APPROACHES FOR TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The number of medications and the ways in which they can be administered have expanded dramatically over the years. One such advance has been the development of transdermal delivery systems. The transdermal route of drug delivery has attracted researchers due to many biomedical advantages associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivery of the drug molecules to the systemic circulation via this route. Various types of transdermal approaches used to incorporate the active ingredients include use of prodrugs/lipophilic analogs, permeation enhancers, sub saturated systems and entrapment into vesicular systems. Innovations in technologies continue to occur at a positive rate, making the technology a fertile and vibrant. This article deals with the innovations in the field of TDDS to improve the release rate and other parameters and most suitable to the patient. The number of medications and the ways in which they can be administered have expanded dramatically over the years. One such advance has been the development of transdermal delivery systems. The transdermal route of drug delivery has attracted researchers due to many biomedical advantages associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivery of the drug molecules to the systemic circulation via this route. Various types of transdermal approaches used to incorporate the active ingredients include use of prodrugs/lipophilic analogs, permeation enhancers, sub saturated systems and entrapment into vesicular systems. Innovations in technologies continue to occur at a positive rate,
making the technology a fertile and vibrant. This article deals with the innovations in the field of TDDS to improve the release rate and other parameters and most suitable to the patient.

**KEYWORDS:** Transdermal delivery, Electroporation, Magnetophoresis. Ultrasound and Patent.

**INTRODUCTION**

Transdermal drug delivery system the medications are administered topically in the form of patches, Patches then applied to the skin for the delivery of drug through the skin at a predetermined and controlled rate. In transdermal drug delivery system (TDDS), transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin for the delivery of drug through the skin and to the systemic circulation at a predetermined rate over a prolonged period of time (Jain NK et al 2002). A high dose of drug is applied inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration in the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch (Narasimhulu A et al., 2015). Transdermal drug delivery system is the system in which the delivery of the active ingredients of a drug occurs penetrate through the skin. This system is designed to improve the therapeutic efficacy and safety of the drugs because drug delivered through the skin at a predetermined and controlled rate (Ajay S et al., 2013). Since the beginning of life on the earth, humans have applied a lot of substances to their skin as cosmetics and therapeutic agents. However, it was the twentieth century when the skin became used as route for long term drug delivery. Today about two third of drugs (available in market) are taken orally, but these are not as effective as required. To improve upon the features the transdermal drug delivery system was emerged. Amongst all techniques which were used for release drugs in a controlled way into them human body, transdermal drug delivery system (TDDS) is widely recognized as one of the most reliable, appealing as well as effective technique. Delivery of drugs through the skin has been an attractive as well as a challenging area for research. Over the last two decades, transdermal drug delivery had become an appealing and patience acceptance technology as it is minimize and avoids the limitations allied with conventional as well as parenteral route of drug administration such as peak and valley phenomenon i.e.
exhibit fluctuation in plasma drug concentration level, pain and inconvenience of injections; and the limited controlled release options of both (Sachan R et al., 2013). Nowadays about 74% of drugs are taken orally and are found not to be as valuable as most wanted. To advance such characters transdermal drug delivery system was emerged. With the creation of current time of pharmaceutical dosage forms, transdermal drug delivery system (TDDS) recognized itself as an important part of novel drug delivery systems. Transdermal dosage forms, still a costly alternative to conventional formulations, are becoming popular because of their exclusive advantages. Improved bioavailability, Controlled absorption, extra uniform plasma levels, painless and reduced side effects easy application and flexibility of terminating drug administration by simply removing the patch to the skin are some of the potential advantages of transdermal drug delivery (Ahmed A et al., 2011). In clinical practice the hypodermic needles are used for the delivery of drug to deliver medications across the skin into the bloodstream. Injections with hypodermic needles are important from a clinical standpoint, but painful. They may also induce hypersensitivity; bruising, discomfort and bleeding at the site of administration, and in some cases are associated with risks of contamination (Kevin I et al., 2015).

Advantages of TDDS
Avoid the risk and inconvenience of intravenous therapy (noninvasive). Avoidance of first pass hepatic metabolism (avoiding the deactivation digestive and liver enzymes) thus increasing bioavailability and efficacy of drugs (Vyas SP et al., 2013). They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug. They can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhoea. To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liver when taken orally. They are noninvasive, avoiding the inconvenience of parenteral therapy. They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Transdermal clonidine 7 day (Mahato RA et al., 2011).

Disadvantages of TDDS
Ionic drugs cannot deliver by the TDDS. High drug levels in blood/plasma cannot not achieve by the TDDS. The large molecular size drugs cannot be delivered by the TDDS. If there is irritation on skin regarding to drug or formulation then TDDS cannot develop. The
drug cannot be delivered by the TDDS in a pulsatile fashion. Limitation of TDDS can be overcome to some extent by novel approaches such as iontophoresis, electroporation and ultrasound (Dipen P et al., 2012). Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation. Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's imperability. Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable. Long time adhere is difficult (Sandhu P et al., 2011).

Methods for enhancing transdermal drug delivery
Skin penetration can be enhanced by following methods shown in figure 1.

![Figure 1. Various methods to enhance the skin penetration (Touitou E et al., 1994)](image)

**Drug/Prodrug**
The prodrug approach has been used to enhance the dermal and transdermal delivery of drugs with unfavourable partition coefficients the prodrug design involves addition of a promoiety to increase partition coefficient and also solubility and transport of the parent drug in the stratum corneum. Upon reaching the viable epidermis, esterases release the parent drug by hydrolysis thereby optimising solubility in the aqueous epidermis. For example: The intrinsic
poor permeability of the very polar 6-mercaptopurine was increased up to 240 times using S6- acyloxyethyl and 9-dialkylaminomethyl promoieties. The prodrug approach has also been investigated for increasing skin permeability of non-steroidal anti-inflammatory drugs, like naltrexone nalbuphine buprenorphin alpha-blocker and other drugs (Heather AE et al., 2005, Touitou E et al., 1994).

**Eutectic system**

Mixture of chemical compounds is called eutectic system or elements that has a single chemical composition that solidifies at a lower temperature than any other composition (Heather AE et al., 2005, Touitou E et al., 1994). According to the regular solution theory, the lower the melting point, the greater the solubility of a material in a given solvent, skin lipids including. The melting point of a drug delivery system can be lowered EMLA cream, a formulation consisting of a eutectic mixture of lignocaine and prilocaine applied under an occlusive film, provides effective local anesthesia for pain-free venepuncture and other procedures.

**Liposomes and vehicles**

Liposome are colloidal particles formed as concentric bimolecular layers that are capable of encapsulating drugs. There are many examples of cosmetic products in which the active ingredients are encapsulated in vesicles. These include humectants such as glycerol and urea, unscreening and tanning agents, enzymes, etc. Phosphatidylcholine from soybean or egg yolk is the most common composition although many other potential ingredients have been evaluated (Touitou E et al., 1994). Cholesterol added to the composition tends to stabilize the structure thereby generating more rigid liposomes. The mechanism of enhanced drug uptake into the stratum corneum is unclear. It is possible that the liposomes either penetrate the stratum corneum to some extent then interact with the skin lipids to release their drug or that only their components enter the stratum corneum.

**Solid lipid nanoparticles**

Solid lipid nanoparticles (SLN) have recently been investigated as carriers for enhanced skin delivery of sunscreens, vitamins A and E, triptolide and glucocorticoids. It is thought their enhanced skin penetration is primarily due to an increase in skin hydration caused by the occlusive film formed on the skin surface (Wissing SA et al., 2003).
Iontophoresis
This method involves permeation of a topically applied therapeutic agent by application of low level electric current either directly to skin or indirectly via dosage form. Parameters that effect design of a ionophoretic skin delivery system include electrode type, current intensity, pH of system. Increased drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms: Electro-repulsion (for charged solutes), electro-osmosis (for uncharged solutes) and electro-perturbation (for both charged and uncharged) shown figure 2 (Guy RH et al., 2000, Ritesh Bathe et al., 2015).

![Figure 2. Basic principle of iontophoresis](image)

Electroporation
It involves the application of high voltage pulses to the skin that has been suggested to induce the formation of transient pores. High voltages (100 V) and short treatment durations (milliseconds) are most frequently employed. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with molecular weights greater that 7kDA shown in figure 3 (Guy RH et al., 2000).
Ultrasound (sonophoresis and phonophoresis)
This technique involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre-treatment. It uses low frequency ultrasound (55 kHz) for an average duration of 15 seconds to enhance skin permeability (Mitragotri S et al., 1995).

Laser radiation and photomechanical waves
Lasers are frequently used for treatment of dermatological conditions like acne and to confer facial rejuvenation. This method involves direct and controlled exposure of a laser to the skin that results in the ablation of the stratum corneum without significantly damaging the underlying epidermis (Lee WR et al., 2001).

Radio frequency
It involves the exposure of skin to high frequency alternating current resulting in formation of heat induced micro channels in the membrane. The rate of drug delivery is controlled by number and depth of micro channels formed by device. Treatment duration takes less than a second

Magnetophoresis
It involves application of magnetic field that acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability shown in figure 4 (Treffel P et al., 1993).
Microneedle based devices

The first ever patents for drug delivery for percutaneous administration of drug was based on this method. These microneedles of length 50-110 micrometre will penetrate SC and epidermis to deliver drug.

Needle-less injection

Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source. The mechanism involves forcing compressed gas (helium) through the nozzle, with the resultant drug particles entrained within the jet flow reportedly traveling at sufficient velocity for skin penetration. This method avoids issues of safety, pain and fear (Brown MB et al., 2008).

Application of pressure

The application of modest pressure i.e. 25kPa provides a potentially non-invasive and simplest method of skin permeability of molecules such as caffeine shown in figure 6.
**Patent papers:** Some of the patent papers of Transdermal Drug Delivery System

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Patent No.</th>
<th>Innovation</th>
<th>Inventors</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>WO2014152454A1</td>
<td>The present invention provides a transdermal drug delivery system, in the form of patch, comprising a drug-containing matrix layer comprising: (a) rivastigmine or a pharmaceutically acceptable salt thereof as an active ingredient; (b) an acrylate-hydrocarbon hybrid polymer as an adhesive and a selection of absorption enhancers.</td>
<td>Je Phil Ryoo et al</td>
<td>2014</td>
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<td>2</td>
<td>US8048019B2</td>
<td>A transdermal drug delivery system (100) for providing controlled doses of a drug through the skin of a human or other animal is disclosed. In one embodiment, the transdermal drug delivery system (100) includes a substrate (110) designed to adhere to skin and a transdermal injector array (140) coupled to the substrate (110).</td>
<td>Giovanni Nisato et al</td>
<td>2011</td>
</tr>
<tr>
<td>3</td>
<td>US2007/0116752A1</td>
<td>A transdermal drug delivery device comprises a reservoir layer, which consists of one or more chambers for containing a drug. A lower surface of the reservoir layer is bounded by a resilient membrane, which is perforated by pores through which the drug may be delivered from the chambers.</td>
<td>Dewan Fazlul Hoque Chowdhary et al</td>
<td>2007</td>
</tr>
<tr>
<td>4</td>
<td>US2006/0078604A1</td>
<td>A transdermal drug delivery system for the topical application of one or more active agents contained in one or morepolymeric and/or adhesive carrier layers, proximate to a non-drug containing polymeric backing layer which can control the delivery rate and profile of the transdermal drug delivery system by adjusting the moisture vapor transmission rate of the polymeric backing layer.</td>
<td>David Kanios et al</td>
<td>2006</td>
</tr>
<tr>
<td>5</td>
<td>US6632457B1</td>
<td>Compositions and methods are provided to control the release of relatively low molecular weight therapeutic species through hydrogels by first dispersing or dissolving such therapeutic species within relatively hydrophobic rate modifying agents to form a mixture.</td>
<td>Amarpreet S. Sawhney et al</td>
<td>2003</td>
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<tr>
<td></td>
<td>Patent Number</td>
<td>Description</td>
<td>Invention Details</td>
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<td>6</td>
<td>US2003/0170296A1</td>
<td>The invention provides a transdermal delivery system for analgesic, anti-pyretic and anti-inflammatory drugs comprising an analgesic, anti-pyretic or anti-inflammatory drug in combination with water-miscible tetraglycol and water for dissolving the drug in hydrogel form.</td>
<td>Amnon Sintov et al 2003</td>
<td></td>
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<tr>
<td>7</td>
<td>WO2002009763 A2</td>
<td>The invention provides a transdermal delivery system for analgesic, antipyretic and anti-inflammatory drugs comprising an analgesic, antipyretic or anti-inflammatory drug in combination with water-miscible tetraglycol and water for dissolving the drug in hydrogel form.</td>
<td>Raphael Gorodischer et al 2002</td>
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<td>8</td>
<td>WO2001087276A1</td>
<td>The present invention relates to a hydrogel composition for transdermal drug delivery, more specifically to a hydrogel composition for transdermal drug delivery containing acrylate polymers like acrylic acid polymer, methacrylic acid polymer, alkyl acrylate polymer, alkyl methacrylate polymer or copolymers thereof as compatibilizers which enable both hydrophilic and lipophilic permeation enhancers to be applicable in the hydrogel composition in order to effectively control skin penetration of drugs.</td>
<td>Ho Chin Kim et al 2001</td>
<td></td>
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<tr>
<td>9</td>
<td>5932240</td>
<td>A multidose transdermal drug delivery system comprises a laminate composite. With a plurality of compartments. Each compartment is a reservoir for a unit dose of a drug active to be transdermally administered. The assembly is adhesively secured to the skin of a patient. Individual seals are provided for resealably enclosing the drug active in each of the reservoirs.</td>
<td>Joseph P.D Angelo et al 1999</td>
<td></td>
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<tr>
<td>10</td>
<td>US005817332A</td>
<td>A controlled release transdermal system for the delivery of at least one therapeutic agent comprises: the therapeutic agent in ionized form, a pH adjusting agent which upon uptake of water is converted to a buffer solution and a cyclized polysaccharide selected from a group consisting of cyclodextrin, cyclodextrin derivative and cyclodextrin polymer.</td>
<td>Arto O. Urtti et al 1998</td>
<td></td>
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Types of transdermal patches

**Single layer drug in adhesive**: In this system drug and excipients is inclusive with skin adhesive which serve as formulation foundation as a single breaking layer. The rate of release of drug through diffusion phenomenon. The rate of release of drug is expressed as (Sachan R et al., 2013).

\[
\frac{dQ}{dT} = \frac{Cr}{\frac{1}{Pa} + \frac{1}{Pm}}
\]

Where,

- \(Cr\) = drug concentration in reservoir compartment
- \(Pa\) = Permeability coefficient of adhesive layer
- \(Pm\) = Permeability coefficient of rate controlling membrane

**Multi-layer drug in adhesive**: The multi-layer drug-in adhesive patch is similar to the singlelayer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different however that it adds another layer of drug-in adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-ayer and a permanent backing (Ghulaxe C et al., 2015).

**Vapor patch**: In the vapour patches the adhesive layer not only used to affix the patch on the skin but also to release the vapour. The vapour patches are new types of transdermal patches on the market. The vapour patches release the essential oils for up to 6 hours, which is mainly used in cases of decongestion primarily. Other vapour patches for various purposes like reduce the quantity of cigarettes smoking and improve the quality of sleep are also available in market (Aarti N et al., 1995).

**Reservoir system**: In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug (Prabhakar V et al., 2012).

**Matrix system**: The two types of matrix systems are.
Drug-in-adhesive system- In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose (Narasimhulu A et al., 2015).

Matrix-dispersion system - The drug is dispersed in hydrophilic (or) lipophilic polymer to produce a homogenous mixture. This is poured on the glass plates which are fabricated with the backing layer. Instead of applying the adhesive on the face of the reservoir, it is speeded along with the circumference to form a strip of adhesive rim (Aarti N et al., 1995).

Micro reservoir system: In this type the drug delivery system is a combination of reservoir and matrix dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogenously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents (Kavitha A et al., 2011).

Basic components of TDDS
1 Polymer matrix / Drug reservoir
2 Drug
3 Permeation enhancers
4 Pressure sensitive adhesive (PSA)
5 Backing laminates
6 Release liner
7 Rate controlling membrane
8 Other excipients like plasticizers and solvents (Narasimhulu A et al., 2015)

Polymer matrix / Drug reservoir: Backbone of TDDS, which control the release of the drug. Polymer should be chemically non-reactive, should not decompose on storage, should be non toxic, cost should not be high. E.g.- cellulose derivatives, zein, gelatin, shellac, waxes, gums, Polybutadiene, hydrid rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, Polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate (Dhiman S et al., 2011).
Natural polymers: e.g. cellulose derivatives, zein, gelatine, shellac, waxes, gums, natural rubber and chitosan etc. Synthetic elastomers: e.g. polybutadiene, hydriin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber etc. Synthetic polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc. The polymers like polyethylene glycol17, eudragits18, ethyl cellulose, polyvinylpyrrolidone19 and \|[hydroxypropyl methylcellulose20 are used as matrix type TDDS. The polymers like EVA 21, silicon rubber and polyurethane are used as rate controlling TDDS (Sahoo KC et al., 2013).

Permeation enhancers: These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. These may conveniently be classified under the following main headings:

A) Solvents - These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide; pyrrolidones – 2 pyrrolidone, N-methyl, 2-pyrrolidone; laurocapram (Azone), miscellaneous solvents – propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

B) Surfactants - These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length. Anionic Surfactants: e.g. Diocyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl sulphoxide etc. Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc. Bile Salts: e.g. Sodium ms taurocholate, Sodium deoxycholate, Sodium tauroglycocholate. Biary system: These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways e.g. Propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid.

C) Miscellaneous chemicals These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m toluamide; calcium thioglycolate; anticholinergic agents. Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di o-methyl-ß-cyclodextrin and soyabean casein (Krishna R et al., 1994).
Pressure sensitive adhesives: The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device. It should not be irritant ii) It should be easily removed. It should not leave an un washable residue on the skin. It should have excellent contact with the skin. Physical & chemical compatibility with the drug. Permeation of drug should not effected (Sandhu P et al., 2014). Several classes of PSAs are used for skin contact application include acrylics, polyisobutylene and silicone polymers (Grossberg GT et al 2010). The functional properties of PSAs such as tackyness, adhesive property, release force, and cohesive strength as well as adhesive formulations having attributes such as enhanced drug flux and skin friendliness. A PSA must be able to performance effectively under a wide range of temperatures, humidity levels, and application frequency (from 24 hrs for some products to one week for others). The effects of mechanical stresses (e.g., stretching) as well as skin irritation and sensitization also must be considered. 21 The human studies of various commercially available transdermals are examined and reported to assess the relative performance capabilities of each type of transdermal design.24 Monolithic TTS was fabricated in PSAs- (a) terpolymer (PSA1) of 2-ethylhexyl acrylate, methyl methacrylate, and acrylic acid, (b) copolymer (PSA2) of 2-ethylhexyl acrylate, methyl methacrylate, acrylic acid, and vinyl acetate, and (c) Eudragit E100 pressure sensitive adhesive (PSA3). The transport of nicorandil via skin can be achieved by the skin permeation enhancer i.e. N-methyl-2-pyrrolidone (NMP) was investigated at different concentrations (5%) in PSAs (Venkatraman S et al., 1998)

Backing laminate: While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipients compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusive to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate. Examples of some backing materials are vinyl, polyethylene and polyester films (Arunachalam A et al., 2010).

Release liner: During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to the skin. It is therefore regarded
as a part of the primary packaging material rather than a part of the dosage form delivering the active principle (Santoro A et al., 2000). However, because the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding the chemical inertness and permeation to the drug, penetration enhancer, and water. In case cross-linking is induced between the adhesive and the release liner, the force required to remove the liner will be unacceptably high (Pfister WR et al., 1990).

**Other excipients:** Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir (Gale R et al., 1981, Rao PR et al., 1997). In addition plasticizers such as dibutylphthalate, triethylicitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch (Rao PR et al., 1997, Gondaliya D et al., 2003).

**VARIOUS METHODS FOR PREPARATION TDDS**

**a) Asymmetric TPX membrane method:** A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX (poly(4-methyl-1-pentene)) asymmetric membrane, and sealed by an adhesive (J. Ashok Kumar et al., 2010).

Asymmetric TPX membrane preparation: These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardner knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs (Baker W et al., 1989).

**b. Circular teflon mould method:** Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the Wquantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butylphthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular teflon mould. The moulds are to be placed on a leveled surface and covered with inverted
funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation (Wiechers J et al., 1992).

c. Mercury substrate method: In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 minutes to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation (Yamamoto T et al., 1990).

d. By using “IPM membranes” method: In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane (Khamis K et al., 1986).

e. By using “EVAC membranes” method: In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device (Anon et al., 1980).

f. Aluminium backed adhesive film method: Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custammade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks (Mayorga P et al., 1996).
g. Preparation of TDDS by using proliposomes: The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°C temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization (Deo MR et al., 1997, Yan- Yu X et al., 2006).

h. By using free film method: Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. 5 ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petridish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution. Aluminium backed adhesive film method is a suitable one (Crawford RR et al., 1997).

Evaluation parameters

Interaction studies- Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can effect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substances, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and...
chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc (Debji B et al., 2010).

**Thickness of the patch**- The thickness of the drug loaded patch was 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 (Gajanan D et al., 2011).

**Flatness**- Longitudinal strips were cut from each films, one from the centre and two from the either side. The length of each strip was measured and the variation in the length because of uniformity in flatness was measured by determining percent constriction, considering 0% constriction equivalent to 100% flatness:

\[
\% \text{ constriction} = \frac{I_1-I_2}{I_2} \times 100
\]

Where \(I_1\) is initial length of each strip, \(I_2\) is final length of each strip (Sahu RK et al., 2014).

**In vitro drug release studies**- The paddle over disc method (USP apparatus V) can be employed for the assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed and fixed over a glass plate with an adhesive. The glass plate then placed in a 500 mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5 °C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5mL aliquots) can be withdrawn at a appropriate time intervals upto 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated (Dipen MP et al., 2011).

**Percentage moisture uptake**- The water absorption capacities of various films were determined at 82% relative humidity (RH). Films were cut into 20 X 20 mm strips, were weighed, kept in desiccators at room temperature for 24 h, removed and exposed to RH conditions of 82% (containing saturated solution of potassium chloride) in different desiccators at room temperature. Weight was taken periodically until a constant weight was obtained. The water absorption capacity of the films (in weight %) was calculated in terms of percentage increase in the weight of film over the initial weight of the strip.
% Moisture uptake = \( \frac{Y - X}{Y} \times 100 \)

Where,

X = Initial Weight
Y = Final Weight

**Water vapour transmission rate**

Glass vial of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. The prepared film was fixed over the edge of the glass vial containing 3 gm of fused calcium chloride as a desiccant by using an adhesive. Then the vial was placed in a desiccator containing saturated solution of potassium chloride. The vial was taken out periodically and weighed for a period of 72 h. The experimental was performed in triplicate and the average values were calculated and given result.

\[ WVT = \frac{W}{L/S} \]

Where,

W = Water vapour transmitting in gm.
L= Thickness of the patch 9n cm.
S= Exposed surface area in cm (Sahu RK et al., 2012).

**Moisture content**

The film was weighed and kept in a dessicator with calcium chloride at room temperature for 24 h. The film was weighed again after specified interval until it showed a constant weight. The moisture content was the difference between the constant weight taken and the initial weight and was reported in terms of percentage moisture content (Sharma S et al., 2010).

\[
\% \text{ moisture content} = \left( \frac{\text{initial weight} - \text{final weight}}{\text{final weight}} \right) \times 100
\]

**Moisture uptake**

The weighed film was kept in a desiccators at room temperature for 24 hrs and then exposed to 84% relative humidity using a saturated solution of potassium chloride. Finally the films were measured periodically to constant weights (Sharma S et al., 2010).

\[
\% \text{ moisture uptake} = \left( \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \right) \times 100
\]
Quick Stick (peel tack) test
In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required to break the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width (Vyas P et al., 2002).

Probe tack test
In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams. Shown in fig. 6. (Vyas SP et al., 2002, Sachan R et al., 2013).

![Figure 6. Probe tack test](image)

Skin Irritation study
Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm²) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury (Aarti N et al., 1995).
Stability studies

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°C and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content (Singh J et al., 1993).

Thumb tack test

It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected (Aarti N et al., 1995).

Flatness test

Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness (Wade A et al., 1994).

Uniformity of dosage unit test

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2μm membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated (Aarti N et al., 1995).

Rolling ball tack test

This test involves measurement of distance travelled by a stainless steel along the upward face of adhesive. In figure 7 the diameter of ball is 7/16o inches and it released on inclined track having angle 22.5°. More the distance travelled, less the tacky polymer. Distance travelled by ball is measured in inches which determine the tackiness of polymer. It determines the softness of adhesive polymer (Sachan R et al., 2013).
Transdermal Market

The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally. The table 1 gives detail information of the different drugs which are administered by this route and the common names by which they are marketed; it also gives the conditions for which the individual system is used.

Table 1 (Hafeez A et al., 2013)

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug</th>
<th>Manufacturer</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alora</td>
<td>Estradiol</td>
<td>Thera Tech/Protocol Smith Kline</td>
<td>Gamble postmenstrual syndrome</td>
</tr>
<tr>
<td>Androderm</td>
<td>Testosterone</td>
<td>TheraTech/Glaxo Smith Kline</td>
<td>Hypogonadism in males</td>
</tr>
<tr>
<td>Catapres-TTS</td>
<td>Clonidine</td>
<td>Alza/Boehniger</td>
<td>Ingelheim Hypertension</td>
</tr>
<tr>
<td>Climaderm</td>
<td>Estradiol</td>
<td>Ethical</td>
<td>Holdings/Wyeth-Ayerest postmenstrual syndrome</td>
</tr>
<tr>
<td>Combi patch</td>
<td>Estradiol</td>
<td>Noven</td>
<td>Inc./Aventis Hormone replacement therapy</td>
</tr>
<tr>
<td>Deponit</td>
<td>Nitroglycerine</td>
<td>Schwarz Pharma</td>
<td>Angina Pectoris</td>
</tr>
<tr>
<td>Duragesic</td>
<td>Fentanyl</td>
<td>Alza/Jansean</td>
<td></td>
</tr>
</tbody>
</table>
Polariscope examination
This test is to be performed to examine the drug crystals in patch this test is to be performed. The test is performed by the polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch (Aarti N et al., 1995).

Percentage elongation break test
The percentage elongation break is to be determined by noting the length just before the break point, the formula of percentage elongation is.

Elongation percentage = \( \frac{L_1-L_2}{L_2} \times 100 \)
Where, \( L_1 \) is the final length of each strip and \( L_2 \) is the initial length of each strip (Lec ST et al., 1991).

Advance development in TDDS

Drug in adhesive technology has become the preferred system for passive transdermal delivery, two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch (Mitragotri S et al., 2001, Blankschtein D et al., 1996).
Conclusion
This review article concluded that, an older drug by formulating them in new dosage forms has generated enthusiasm among the pharmaceutical scientists to develop new dosage forms. In addition, new dosage forms are essential for other drugs in order to enhance their performance by reducing their dose, increasing absorption, delivering to the target site etc. The patented innovations in transdermal drug delivery arena aim at these goals. However, the ultimate test that an innovative technique should pass relates to its successful performance in vivo.

REFERENCES
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