INTRODUCTION

Currently, transdermal drug delivery (TDD) is one of the most promising methods for drug application. Increasing number of drugs are being added to the list of therapeutic agents that can be delivered to systemic circulation via skin. The skin as a route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic systems in the form of patches. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a time-released dose of medication systemically for treating illnesses. Since early 1980s, this dosage form of transdermal therapeutic system has been available commercially. Transdermal drug delivery system (TDDS) allow delivery of contained drug into the systemic circulation via permeation through skin layers at a controlled rate. An essential prerequisite for the development of TDDS is that the drug must be capable of passing through skin at a sufficiently high rate to achieve therapeutic plasma concentrations. However, the outermost layer of skin, stratum corneum (SC), forms a major barrier to most exogenous substances including drugs.

The discovery of TDDS is a breakthrough in the field of controlled drug delivery systems. The ability of TDDS to deliver drugs for systemic effect through intact skin while bypassing first pass metabolism has accelerated transdermal drug delivery research in the field of pharmaceutics. Over a decade of such extensive research activities, many transdermal patches have been developed and successfully commercialized. Preparation of TDDS consists of three basic designs: membrane control or reservoir patches (RPs), matrix or monolithic patches (MPs), and Drug in adhesive patches (DIAPs). TDD avoids problems such as gastrointestinal irritation, metabolism, variations in delivery rates and interference due to the presence of food. It is also suitable for unconscious patients. The technique is generally non-invasive well accepted by patients and can be used to provide local delivery over several days.

Among the different types of systems drug in adhesive layer contacting the skin, are very commonly used, being thin, conformable and comfortable. Transdermal patches are generally occlusive i.e., they do not allow water to be released from skin surface, and this is often the reason for skin irritation. On other hand occlusion generally increases drug transport because it augments the water content of the stratum corneum, although the effect is not same for different permeants.
Advantages of Transdermal Drug Delivery System:\(^8\)
- Improved bioavailability for many drugs.
- Reliable blood levels of drug.
- Sustained therapeutic effect, allowing use of drugs with short half-lives.
- Diminished side effects.
- Daily, multiday or weekly dosing to improve patient compliance.
- Simple, noninvasive administration particularly important for patients who are unable to take medication orally.
- Reduced overall treatment costs in many instances.

These advantages of transdermal therapy may yield enhanced safety, efficacy, reliability and acceptability of drug treatment.

Limitations of transdermal delivery:
- As with the other routes of drug delivery, transport across the skin is also associated with several disadvantages, the main drawback being that not all compounds are suitable candidates.
- A number of physicochemical parameters have been identified that influence the diffusion process and variations in permeation rates can occur between individuals, different races and between the old and young.
- Furthermore, diseased skin, as well as the extent of the disease can also affect permeation rates.
- The metabolic enzymes in the skin can also pose a problem and some drugs are almost completely metabolized before they reach the cutaneous vasculature.
- Another problem that can arise which is sometimes overlooked is that, some drugs can be broken down before penetration through the SC by the bacteria that live on the skin surface.
- One of the major limitations of TDDS is that sometimes it may induce an irritation or sensitization reaction of the skin.

The earliest TDDS were reservoir-type devices that used membranes to control the rate of drug release.\(^9\) RPs contain the drug in a raised compartment, diffusing it through a polymeric membrane that controls the release rate, usually
providing true zero-order kinetics. MPs combine the drug, polymeric membrane, and adhesive into a single layer, the polymeric matrix. Drug is diffused through the polymeric matrix and through the skin. The drug closest to the skin is released first, and drug deeper within the patch travels a longer diffusional path before being released. This pattern departs slightly from zero-order kinetics, but the difference is generally not clinically significant. MPs are smaller and thinner than RPs, features that have increased patch acceptability among patients.¹⁰

Monolithic matrix systems consist of a polymeric material in which the drug is dispersed or dissolved, acting simultaneously as a combined drug reservoir and skin contact adhesive layer.¹¹ Today, a drug is more commonly dispersed or dissolved in a pressure-sensitive adhesive (PSA) matrix also called as drug in adhesive patches. In the simplest form, the adhesive matrix or drug-in-adhesive (DIA) design in which the drug is directly loaded or dispersed into the PSA polymer. The adhesive matrix provides several functions including skin adhesion, storage of the drug, and control over drug/enhancer delivery rate, and it also governs their partitioning into the SC.

When the characteristics of these three different patches are compared (Table 1), DIAPs and MPs are clearly superior to RPs in terms of patient compliance. It might also be expected because of their simple structure that DIAPs and MPs are superior from the commercial viewpoint in terms of the manufacturing process control, quality control and continuous product improvement. Moreover, the thinner construction of MPs and DIAPs may improve wearing comfort for the patient. However, drug formulations for MPs are more challenging to produce, particularly for those patches that incorporate the drug in the adhesive.

Several factors should be considered before choosing an appropriate design for a particular compound: drug solubility, stability and release rate. As a rule of thumb, if a drug permeates or crosses the skin faster than desired, RPs can slow down or control the permeation. Alternatively, if a drug passes through skin at a slower rate than the releases it, MPs probably containing a suitable chemical penetration enhancer may suffice.
Table 1: Characteristics of drug-in-adhesive and matrix patches vs. reservoir patches:

<table>
<thead>
<tr>
<th>Type</th>
<th>Structure</th>
<th>Formulation</th>
<th>Skin conformability</th>
<th>Size adjustment</th>
<th>Dose dumping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug in adhesive (DIA) or matrix patch (MP)</td>
<td>Simple thin layer</td>
<td>Complex</td>
<td>Good</td>
<td>Easy</td>
<td>Low potential</td>
</tr>
<tr>
<td>Reservoir Patch (RP)</td>
<td>Complex multi-layer</td>
<td>Simple</td>
<td>Some discomfort</td>
<td>Difficult</td>
<td>Possible breakage of rate controlling layer.</td>
</tr>
</tbody>
</table>

Diabetes Mellitus: 12, 13, 14

It is a metabolic disorder characterized by hyperglycemia, glycosuria, hyperlipidaemia, negative nitrogen balance and sometimes ketonaemia. A widespread pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and peripheral vascular insufficiency.

Two major types of diabetes mellitus are:

Type I: Insulin-dependent diabetes mellitus (IDDM), juvenile onset diabetes mellitus

There is beta cell destruction in pancreatic islets; majority of cases are autoimmune (Type 1A) antibodies that destroy β cells are detectable in blood, but some are idiopathic (Type 1B) — no β cell antibodies found. In all cases of type I diabetes, circulating insulin levels are low or very low, and patients are more prone to ketosis. This type is less common and has low degree of genetic predisposition.

Type II: Noninsulin-dependent diabetes mellitus (NIDDM), maturity onset diabetes mellitus

There is no loss or moderate reduction in β cell mass; insulin in circulation is low, normal or even high, no anti-β–cell antibody is demonstrable; has a high degree of genetic predisposition; generally has a late onset (past middle age). Over 90% cases are type II diabetes mellitus.
Type-II Diabetes mellitus is a complex and heterogeneous disorder. The pathogenesis involves multiple mechanisms which contribute to hypoglycemia, mostly notable impaired insulin secretion by pancreatic α-cells, reduced glucose uptake by skeletal muscles and adipose tissue (peripheral insulin resistance) and increased hepatic glucose production. Although basal insulin secretion may remain with the normal range, the meal-time insulin response is blunted or delayed in patients with type-II diabetes mellitus, which cause post-prandial hypoglycemia.

In patients with type-II diabetes mellitus blood glucose control may initially be achieved with appropriate body weight reduction, diet and exercise. But most patients eventually require drug therapy to maintain adequate glycemic control. Various oral hypoglycemic agents have been developed over the past 40 years. These include sulphonyl ureas, biguanides, α-glucosidase inhibitors and thiazolidinediones. These drug act through different mechanisms of action and can be used as monotherapy or in various combinations.

Table 2: List of Oral hypoglycemic Agents\textsuperscript{15}

<table>
<thead>
<tr>
<th>Class of agent</th>
<th>Generic name</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas: 1\textsuperscript{st} generation</td>
<td>tolbutilamide, chlorpropamide, tolazamide</td>
<td>Orinase\textsuperscript{®}, Diabinese\textsuperscript{®}</td>
</tr>
<tr>
<td>Sulphonylureas: 2\textsuperscript{nd} generation</td>
<td>glyburide, glipizide, glimepiride</td>
<td>Diabeta\textsuperscript{®}, Micronase\textsuperscript{®}, Glynase\textsuperscript{®}, Glucotrol\textsuperscript{®}, Glucotrol XL\textsuperscript{®}, Amaryl\textsuperscript{®}</td>
</tr>
<tr>
<td>Benzoic Acid Derivatives</td>
<td>repaglinide</td>
<td>Prandin\textsuperscript{®}</td>
</tr>
<tr>
<td>Biguanides</td>
<td>metformin</td>
<td>Glucophage\textsuperscript{®}</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>troglitazone, roziglitazone, pioglitazone</td>
<td>Rezulin\textsuperscript{®}, Avandia\textsuperscript{®}, Actos\textsuperscript{®}</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>acarbose, miglitol</td>
<td>Precose\textsuperscript{®}, Glyset\textsuperscript{®}</td>
</tr>
</tbody>
</table>
Transdermal drug delivery system designs:

TDD can be achieved via active or passive systems depending on whether external energy is used to assist the transport of the drug through the skin. The active systems use heat, electric current (iontophoresis), sound waves (sonophoresis), or transient high-voltage electrical pulses (electroporation) to enhance the delivery of drugs into the systemic circulation.

In passive TDDS, the drug diffuses through the skin into the systemic circulation by passive means. The concentration gradient of the drug across the skin and the difference in solubility between the adhesive and skin are the driving force for delivery to the surface of the skin. In general, chemical permeation enhancers (pharmaceutical excipients) are required for passive delivery to achieve the required delivery of the drug from a patch of a reasonable size (that is, a surface area of ≤ 40 cm²).

Approaches used in the development of transdermal drug delivery systems¹⁶:

Four different approaches have been utilized to obtain transdermal drug delivery systems.

1) Membrane Permeation – Controlled Systems

In this type of system, the drug reservoir is totally encapsulated in a shallow compartment moulded from a drug-impermeable metallic laminate and a rate controlling membrane which may be microporous or non-porous.

The drug molecules are permitted to release only through the rate-controlling membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium such as silicone fluid to form a paste like suspension.

A thin layer of drug compatible, adhesive polymer like silicone or polyacrylate adhesive may be applied to the external surface of the rate controlling membrane to achieve an intimate contact of the transdermal system and skin surface.

The rate of drug release from this type of system can be varying the polymer composition, permeability coefficient and thickness of the rate limiting membrane and adhesive.
The major **advantage** of membrane permeation controlled transdermal system is the constant release of drug. However, a rare risk also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or a rapid release of the entire drug content.

**Examples:**

a. Nitroglycerin-releasing transdermal system (Transdermal-Nitro/Ciba, USA) for once a day medication in angina pectoris.

b. Scopolamine-releasing transdermal system (Transdermal-Scop/Ciba, USA) for 72 hrs prophylaxis of motion sickness.

c. Clonidine-releasing transdermal system (Catapres/Boehriger Ingelheim, USA) for 7-day therapy of hypertension.

d. Estradiol-releasing transdermal system (Estraderm/Ciba, USA) for treatment of menopausal syndrome for 3-4 days.

2) **Adhesive Dispersion-Type Systems**

This system is a simplified form of the membrane permeation-controlled system. Here the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g., Poly (isobutylene) or Poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer.
On the top of the drug reservoir layer, thin layers of non-medicated, rate controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion-controlled delivery system.

**Example:**

- Isosorbide dinitrate-releasing transdermal therapeutic system (Frandol tape/Yamanouchi, Japan) once-a-day medication of angina pectoris.

3) **Matrix Diffusion-Controlled Systems**

In this approach, the drug reservoir is prepared by homogenously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness.

The drug reservoir can be formed by dissolving drug and polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vaccum. The drug reservoir containing polymer disc is then pasted onto an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing. The adhesive polymer is then spread along the circumference to form a strip of adhesive rim around the medicated disc.

The **advantage** of this type of system is the absence of dose dumping since polymer cannot rupture.
Example:

- Nitroglycerin-releasing transdermal therapeutic system (Nitro-dur and Nitro-Dur II / Key Pharmaceuticals, USA).

4) Microreservoir Type or Microsealed Dissolution Controlled Systems

This system is a combination of the reservoir and matrix diffusion type drug delivery systems. The drug reservoir is formed by first suspending the drug solids in an aqueous solution of water-soluble liquid polymer viz. silicone elastomers by high-energy dispersion technique to form several discrete, unleachable microscopic spheres of drug reservoirs.

The quick stabilization of this thermodynamically unstable dispersion is accomplished by immediately cross-linking the polymer chains \textit{in situ}, which produces a medicated polymer disc with a constant surface area and fixed thickness. Positioning the medicated disc at the center and surrounding it with an adhesive produce a transdermal therapeutic system.
Example:

- Nitroglycerin releasing transdermal therapeutic system (Nitrodisc, Searle, USA) for once a day therapy of angina pectoris.

**Anatomy of Transdermal drug delivery systems:**

1. **Additives:**
   1. **Release Liner:**

      Important properties for the release liner, the system component that is removed before application to the skin, include easy removability and excipient resistance. To maintain potency and predictable delivery characteristics, the liner must be resistant to drugs within the preparation and to humidity.

2. **Backung Layer:**

   Backings are chosen for appearance, flexibility and need for occlusion. Examples of backings are polyester film, polyethylene film and polyolefin film. Backing Layer is visible after the system is applied; the backing layer should exhibit excipient resistance, a low moisture vapor transmission rate and nontoxic composition. Non-excipient-resistant backings may allow leaching of additives from the backing and alteration of the drug. A low moisture vapor transmission rate is
essential to retaining skin moisture and hydrating the area where by increases drug penetration.

3. Adhesive Layer:

Adhesives are used to maintain intimate contact between the patch and the skin surface. Many classes of adhesives are available that might be considered for use with TDDS, although in practice pressure sensitive adhesives (PSAs) are preferred. PSAs are generally defined as materials that adhere to a substrate with light pressure and which leave no residual adhesive upon their removal and offer the following advantages:

- Convenience of use (PSAs do not require water/solvents or heat in order to achieve adhesion).
- Good stability (PSAs are generally not sensitive to environmental humidity or temperature degradation).
- Simplicity of manufacture.
- Good appearance.

Three types of PSAs are commonly used in TDD devices: polyisobutylenes (PIBs), polysiloxanes (silicones) and polyacrylate copolymers (acrylics). Natural rubber / karaya gum-based adhesives are another class of PSAs used in many over the counter (OTC) dermal therapeutic systems.

Adhesives in TDDS must be effective for 1 to 7 days, allow reasonably atraumatic removal, leave the skin, residue free after removal and worn comfortably without any local, mechanical, chemical or allergic reactions.

4. Overlay:

A TDDS may include a drug free adhesive coated film, foam or nonwoven component designed to be placed over a transdermal patch that has been applied onto the skin. This overlay secures the medicated patch to the skin of the patient.

5. Membrane:

A membrane may be sealed to the backing to form a pocket to enclose the drug containing matrix or used as a single layer in the patch construction. The diffusion properties of the membrane are used to control availability of the drug and/or excipients to the skin.
6. Chemical Permeation Enhancers:

The skin’s physical structure provides a barrier that may limit the permeation of some agents. Skin permeation enhancers broaden the range of drugs that can be delivered transdermally by increasing the penetration of permeants through enhanced diffusion of the SC and/or by increasing the solubility of the penetrant. Protein denaturation may disrupt the barrier as many fluidization and randomization of intercellular lipids or intercellular delamination and expansion.

Ideally, a permeation enhancer functions only to reduce the barrier resistance of the SC and does not damage any viable cells. The ideal enhancer is:

- Pharmacologically inert.
- Nontoxic.
- Nonirritating.
- Nonallergenic.
- Rapid-acting with duration of activity that is predictable and suited to its use.
- Chemically compatible and easily formulated into a variety of systems.
- Inexpensive.
- Odorless.
- Tasteless.
- Colorless.

The enhancer should not extract endogenous material out of the skin but should spread well on skin and have a suitable skin feel. If the substance is a liquid and is to be used at high volume fractions, it should be a suitable solvent for drugs.

Due to their systemic and localized toxicity, many effective chemical permeation enhancers have not been explored yet. Hence natural products have increasingly been used as enhancers due to their better safety profile. Terpenes are essential oils, which are used as fragrance, flavourings, and medicines. They have been found effective penetration enhancers for a number of hydrophilic and lipophilic drugs. Terpenes are highly lipophilic due to their isoprene (C₅H₈) units. They are generally recognized as safe (GRAS) by the FDA. They increase the drug diffusivity in the SC for hydrophilic drugs and they enhance partitioning of drug into the SC for lipophilic drugs, besides causing increased diffusivity.
II. Selection of Drug:

Drug should be chosen with great care, various parameters to be considered for the selection of drug includes:

1) Physicochemical properties of drug
   1. Should have molecular weight less than 1000 daltons.
   2. Should have affinity for both lipophilic and hydrophilic phase.
   3. Should have low melting point.

2) Biological properties of drug.
   1. Should be potent with daily dose of few mg.
   2. Should have short half life.
   3. Drug must not induce cutaneous irritation or allergic response.
   4. Drug which degrade in GIT or are inactivated by hepatic first pass effect are suitable candidates.
   5. Tolerance to drug must be developed under near zero order release profile of transdermal delivery.
   6. Drugs which have to be administered for long period of time or which causes adverse effect to non target tissues can also be formulated.