

TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW**Akshay H. Bhoje*¹, AbdulKhalique A. Shaikh², Dr. Dhiren P. Shah³ and Tejas J. Patel⁴**Department of Pharmaceutics*¹⁻², Principal³, Assistant Professor⁴

Shree Naranjibhai Lalbhai Patel College of Pharmacy (268), Umarkh, Bardoli, Surat.

Article Received on
01 Feb. 2018,Revised on 22 Feb. 2018,
Accepted on 12 March 2018

DOI: 10.20959/wjpr20187-11535

Corresponding Author*Akshay H. Bhoje**Department of
Pharmaceutics, Shree
Naranjibhai Lalbhai Patel
College of Pharmacy (268),
Umarkh, Bardoli, Surat.**ABSTRACT**

Transdermal drug delivery system are topically administered medicaments. Transdermal patches are pharmaceutical preparation of varying sizes, containing, one or more active ingredient, intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers, and it avoid first pass effect. Transdermal patches delivers the drugs for systemic effects at a predetermined and controlled rate. Through a diffusion process, the drug enters the bloodstream directly through the skin. 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, Diffusion.**INTRODUCTION****Transdermal Drug Delivery System**

Transdermal drug delivery systems (TDDS), also known as “patches,” are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin. In order to deliver therapeutic agents through human skin for systemic effects, comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered.

Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus, various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Trans-mucosal delivery systems etc. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug.^[1]

Advantages of Transdermal Drug Delivery System

- ✓ Avoidance of first pass metabolism
- ✓ Avoidance of gastro intestinal incompatibility
- ✓ Predictable and extended duration of activity
- ✓ Minimizing undesirable side effects
- ✓ Provides utilization of drugs with short biological half-lives, narrow therapeutic window
- ✓ Improving physiological and pharmacological response
- ✓ Avoiding the fluctuation in drug levels
- ✓ Inter and intra patient variations
- ✓ Maintain plasma concentration of potent drugs
- ✓ Termination of therapy is easy at any point of time
- ✓ Greater patient compliance due to elimination of multiple dosing profile
- ✓ Provide suitability for self administration
- ✓ Enhance therapeutic efficacy^[2]

Disadvantages of Transdermal Drug Delivery System

- ✓ Many hydrophilic drugs cannot pass or very slowly permeates to skin. This will affect therapeutic efficacy of drug.
- ✓ Many problems like itching, edema, erythema etc. may be seen due to patches.
- ✓ The barrier function of skin may change from person to person, or with ages or with different sites on same person.
- ✓ There may be some possibility of irritation at the site of drug administration.
- ✓ Uneconomic system of drug delivery.
- ✓ It is not use in acute condition, only used in chronic conditions

- ✓ TDDS is not compatible with ionic drugs.
- ✓ Dumping of dose may occur.
- ✓ Drugs having affinity for both lipophilic and hydrophilic phases are used.
- ✓ High drug level in blood cannot be attained.^[3]

Technology for Developing Transdermal Drug Delivery System

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

1. Polymer membrane partition controlled TDDS

Membrane permeation - Controlled System: membrane permeation controlled system is important for determination of capacity of drug material or preparation to penetrate surface of skin and mucus membrane. Drug material is mainly dissolved in solid matrix of polymer system and they are suspended to Viscous Liquid medium. Material was allowed to Encapsulate in a shallow compartment and drug material is impermeable to metallic plastic laminate. Release of drug molecule is only penetrate through rate controlling polymeric membrane system. Micro porous or non-porous polymeric membrane having a rate limiting membrane system is responsible for known drug permeability property. Thin or transparent layer drug molecule is compatible with hypoallergenic adhesive polymer system, This type of system is important to maintain appropriate contact between drug delivery system with surface of skin. Polymer composition, permeability of system, Thickness of rate limiting membrane System and quantity of adhesives are changing is responsible for determination of rate of release of drug from Transdermal drug delivery System.^[4]

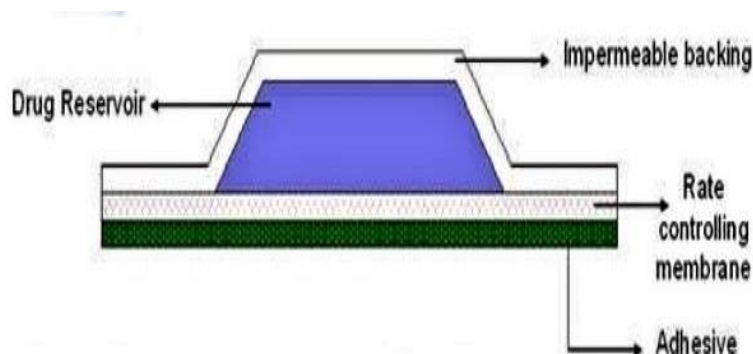


Figure 1: Polymer membrane partition controlled TDDS.

2. Polymer matrix diffusion controlled TDDS

Drug material is dispersed in insoluble form of matrix contain in rigid and non swellable hydrophobic material. Material used in formation of rigid matrix they are insoluble plastic materials, such as PVC and fatty materials like stearic and beeswax. Plastic material of drug is react with the solution of polyvinyl chloride is act as an organic solvent and they are granulated with waxy matrix from of material is prepared by dispersion of drug material molten fat and they followed by congealing. Granules of material undergoes compression to from tablets are swellable matrix system are popular for sustained activity for highly water soluble drug materials. Material such as naturally, semi synthetically and synthetically occurring drug material. Gums are granulated by come into contact with solvent material. Release of drug is depends on dehydration of hydrogels involves simultaneous absorption of water and drug material having diffusion mechanism of controlled swelling. Gum material are swells and they are diffuses or transported. Diagrammatic representation of Matrix diffusion - controlled system is shown in (Figure No.2).^[4]

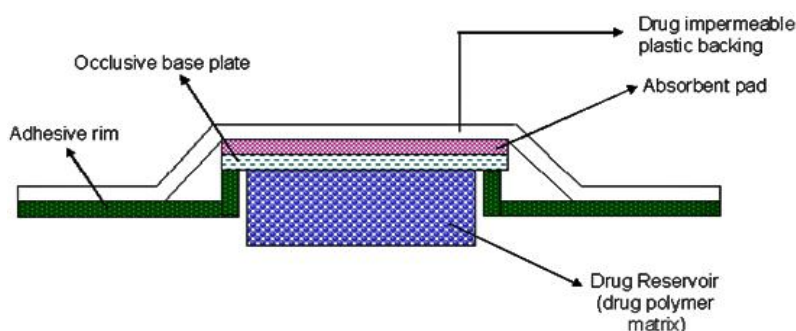


Figure 2: Polymer matrix diffusion controlled TDDS.

3. Drug reservoir gradient-controlled TDDS

Polymer matrix drug dispersion-type TDDS can be modified to have drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across multi laminate adhesive layers. Thus, theoretically this should increase a more constant drug release profile.^[4]

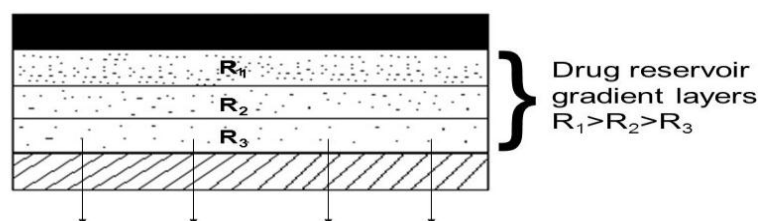


Figure 3: Drug reservoir gradient-controlled TDDS.

4. Microreservoir dissolution controlled TDDS

It is most important type of approach in Transdermal drug delivery system. In this Microreservoir system is a combination of Reservoir and matrix drug delivery system. Drug reservoir system is formed by suspending the solids of drug in aqueous solution of water soluble nature of polymeric system. Suspension of drug material is dispersed in homogeneously with lipophilic nature of polymer with help of high energy dispersion technique of Unreachable microspheres of reservoir. Dispersion of drug material homogeneously and maintain their thermodynamic stability by immediately cross linking the polymeric chains. In-situ procedure of medicated polymeric disk can maintain constant surface area and fixed thickness and example is a Nitro disks.^[4]

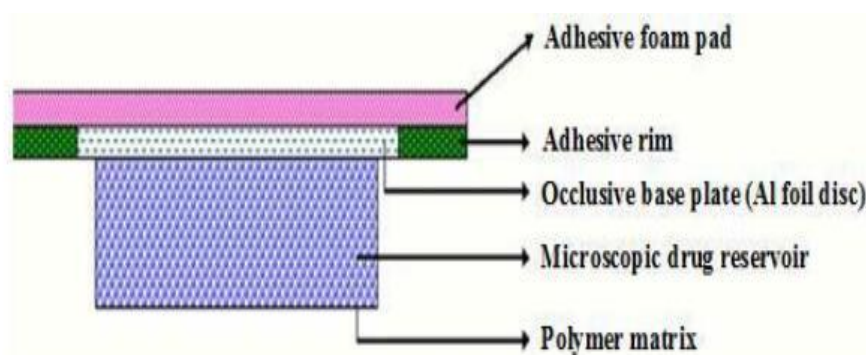


Figure 4: Micro-reservoir dissolution controlled TDDS.

Types of Transdermal Drug Delivery System

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.^[5]

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.^[5]

c) Vapor patch

The patch containing the adhesive layer not only serves to adhere the various surfaces together but also serves as to release the vapor. The vapor 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.^[5]

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.^[5]

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.^[5]

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.^[5]

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.^[5]

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.^[6]

Table 1: Patent papers: Some of the patent papers of Transdermal Drug Delivery System.

SR. NO	PATENT NO.	INNOVATION	INVENTORS	YEAR
1.	WO 2017136303 A1	The presented invention provide Fluorosilicone containing release liners for transdermal drug delivery systems, such as transdermal patches, transdermal drug delivery systems containing such release liners, and methods of delivering active pharmaceutical ingredients.	Daniel CARVAJAL et al	2017
2.	US 20160184246 A1	The presented invention provide compositions and methods for the transdermal delivery of agomelatine. The agomelatine compositions and methods are useful, for example, in the treatment of depression.	Puchun Liu et al	2016
3.	WO 2015066647 A3	The compositions and methods described are topically applied to the skin with negligible or no skin irritation and can direct or prevent transport through the skin. The compositions contain neat ionic liquids, optionally in combination with a drug to be delivered.	Michael Zakrewsky et al	2015
4.	WO 2003009829 A2	This invention relates to a stable, sterilized, purified composition having a polymer matrix and a therapeutically effective amount of a drug, wherein the drug can be used to prevent or treat drug-induced, alcohol-induced, biologically-induced, trauma-induced or pain-induced nausea, vomiting and dizziness.	Alan Drizen, Gary M. Nath	2014
5.	US 8435944 B2	The invention is directed to a transdermal drug delivery composition which includes at least one physiologically active agent; and at least one volatile solvent; and at least one viscosity modulating agent. The invention extends to methods of administering such a composition to a subject and treatment of subjects using the composition.	Tony DiPietro et al	2013
6.	US 8246979 B2	An improved transdermal delivery system (TDS) comprises a self-adhesive matrix comprising a solid or semi-solid semi-permeable polymer which contains rotigotine in its free base form as a multitude of microreservoirs within the matrix.	Dietrich Wilhelm Schacht et al	2012
7.	US 20100285133A1	In a first aspect, the invention disclosed in transdermal system in a matric form capable of enhancing granisetron carrying efficiency and improving transdermal absorption While inhibiting recrystallization.	Hoo-Kyun Choi, Gwangju (KR)	2010

Marketed Formulation of TDDS^[7]**Table 2: Marketed Formulation of TDDS.**

	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	Ortho Evra®	Ortho-McNeil
2005	Lidocaine/tetra Caine	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^[1,8,9]**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 is sonicated and filtered. Solution mixture is analysed by spectrophotometrically by preparing specific dilution.

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 clamps. 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.

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

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.

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.

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.

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 $32 \pm 0.5^\circ\text{C}$ 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. The transdermal drug delivery has capable advantage of avoiding hepatic first pass metabolism, improve to bioavailability, decrees gastro intestinal irritation due to local contact with gastric mucosa, maintaining constant blood level for a longer period of time resulting in decrees of dosing frequency and improved patient compliance. In recent years it has proved that benefits of intravenous drug infusion can be closely duplicated without harmful effects by using skin as part of drug administration to provide continuous transdermal drug infusion through intact skin.

REFERENCES

1. Kumar J.A., "Transdermal Drug Delivery System: An Overview" *International Journal of Pharmaceutical review and research*, 2010; 3: 49-50.
2. Jalwal, P., Jangra, A., Dahiya, A., Sangwan, Y., Saroha, R., "A Review on Transdermal Patches" *The Pharma Research (T. Ph. Res.)*, 2010; 3: 139-149.
3. Ghulaxe, C., Verma, R., "A review on transdermal drug delivery system" *The Pharma Innovation Journal*, 2015; 4(1): 37-43.
4. Savale, S., "A review on transdermal drug delivery system" *Asian Journal of Research in Biological and Pharmaceutical Sciences*, 2015; 3(4): 150-161.
5. Md. Intakhab Alam, Nawazish Alam, "Type, preparation, and evaluation of transdermal patch: A review." *Research gate*, 2013; 2(4): 2199-2233.
6. Amit Kumar, "Antiemetic's: A review", *International journal of pharmaceutical sciences and research*, 2013; 4(1): 113-123.
7. Arti K., "Theoretical aspects of transdermal drug delivery system." *Bulletin of pharmaceutical research*, 2013; 3(2): 78-89.
8. Kesarwani, A., Yadav, A., Singh, S., Singh, N., Sharma, A., and Yadav, C., "Theoretical Aspect of transdermal drug delivery system" *Bulletin of Pharmaceutical Research*, 2013; 3(2): 78-89.
9. Sharma, N., Bharat, P., Sharma, S., and Mahajan, U., "Blooming Pharma Industry with Transdermal Drug Delivery System" *Indo Global Journal of Pharmaceutical Sciences*, 2012; 2(3): 262-278.