response at much lower doses than deeper injections. Elimination of the need for hypodermic needles motivates transdermal vaccine development. In a world where needle reuse kills at least 1.3 million people per year from hepatitis B and AIDS, needle free, patch based vaccination could have large impact. Excitement about this approach is exemplified by completion of phase 3 trials and submission for registration in Europe by Sanofi Pasteur (Paris) and Becton Dickinson for their micro needle based influenza vaccine.

Three Possible Generations of TDDS in Future
- First generation- that produced many of the today’s patches by judicious selection of drugs that can cross the skin at therapeutic rates with little or no enhancements.
- Second generation- that has yielded additional advances for small molecule delivery by increasing skin permeability.
- Third generation- that will enable transdermal delivery of small molecule drugs, macromolecules and vaccines etc. by targeted permeabilization of the stratum corneum.

Ideal Properties of Adhesives to be Used in TDDS
- It should not sensitize or irritate the skin during its contact time with the skin.
- It should aggressively adhere to the skin and its position should not get disturbed during bathing, exercise etc.
Peel Adhesion

Modes of Failure in Transdermal Drug Delivery System
When the patch is peeled, it is expected that it will strip cleanly from the skin, leaving no visible residue. This type of failure is an adhesive failure, case 1. If the adhesive transfer to the skin, leaving no adhesive on the TDDS, this type of failure is an adhesive failure, case 2. Cohesive failure, case 3, is when adhesive is left on the TDDS and on the skin. Based on the type of failure mode, it is possible to find out the potential cause of the failure.

Techniques to Measure Adhesive Properties
The adhesive action of TDDS is a critical factor as it determines its drug delivery, therapeutic action, patient compliance. Several in vitro techniques are used to monitor adhesive action such as peel adhesion, tack property and shear strength measurement. These are not true material properties because they depend upon the substrate, backing material and test parameters. The adhesive property of the TDDS must be measured in its final form to ensure acceptable adhesive quality.

Peel Adhesion
Peel adhesion measures the force required to peel away an adhesive once it has been attached to a surface. Recently used test methods for TDDS peel adhesion are based on methods developed for industrial tapes. In these methods stainless steel panel, skins, HDPE are used as substrates. Peel angle must be 90° or 180°. Sample must be cut into exact width, dwell time of one minute and a peel speed of 300 mm/min is required. The peel adhesion measurement is greatly influenced by the experimental parameters like dwell time, substrate, peel angle, peel speed etc. Peel adhesion measurement also depends on the TDDS backing and adhesive thickness.

Tack Property
Initially, the tack property of an adhesive was evaluated by “thumb test”. Then probe tack test was developed in order to refine and stimulate thumb test. In probe tack test, a probe touches the adhesive surface with a light pressure and the force required to break the bond after a short time period of contact is measured. Tack property is not just a function of the material properties of the adhesive but also depends on the experimental parameters. It depends upon the contact area, the contact pressure, time of contact, rate of separation and test environment. Tack test is relative to both the substrate material and the sample adhesive.

Shear Adhesion
It is also known as the creep compliance. It is a measure of the cohesive strength. Higher shear adhesion indicates a lower cohesion. This can be observed by the TDDS leaving the adhesive residue on the outer edges of the TDDS, liner or pouch. The adhesive residue from the cold flow or “creeping” of the TDDS may contain drug if the system is a type that contain drug in adhesive. This cold flow will make it difficult for the patient to remove TDDS from the release liner. Low creep compliance is desirable; however, too low of a value leads to the loss of tack and peel adhesion. Hence, the adhesive must exhibit an elastic cohesiveness and a resistance to flow under stress.

Scoring system for a TDDS
0 = 90 % adhered (no lift off the skin)
1 = 75 % to < 90 % adhered (some edges only lifting off the skin)
2 = 50 % to < 75 % adhered (less than half of the system lifting off the skin)
3 = < 50 % adhered but not detached (more than half the system lifting off the skin without falling off the skin)
4 = patch detached (patch completely off the skin)

Future Outlook
Looking to the future, it is likely that first- generation patch technology will continue to be used for delivery of small molecule drugs with the right set of properties, especially those drugs that are currently administered orally and by injection that are coming off patient. Second generation chemical enhancers should find continued use as formulation excipients in dermatological creams and ointments and some systemic patches for small molecule drugs. They will probably have a little impact on delivery of hydrophilic drugs and macromolecules because generally the most effective chemical enhancers diffuse out of the stratum corneum and irritate deeper tissues. Third generation chemical enhancers offer strategies for more targeted enhancements, but are still in early stages of development. Second- generation physical enhancement using iontophoresis has already made clinical impact, especially for rapid, localized delivery to skin. It provides controlled drug dosing to the patient. Iontophoresis along with some other methods may find use in the delivery of macromolecule or vaccines. Non-cavitational ultrasound has found use for transdermal delivery of anti-inflammatories, but does not appear to be suitable for delivery of large molecules. Third generation physical enhancement using cavitation ultrasound and electroporation enhance
transdermal delivery by disrupting stratum corneum on the nanometer scale. Cavitation ultrasound has already been approved for transdermal delivery of lidocaine and may be approved for peptides and other small molecules in future. Third generation methods appear to be more promising because they appear capable of delivering small molecules, macromolecules and vaccines as well. Published data suggests that these methods can be safe and effective. Moreover, unpublished clinical trials appear to yield promising results. Overall, transdermal drug delivery offers compelling opportunities to address the low bioavailability of many oral drugs, the pain and inconvenience of injections. First-generation patches, second- generation chemical enhancers and iontophoresis are expanding delivery capabilities for small molecules. Third-generation physical enhancers could enable transdermal delivery of macromolecules and vaccines. These scientific and technological advances that enable targeted disruption of stratum corneum while protecting deeper tissues have brought the field to a new level of capabilities that position transdermal drug delivery for increasingly widespread impact on medicine.

**Table 1: Transdermal products that are in clinical development in the United States**

<table>
<thead>
<tr>
<th>Compound</th>
<th>TDD technology</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprostadil</td>
<td>Gel</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Patch</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Iontophoresis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Dextrosamphetamine</td>
<td>Patch</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Patch</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Dihydrotestosterone</td>
<td>Gel</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Gel</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Androgen/Estradiol</td>
<td>Patch</td>
<td>Phase 2&lt;sup&gt;nd&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Table 2: Expected effects of skin delivery system on horny layer hydration and skin permeability**

<table>
<thead>
<tr>
<th>Delivery system</th>
<th>Examples/constituents</th>
<th>Effect on skin hydration</th>
<th>Effect on skin permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occlusive dressing</td>
<td>Plastic film, imperforated waterproof plaster</td>
<td>Prevents water loss; Full hydration</td>
<td>Marked increase</td>
</tr>
<tr>
<td>Occlusive patch</td>
<td>Most transdermal patches</td>
<td>Prevents water loss; Full hydration</td>
<td>Marked increase</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Currently, many of the clinical trials uses placebo patches to determine the adhesion performance of new drug products. Adhesion properties of TDDS depend on type and concentration of drug used, compatibility of drug with excipients and with the components of TDDS. Some patient instructions allow for taping of edges of a patch that is lifting. The patch should be manufactured in such a way that it does not fall off over the entire period of application. Novel dosage forms are developed to target drug delivery, better patient compliance, decrease toxicity. Novel dosage forms must be stability indicating, assure best consistency, product performance and they must be reproducible. TDDS are novel dosage forms which mainly rely on food adhesion over a period of many hours or days to ensure proper drug delivery. Skin adhesion is one of the most important functional properties for a TDDS. Poor adhesion results in improper dosing of patients. Consistent methodology to test the adhesion properties of TDDS and ensure their safety does not exist; although, in vivo human skin testing is the most reliable method for TDDS evaluation. So, it is important to develop in vitro adhesion testing methods. It is desirable that the vitro adhesion testing co-relates with in vivo skin adhesion. The adhesion of a TDDS needs to be a part of the upfront design of the transdermal drug delivery system.

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