

**TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW**Anjali V. Patel*¹ and Biren N. Shah²¹Department of Pharmaceutics, Shree Naranjibhai Lalbhai Patel College of Pharmacy, Umargh, Bardoli, Surat¹Department of Pharmacognosy, Shree Naranjibhai Lalbhai Patel College of Pharmacy, Umargh, Bardoli, Surat**ABSTRACT**

The administration of drugs by transdermal route offers the advantage of being relatively painless. The appeal of using the skin as a portal of drug entry lies in ease of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks and the noninvasive nature of drug delivery. Delivery of drugs through the skin for systemic effect, called transdermal delivery was first used in 1981, when Ciba-Geigy marketed Transderm V (present day marketed as Transderm Scop) to prevent the nausea and vomiting associated with motion sickness. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and inpatient variation.

KEYWORDS: Transdermal Delivery, Patches, Topical**INTRODUCTION****NOVEL DRUG DELIVERY SYSTEM:^[1]**

During the past few years, interest in development of novel delivery system for existing drug molecules has been renewed. Development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent. When properly designed and developed for particular drug, novel delivery system can overcome specific hurdles associated with conventional methods of delivery e.g., drugs undergo partial or complete degradation before reaching site of action could be effectively delivered with improved bioavailability by using novel concept of time or pulsatile release, or gastro-resistant delivery.^[1]

During past 20 years, advances in drug formulations and innovative routes of administration have made. Our understanding of drug transport across tissues has increased. While topical products or drug delivery systems have been used for centuries for the treatment of local skin disorders, use of the skin as a route for systemic drug delivery is of relatively recent origin. Administration of drugs by transdermal route offers advantage of being relatively painless.

Appeal of using skin as a portal of drug entry lies in case of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks and noninvasive nature of drug delivery. Delivery of drugs through skin for systemic effect, called transdermal delivery was first used in 1981, when Ciba-Geigy marketed Transderm V (present day marketed as Transderm Scop) to prevent nausea and vomiting associated with motion sickness.^[1]

Throughout past two decades, transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms. It constitutes a new trend in controlled delivery system and has opened new scientific horizon in innovations. Delivery of drugs transdermally (through the skin) provides several important advantages over traditional oral and intravenous delivery routes. Transdermally delivered drugs avoid risk and inconvenience of intravenous therapy, usually provide less chance of an overdose or underdose, allow easy termination, and permit both local and systemic treatment effects. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. Main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and inpatient variation. In addition, because transdermal patches are user friendly, convenient, painless, and offer multi day dosing, it is generally accepted that they offer improved patient compliance.^[1]

TRANSDERMAL PATCH:^[2]

A transdermal patch is defined as adhesive medicated patch that is placed on to above skin to deliver an exact dose of drug through skin into the bloodstream with a predetermined rate of release to reach in the body. Today most common transdermal system present in market mainly based on semi permeable membranes which were called as patches. Transdermal drug delivery systems (TDDS), also known as “Transdermal patches” or “Skin patches” are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin and in bloodstream.^[2]

ADVANTAGES:^[3]

- Hepatic first pass metabolism, salivary metabolism and intestinal metabolism are avoided.
- Ease of usage makes it possible for patients to self-administer these systems.
- In case of an emergency, removing the patch at any point of time during therapy can instantly stop drug input.

-
- Since the composition of skin structurally and biologically is the same in almost all humans, there is minimal inter and intra patient variation.
 - Drugs showing gastrointestinal irritation and absorption can be suitably administered through skin.
 - Continuous, non-invasive infusion can be achieved for drugs with short biological half life which would otherwise require frequent dosing.
 - Due to reduced frequency of dosing there is better patient compliance.
 - Therapeutic failures associated with irregularities in dosing with conventional therapies can be avoided.
 - Adverse effects are minimized due to a steady and optimum blood concentration time profile.
 - Risks, pain and inconvenience associated with parenteral therapy are evaded. Release is more prolonged than oral sustained drug delivery systems.
 - At times the maintenance of the drug concentration within the biophase is not desired; therefore transdermal systems are suitable in this case.
 - Daily dose of drug required is lower than that with conventional therapies.
 - Drug release is such that there is a predictable and extended duration of activity.

DISADVANTAGES: [3]

- There is possibility of skin irritation due to the one or many of formulation components.
- Binding of drug to skin may result in dose dumping.
- It can be used only for chronic conditions where drug therapy is desired for a long period of time including hypertension, angina and diabetes.
- Lag time is variable and can vary from several hours to days for different drug candidates.
- Cutaneous metabolism will affect therapeutic performance of the system. Transdermal therapy is feasible for certain potent drugs only.
- Transdermal therapy is not feasible for ionic drugs.
- It cannot deliver drug in pulsatile fashion.

TECHNOLOGY FOR DEVELOPING TRANSDERMAL DRUG DELIVERY SYSTEM:[5]

The technologies can be classified in four basic approaches

1. Polymer membrane partition controlled TDDS

2. Polymer matrix diffusion controlled TDDS
3. Drug reservoir gradient controlled TDDS
4. Micro reservoir dissolution controlled TDDS

MEMBRANE PERMEATION – CONTROLLED SYSTEMS^[5]

In this type of system, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug-impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro-porous or non-porous e.g., ethylene vinyl acetate (EVA) copolymer, with a defined drug permeability property. A cross-sectional view of this system. 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, hypoallergenic adhesive polymer e.g. silicone or Polyacrylate adhesive may be applied to the external surface of the rate controlling membrane to achieve an intimate contact of the trans-dermal system and the skin surface the rate of drug release from this type of trans-dermal drug delivery system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate limiting membrane and adhesive. The constant release rate of the drug is the major advantage of membrane permeation controlled trans-dermal system. 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.

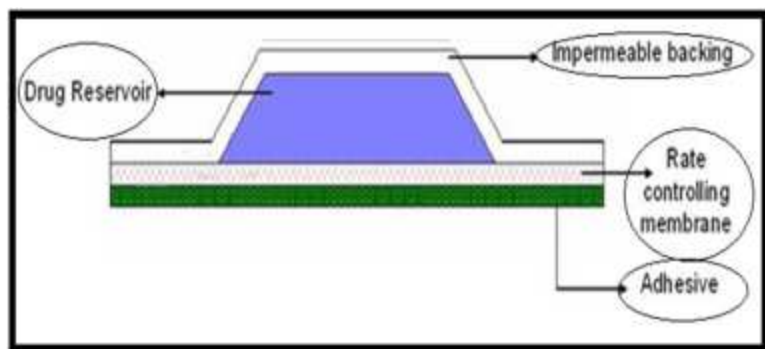


Figure: 1 Membrane permeation type TDDS.

ADHESIVE DISPERSION TYPE SYSTEMS ^[5]

This is a simplified form of the membrane permeation controlled system. As represented in the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer Eg. Poly (isobutylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent

casting or hot melt, on to the flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On 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.

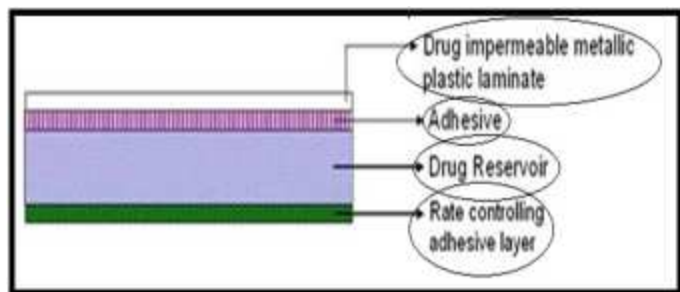


Figure 2: Adhesive Dispersion Type System

MATRIX DIFFUSION CONTROLLED SYSTEMS [5]

In this approach, the drug reservoir is prepared by homogeneously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then molded into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in the polymer matrix can be accomplished by either homogeneously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of the polymer chains or homogeneously blending drug solids with a rubbery polymer at an elevated temperature. The drug reservoir can also be formed by dissolving the drug and polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or under vacuum. This drug reservoir containing polymer disc is then pasted on to an occlusive polymer is then spread along the circumference to form a strip of adhesive rim around the medicated disc.

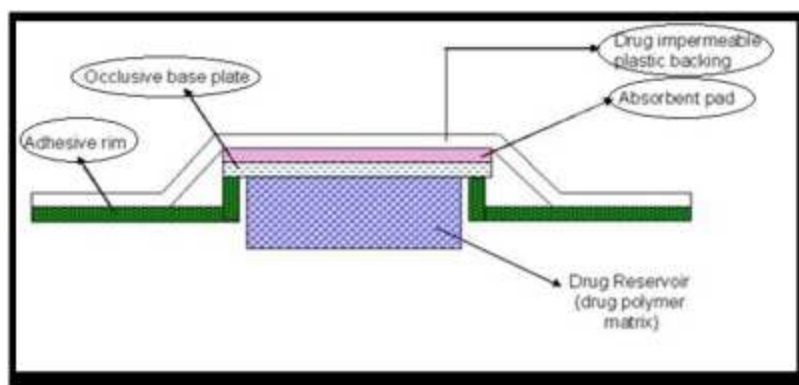


Figure 3: Matrix diffusion controlled type TDDS.

MICRO-RESERVOIR TYPE OR MICRO-SEALED DISSOLUTION CONTROLLED SYSTEMS :^[5]

This can be considered a combination of the reservoir and matrix diffusion type drug delivery systems. Here the drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water soluble liquid polymer and then dispersing the drug suspension homogeneously in a lipophilic 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 in situ which produces a medicated polymer disc with a constant surface area and a fixed thickness. Depending upon the physiochemical property of the drug and the desired rate of drug release, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and rate of drug release. A trans-dermal therapeutic system is produced by positioning the medicated disc at the center and surrounding it with an adhesive rim.

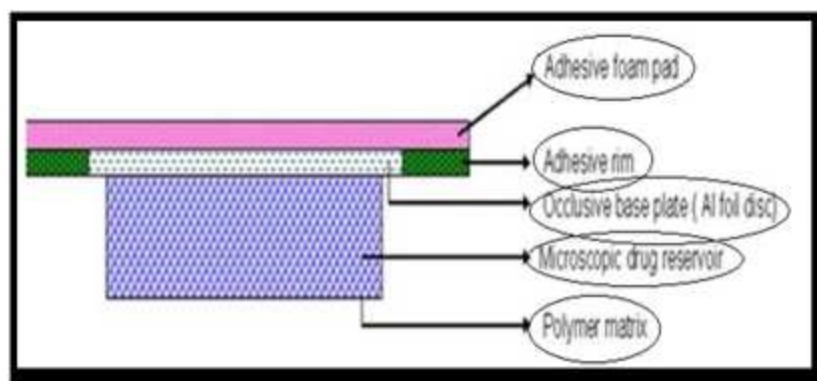


Figure 4: Micro reservoir type of TDDS

TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM:^[4]

a) Single layer drug in adhesive:

In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

b) Multi-layer drug in adhesive:

This type is also similar to the single layer but it contains an immediate drug-release-layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

c) Vapour patch:

The patch containing the adhesive layer not only serves to adhere the various surfaces together but also serves as to release the vapour. The vapour patches are new to the market, commonly used for releasing the essential oils in decongestion. Various other types of vapour patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

d) 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.

e) Matrix system:**i. Drug-in-adhesive system:**

This type of patch is formulated by mixing the drug with adhesive polymer to form drug reservoir. It then followed by spreading on an impervious backing layer by solvent casting or melting method. The top of the reservoir is protected by an unmediated adhesive polymer layers. It may further be categorized into single-layer and multi-layer drug-in-adhesive. The system is considered to be compatible with a wide variety of drugs. Moreover the system is competent to deliver more than one drug in a single patch. It offers advantages in reduced size and thickness and improved conformability to the application site, helping drive patient preference.

ii. Matrix-dispersion system:

The drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. It is then altered into a medicated disc with the definite shape and thickness. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

f) Micro reservoir system:

The system consists of microscopic spheres of drug reservoirs which releases drug at a zero order rate for maintaining constant drug levels. Micro reservoir system is a

combination of reservoir and matrix-dispersion system. The aqueous solution of water soluble polymer is mixed with drug to form a reservoir. It is then followed by dispersing the solution homogeneously using high shear mechanical force in a lipophilic polymer to form thousands of microscopic drug reservoirs. Cross linking agents are added to stabilize the thermodynamically unstable dispersion by in-situ cross-linking the polymer.

BASIC COMPONENT OF TDDS:^[6]

Both matrix patches and liquid reservoir patches comprise of various components. Some are similar in both classes, while others are type-specific. The common components include:

1. **Backing Films:** Backing films play a vital role in the transdermal patch and also while using the system. The role of the film is to protect the active layer and safeguard the stability of the system, and to affect skin permeation and tolerance, depending on occlusion or breathability. In order to avoid any type of incompatibility the release liner must be fully inert to the ingredients. It must also be flexible, comfortable and must have good affinity with the adhesive and excellent printability. The most common release liners are polypropylene, polyesters, PVC and nylon.
2. **Release Liners:** An anti-adherent coating will be covering the release liners. The role of the release liner is to protect the system when it is in the package, it will be removed just before the application of TDDS to the skin. Release liners play an important role in the stability, safety and affectivity of the patch. Care should be taken to choose the release liners. An incorrect release liner will not permit the easy release of the patch, and can interfere with the active(s) or other components, thereby reducing its shelf life. The most common films used as release liners are paper-based, plastic film-based and composite films. The two major classes of coating are silicones and fluoro-polymers.
3. **Pressure Sensitive Adhesives:** For both types of TDDS, pressure-sensitive adhesive(PSAs)play an important role, by serving as the matrix that carries the active like additives and permeation enhancers and the means for making the patch stick to the skin. There are three categories in PSAs: rubber-based, acrylic in the form of acrylic solutions, emulsion polymers or hot melts, and silicon PSAs. For each category there are several sub-categories that give the required flexibility to the patch.
4. **Penetration Enhancers:** These are the completely different chemical substances that belong to the same family by characteristics. They increase the permeation rate by several times of the active ingredient through the skin. This enhances the feasibility of a system, because most of the actives do not enter the skin in the required dosage

through a relatively small area. Sometimes a combination of these ingredients is needed to create the correct enhancing effect.

5. **Micro porous or Semi-Permeable Membranes:**

Porous membrane is a special type of membrane mostly used in all liquid transdermal patches and some of the matrix type patches. Its role is to regulate the flow of the semi-solid content from the liquid reservoir, and to act as a rate limiting membrane for the systems. The ability of the membrane depends on the design of the system, size of the active component and the need to have rate-limiting factor in order to satisfy the release and absorption characteristics of the system. Permeation rate depend on chemical composition.

There are two types of porous membranes as shown below.

A. Ethylene Vinyl Acetate Membrane.

B. Micro porous Polyethylene Membrane

6. **Pouching Material:**

Most of the TDDS that are available in the market are packaged as Unit doses in sealed pouches. The pouching material should be inert and should maintain the stability and integrity of the product. When there are two films with similar desired characteristics, the one with the lower cost, better function and printability will be chosen. There are three main layers in the composite materials used for pouches a) Internal plastic heat sealable layer, b). The aluminum foil layer, c). The external printable layer. If the film is a lamination, an adhesive is used to keep the layers intact.

- a. **Heat Sealable Layer:** This layer play an important role in the functionality, stability and protection of the patch. Several plastic films or coatings can be used for its formation, including polyethylene.
- b. **Aluminum Foil Layer:** This layer plays an important role in protecting the product from light and oxygen. In ideal conditions the foil needs to have a thickness of more than 1mil or 25 micrometers to be a real barrier. If any less than this thickness level is used, there will always be pinholes reducing the barrier properties.
- c. **External Layer:** The external layer of a composite film is responsible to achieve a better finishing and printing quality. It acts synergistically with the aluminum foil. Paper or polyester film is used as an external layer, but the polyester film creates a better-looking pouch and better barrier.

MARKETED FORMULATION OF TDDS:[6]**TABLE 2: MARKETED FORMULATION OF TDDS**

APPROVAL YEAR	DRUG	INDICATION	PRODUCT NAME	MARKETING COMPANY
1991	Nicotine	Smoking cessation	Nicoderm®, Habitrol®, proStep®	GSK, Novartis, Elan
1993	Testosterone	Testosterone deficiency	Testoderm®	Alza
2001	Estradiol/norelgestromin	Contraception	OrthoEvra®	Ortho-McNell
2005	Lidocaine/tetracaine	Local dermal analgesia	Synera®	Endo pharmaceuticals
2006	Methylphenidate	Attention deficit hyperactivity disorder	Daytrana®	Shire
2007	Rotigotine	Parkinson's disease	Neupro®	Schwarz pharma
2013	Sumatriptan	Migraine	Zecuity®	Nupathes Inc.

Physicochemical evaluation:^[7]**Thickness:**

Thickness of drug prepared transdermal patch is determined by digital micrometer at different points of patch and determines average thickness and standard deviation for same to ensure thickness of prepared patch.

Weight Uniformity:

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. Individual weight should not deviate significantly from average weight.

Drug content determination:

Drug content is important for determination of percent content of drug product. Accurate quantity of drug material is weighed and added into the 100 ml of suitable solvent. Mixture of solvent is shaken continuously for 24 h in shaker incubator. The complete mixture of drug containing specific dilutions

Percent Moisture content:

Prepared films are weighed individually and kept in desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. Percentage moisture content is calculated using following formula.

$$\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Percentage moisture uptake:

Weighed films are kept in a desiccator containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 h, reweigh patch and determine the percentage moisture uptake from the below mentioned formula:

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Flatness:

Three longitudinal strips are cut from different portions of the films. Length of the each strip is measured and variation in length because of non-uniformity in flatness is measured by determining percentage constriction, with 0% constriction equivalent to 100% flatness.

Folding Endurance:

A strip of specific area is cut evenly and repeatedly folded at same place till it breaks. Number of times film could be folded at same place without breaking gives the value of folding endurance.

Peel adhesion test:

In this test, the force required to remove an adhesive coating from a substrate is referred to as peel adhesion. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180° angle, and required to pull tape is measured.

Thumb tack test:

This test applied for tack property determination of adhesive. Thumb is simply pressed on the adhesive and the relative tack property is detected.

Probe tack test:

In this, the tip of probe with defined surface roughness brought in to contact with adhesive and when bond is formed between adhesive and probe, removal of probe at a fixed rate away from

adhesive which break the bond. Force required to break the bond is recorded as tack and it is expressed in grams.

Tensile strength:

Tensile strength was determined by using a modified pulley system. It contains two clamps, one was fixed and other was movable. Strip of patch (2x2 cm²) was cut and set between two clams. Weight was gradually increased on pan, so as to increase pulling force till patch broke. Force required to break film was consider as a tensile strength (kg/cm²). Tensile strength was determined by following equation.

$$\text{Tensile strength} = F/a \times b (H/L/l)$$

Where, F= force required to break;

a=width of film;

b= thickness of film;

L= length of film;

L= elongation of film at break point.

Flux and Permeability coefficient:

Flux (mg cm⁻² hr⁻¹) of meclizine HCl was calculated from slope of plot of cumulative amount of meclizine HCl permeated per cm² of skin at steady state against time using linear regression analysis. steady state permeability coefficient (K_p) of drug through rat epidermis was calculated by using following equation.

$$K_p = J/C$$

Where , J= flux

C= concentration meclizine HCl patch.

In-vitro Permeation study:

An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. Hair from abdominal region is to be removed carefully by using a electric clipper; dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of diffusant. Temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. Isolated rat skin piece is to be mounted between the compartments of diffusion cell, with epidermis facing upward into donor compartment. Sample volume of definite volume is to be removed from the

receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as slope of curve between the steady-state values of amount of drug permeated (mg cm^{-2}) vs. time in hours and permeability coefficients were deduced by dividing the flux by initial drug load (mg cm^{-2}).

CONCLUSION

Transdermal drug delivery systems represent a beneficial innovation for drug delivery, particularly in patients who cannot swallow or remember to take their medications. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effect and sometimes, and improved efficacy over other dosage form. It offer the delivery of drug at lowered dose that can save the recipient from the harm of large doses with improved bioavailability. Transdermal patches have become a proven technology that offers variety of significant clinical benefits over other dosage form.

REFERENCES

1. Pawan Jaiswal, "A review on transdermal patches." The pharma research, a journal, Jun 2010, 3, 139-149.
2. Chetan G., Rameshwar V., "A review on transdermal drug delivery system." the pharma innovation journal 2015; 4(1): 37-43.
3. Md. Intakhab Alam, Nawazish Alam, "Type, preparation, and evaluation of transdermal patch: A review." Research gate 2013 Vol. 2, Issue 4, and 2199-2233.
4. Pravin C., "A novel approach on transdermal drug delivery system [TDDS]", World journal of pharmacy and pharmaceutical sciences, 2016 Vol. 5, Issue 4, 932-958.
5. Dharmaraj B., "Technologies in transdermal drug delivery system: A review", International journal of pharmaceutical and chemical sciences, Vol. 3(2) Apr-Jun 2014, 528-541.
6. Arti K., "Theoretical aspects of transdermal drug delivery system." Bulletin of pharmaceutical research 2013; 3(2): 78-89.
7. Dhanusha.B, "Review on transdermal drug delivery system." Research and reviews: Journal of pharmacy and pharmaceutical sciences, Vol. 3(3) Jul-Sep 2014, 94-105.