IJPSR (2019), Volume 10, Issue 5 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 September 2018; received in revised form, 22 November 2018; accepted, 24 November 2018; published 01 May 2019

PERMEATION ENHANCERS COMPATIBLE WITH TRANSDERMAL DRUG DELIVERY SYSTEMS OVERCOMING THE SKIN BARRIER FUNCTIONS: CURRENT AND FUTURE PROSPECTS

A. Deevan Paul, Chitra Prasanthi *, N. Sumiya, P. V. Prasad and J. Vinay Kumar

SVU College of Pharmaceutical Sciences, SV University, Tirupathi - 517502, Andhra Pradesh, India.

Keywords:

Permeation enhancers, Systemic blood circulation, Polymer matrix, Diffusion

Correspondence to Author:
Chitra Prasanthi

M. Pharma (Pharmaceutics), SVU College of Pharmaceutical Sciences, SV University, Tirupathi - 517502, Andhra Pradesh, India.

E-mail: chitraprasanthi3164@gmail.com

ABSTRACT: Transdermal drug delivery system (TDDS) provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding the 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 the systemic circulation, which often causes undesirable side effects. The oral route of transdermal drug delivery enables avoidance in gastrointestinal absorption. One of the greatest innovations of novel drug delivery in transdermal patch skin adhesion is the most important functional properties for a TDDS. Poor adhesion results in improper dosing of patients and potential accidental dosing of patients, who may pick up fallen patches. The adhesive of the TDDS is critical to the safety, efficacy, and quality of the product. Drug therapy may be terminated rapidly by the removal of the application from the surface of the skin. This article provides a framework for scientific work to improve transdermal adhesive performance and provides an overview of types of transdermal, their anatomy, and the role of adhesion, the possible adhesion failure modes and how adhesion can be measured. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. FDA reports on the lack of adhesion of transdermal system products are presented. Pros and cons of *in-vitro* techniques, such as peel adhesion, tack and shear strength *in-vivo* techniques used to evaluate adhesive properties are discussed.

INTRODUCTION: Since, the beginning of life on the earth, humans have applied a lot of substances to the skin as cosmetics and therapeutic agents. However, it was the twentieth century when the skin became used as a route for long-term drug delivery. Today about two third of drugs are taken orally, but these are not as effective as required.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(5).2143-55

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(5).2143-55

Any drug delivery system aim is to provide a therapeutic amount of drug to the proper site in the body and then maintain the desired drug concentration. Drugs are administered by various routes such as oral, parental, nasal, transdermal, rectal, intra-vaginal, ocular, *etc*. [1]

Among all of them, the oral route is most common and popular, but this route of administration has some drawback first pass metabolism, drug degradation in the gastrointestinal tract due to pH, enzyme. To overcome these difficulties, there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (*i.e*., site-

specific), spatial and temporal placement within the body thereby reducing both the size and number of doses. New drug delivery system is also essential for the delivery of novel, genetically engineered pharmaceuticals (*i.e*., peptides, proteins) to their site of action, without incurring significant immunogenicity or biological innovation. A transdermal patch is defined as a medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the bloodstream. Today the most common transdermal system present in the market mainly based on semi-permeable membranes which were called as patches. As mentioned in **Fig. 1A**. Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation effects. In the Drug Quality Reporting System (DQRS), the United States Food and Drug Administration (FDA) has received numerous reports of ‘‘adhesion lacking’’ for transdermal drug delivery systems. The adhesive of the TDDS is critical to the safety, efficacy, and quality of the product. To begin with, the therapeutic effect of the drug is linked to the adhesive performance of the TDDS. Reduction in the surface area of contact as a result of patch lift, or even the patch falling off, diminishes the delivery of drug from the patch. In other words, poor adhesion results in improper dosing of patients. Secondly, patches that fail to adhere to their prescribed period must be replaced more often, thereby increasing the patient’s cost. Thirdly, lack of adhesion is a safety issue. There is potential accidental dosing of children who may pick up fallen patches. Death and other serious medical problems have occurred when accidentally exposed to certain patches mentioned in **Fig. 1B** *e.g.* transfer of a patch from an adult to a child while hugging, accidentally sitting or lying on a patch [1, 2].

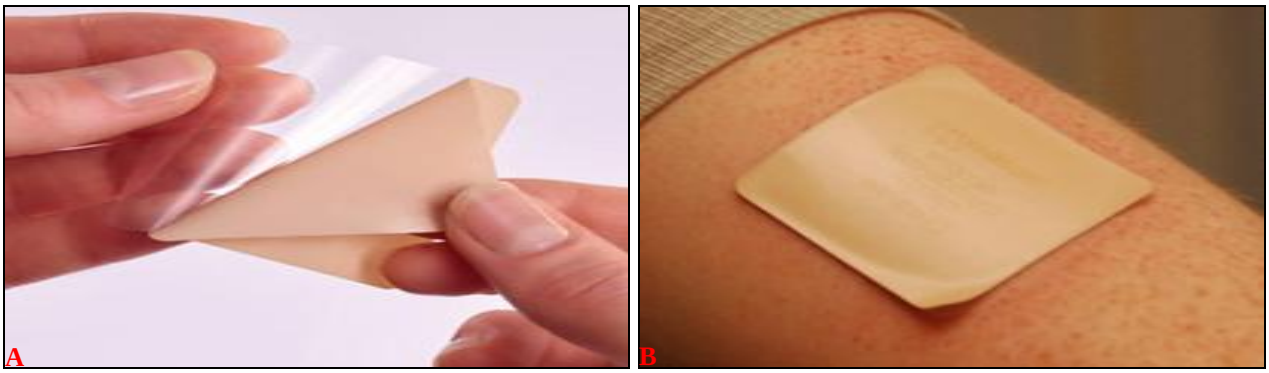

FIG. 1: TRANSDERMAL PATCH. (A) Releasing surface of the patch is covered by a protective liner which is removed before applied to the skin, (B) After applying the patch, slowly deliver the active substances through the intact skin.

Anatomy and Physiology of Skin: Human skin comprised of three distinct but mutually dependent tissues: The stratified, vascular, cellular called as “epidermis” underlying dermis of connective tissues, hypodermis.

Epidermis: The multilayered epidermis varies in thickness, depending on cell size and number of cell layers of the epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum is the outermost layer of skin also called as a horny layer. It is approximately 10 mm thick when dry but swells to several times thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of the drug. The architecture of the horny layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein “bricks” embedded in lipid “mortar.” The lipids are arranged in multiple bilayers.

There is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bilayer form. A viable number of the epidermis is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it consists of various layers like stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. Histochemically it is undergoing keratinization to form the outermost

layer of stratum corneum. In the basal layer, mitosis of the cells constantly renews the epidermis, and this proliferation compensates the loss of dead horney cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemically undergoing keratinization to form the outer most layer of the stratum corneum [3].

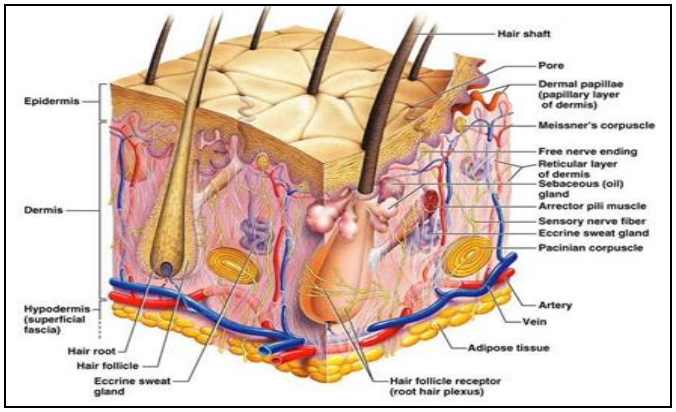

FIG. 2: TRANSDERMAL ROUTE OF MEDICATION IS POSSIBLE THROUGH THE SKIN BARRIER INTO THE CIRCULATING BLOOD

Dermis: The dermis is 3 to 5 mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels, and nerves. The cutaneous blood supply has an essential function in the regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of the skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low and the resulting concentration difference across the epidermis provides essential concentration gradient for transdermal permeation.

Hypodermis: The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanically protection. It carries principal blood vessels and nerves to the skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired as mentioned in **Fig. 2**.

Advantages:

- They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink, and another oral administration drug.
- They can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.
- To avoid the first pass effect, *e.g.* transdermal nitroglycerin. It is rapidly metabolized by the liner when taken orally.
- They are non-invasive, 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 day.
- The activity of drugs having a start half-life is extended through the reservoir of the drug in the therapeutic delivery system and its controlled release.
- Drug therapy may be terminated rapidly by the removal of the application from the surface of the skin.

Disadvantages:

- 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 a transdermal patch because of the natural limits of drug entry imposed by the skin's portability.
- Some drugs, *e.g.* scopolamine transdermal patch placed behind the ear, it is uncomfortable.
- Long-time adhere is difficult [4, 5, 6].

Limitations of Transdermal Drug Delivery System: Transdermal delivery is not suitable for delivery of large doses of drugs. It cannot administer drugs that require high blood levels. A drug which may cause irritation or sensitization is not given by this route. This route is limited when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin. For a drug, which doesn't possess a favourable o/w partition coefficient this route cannot be used. From one site to another on the same person, from person to person and with age the barrier functions of the

skin changes which hinders transdermal drug penetration [7, 8].

Biological Properties:

- The drug should be potent with a daily dose of the order of a few mg/day.
- The half-life ($t_{½}$) of the drug should be short.
- The drug must not produce an allergic response.
- Tolerance to the drug must not develop under the near zero-order release profile of transdermal patches.

Biological Factors:

Skin Condition: Acids and alkalis, many solvents like chloroform, methanol damage the skin cells and promotes penetration. A diseased state of patient alters the skin conditions. The intact skin is a better barrier, but the above-mentioned conditions affect penetration.

Skin Age: The young skin is more permeable than older. Children are more sensitive to skin absorption of toxins. Thus, skin age is one of the factors affecting the penetration of the drug in TDDS.

Blood Flow: Changes in peripheral circulation can affect transdermal absorption. Regional skin sites Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect penetration significantly. Skin metabolism skin metabolizes steroids, hormones, chemical carcinogens, and some drugs. So skin metabolism determines the efficacy of drug permeated through the skin.

Species Differences: The skin thickness, density of appendages and keratinization of skin vary from species to species, so affects the penetration [9].

Types of Transdermal Drug Delivery System:

Single-layer Drug-in-Adhesive System: In this type of patch the adhesive layer of this system contains the drug.

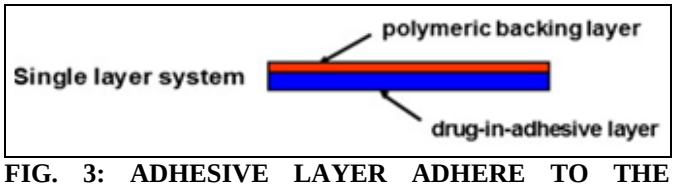

FIG. 3: ADHESIVE LAYER ADHERE TO THE VARIOUS LAYERS TOGETHER ALONG WITH THE ENTIRE SYSTEM OF THE SKIN

The adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but it is also responsible for releasing the drug. The adhesive layer is surrounded by a temporary liner and a backing. As mentioned in **Fig. 3**.

Reservoir System: In this system, the drug reservoir is kept in between the backing layer and a rate controlling membrane. And drug releases through microporous rate controlled membrane. The drug can be in the form of a solution, suspension, or gel or dispersed in a solid polymer matrix in the reservoir compartment as represented in **Fig. 4**.

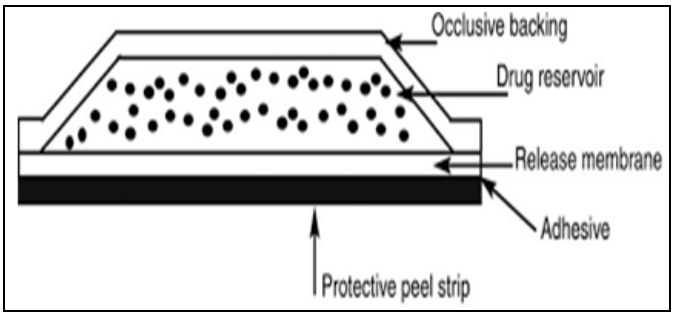

FIG. 4: DRUG CAN BE RELEASED THROUGH THE MICROPOROUS RATE CONTROLLED MEMBRANE IN THE RESERVOIR SYSTEM

Matrix System: This system is of two types:

Drug-in-Adhesive System: For the formation of the drug reservoir, the drug dispersed in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesives) on to an impervious backing layer.

Matrix-Dispersion System: In this system, the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix.

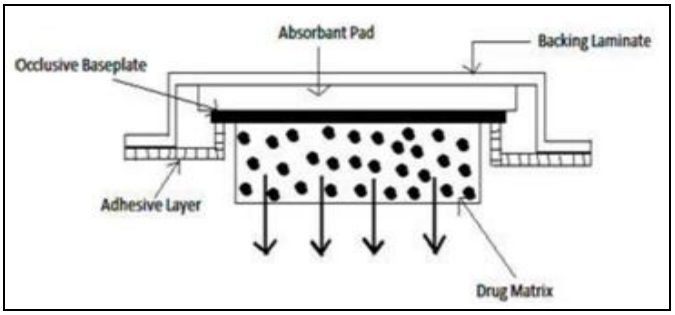

FIG. 5: ADHESION IS SPREAD AND FORMING AN ADHESIVE STRIP IN THE MATRIX RESERVOIR SYSTEM

And this containing polymer along with drug is fixed onto an occlusive base plate in a compartment fabricated from a drug- impermeable backing layer. In this system, the adhesive is spread along the circumference instead of applying on the face of drug reservoir to form a strip of the adhesive rim as mentioned in **Fig. 5**.

Micro-Reservoir System: This system is a combination of reservoir and matrix- dispersion systems. In which drug is suspended in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoir as mentioned in **Fig. 6**. [10]

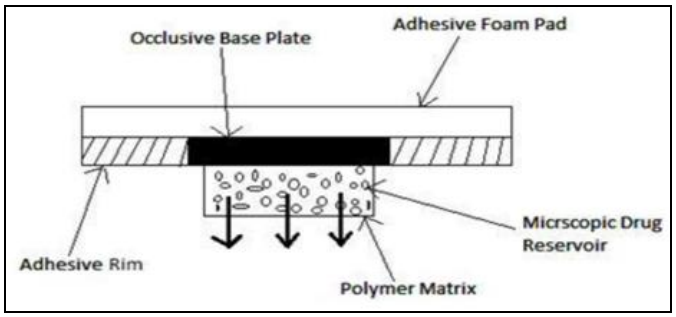

FIG. 6: MICROSCOPIC SPHERES OF A DRUG RESERVOIR IN MICRO RESERVOIR SYSTEM

Components of Transdermal Drug Delivery System:

- Polymer matrix/ Drug reservoir.
- Drug.
- Permeation enhancers.
- Pressure sensitive adhesive (PSA).
- Backing laminate.
- Release liner.
- Other excipients like plasticizers and solvents.

Polymer Matrix / Drug Reservoir: It is prepared by dispersing the drug in liquid or solid state synthetic polymer base. It should have bio-compatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers.

Additionally, they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status. Polymers used in transdermal drug delivery systems are classified as-

Natural Polymers: *e.g.*, cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber, and chitosan, *etc*.

Synthetic Elastomers: *e.g.*, polybutadiene, hydrin rubber, silicon rubber, polyisobutylene, acrylonitrile, neoprene, butyl rubber, *etc*.

Synthetic Polymers: *e.g.*, polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinyl-pyrrolidone, polymethylmethacrylate.

Permeation Enhancers: The flux J. of the drug across the skin can be written as-

$$J = D\, dc/dx$$

Where, J = the flux, D = Diffusion coefficient, C = Concentration of the diffusing speed, X = Spatial coordinate.

Solvent: These compounds increase penetration possibly by swelling the polar pathway. *e.g.*, water alcohols, methanol and ethanol/dimethylacetamide, propylene glycol and glycerol.

Surfactants: The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length. As mentioned in **Fig. 8**.

I. Anionic Surfactant: Sodium lauryl sulphate, diacetyl sulphosuccinate.

II. Nonionic Surfactant: Pluronic F127, pluronic F68.

III. Bile Salt: Sodium taurocholate and Sodium deoxycholate.

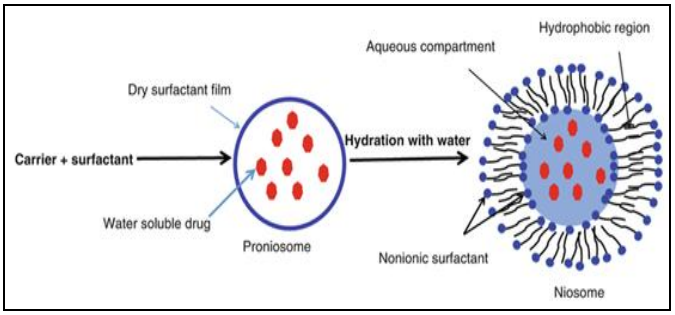

FIG. 7: ALTER THE PERMEATION OF TRANS-DERMAL PATCH THROUGH THE SURFACTANTS

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 soybean casein.

Enhance the Permeation: *e.g.,* Urea, calcium thioglycolate [11].

Role of Adhesion in Drug Delivery: Adhesion or the lack of adhesion of transdermal systems to the skin is a critical factor directly related to drug delivery and therapeutic effect. Since the drug absorption process is related to the drug partition between the TDDS and the skin and the drug permeation process, complete skin contact over the entire delivery surface for the entire label application period is essential. If the TDDS lifts or partially detaches, the effective area of TDDS/skin contact, and thus the drug absorption, changes unpredictably. Therapeutic failure can then occur. Only a constant TDDS/skin contact over the whole application period allows for consistent delivery and absorption of the drug.

FIG. 8: TRANSDERMAL PATCH MEDICATED ADHESIVE ON THE SKIN INTO THE BLOODSTREAM

Absorption of drug through the skin is affected by a number of factors such as skin sites, skin thickness, skin temperature, body temperature, blood flow, lipid concentration, number of hair follicles, skin cleansing, hydration status, sweat gland function, ethnic group, pH of skin surface and the state and integrity of the stratum corneum. Hydration of the skin and subsequent swelling of the stratum corneum result from occlusive products which tend to weaken the cohesive strength of the stratum corneum. The force required to remove a TDDS may decrease because of reduced adhesive contact, diminished drug concentration and a gradual sloughing of the outermost layers of the stratum corneum as represented in **Fig. 9**.

Peel Adhesion: Peel adhesion measures the force required to peel away an adhesive once it has been attached to a surface. Most currently used test methods for TDDS peel adhesion are based on methods developed for industrial tapes. These typically call for the use of a stainless steel test panel as the substrate, peel angles of 90º or 180º, cutting the sample into an exact width, dwell times of one minute and a peel speed of 300 mm/min.

The peel adhesion measurement is greatly influenced by the experimental parameters such as dwell time, the substrate (*e.g.*, stainless steel, skin, HDPE), peel angle, peel speed, *etc*. The measurement also depends on the TDDS backing and adhesive thickness. There are several complications with measuring *in-vitro* peel adhesion [12, 13, 14]. To begin with, cutting the TDDS to measure peel adhesion can be difficult. Peel adhesion is the force per unit width required to break the bond between an adhesive and the substrate as mentioned in **Fig. 10**.

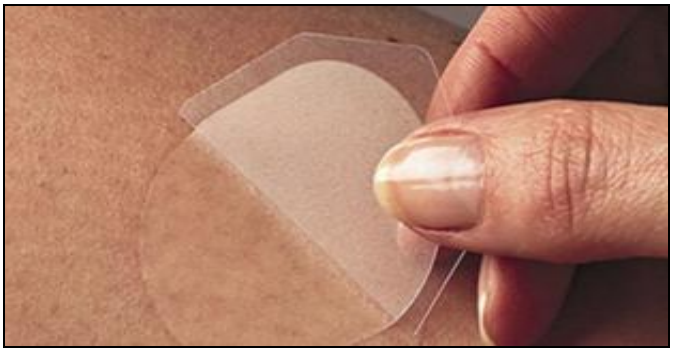

FIG. 9: PEEL ADHESION IS THE FORCE PER UNIT WIDTH REQUIRED TO BREAK THE BOND BETWEEN AN ADHESIVE AND THE SUBSTRATE

Techniques to Measure Adhesive Properties: The adhesive performance of TDDS is a critical factor in determining its drug delivery, therapeutic effect, and patient compliance. Several *in-vitro* techniques have been used to monitor adhesive performance such as tack and shear strength. However, these tests were developed for industrial pressure sensitive tapes. Tack and shear measurements are not true material properties of the adhesive since they depend on the substrate, backing material, and test parameters. The following points should be considered when developing adhesive tests for TDDS: the methods

developed should assure lot-to-lot quality for the product causes of instability such as the drug and excipients undergoing phase changes *(e.g.,* dissolved drug may crystallize, the dispersed drug may agglomerate) could adversely affect adhesive properties. Adhesive customization is important in product development.

Tack Adhesion Technique: The tack of an adhesive was initially evaluated by a highly subjective ‘‘thumb test’’ (*i.e.,* touching the surface of the adhesive with the thumb and sensing the force required to break the bond). The probe tack test was developed in an attempt to simulate and refine the thumb test. For a probe tack test, a probe touches the adhesive surface with light pressure, and the force required to break the bond after a short period of contact is measured. With some tack instruments (*e.g.,* Texture Analyzer), not only can the peak force at separation be measured, but also the area under the curve, the presence and magnitude of a shoulder in the curve and the displacement upon de-bonding. Rather than use the maximum force experienced during the bond separation as the indication of tack, Zosel has suggested that the tack energy as represented by the area under the curve correlates best with the thumbtack test. Tack is not simply a function of the material properties of the adhesive but is greatly influenced by the experimental parameters.

Tack depends on the contact area, the contact pressure, the time of contact (or dwell time), the rate of separation and the test environment. As with peel adhesion testing, tack is relative to both the substrate material (*e.g.* stainless steel) and the sample adhesive as represented in **Fig. 11**.

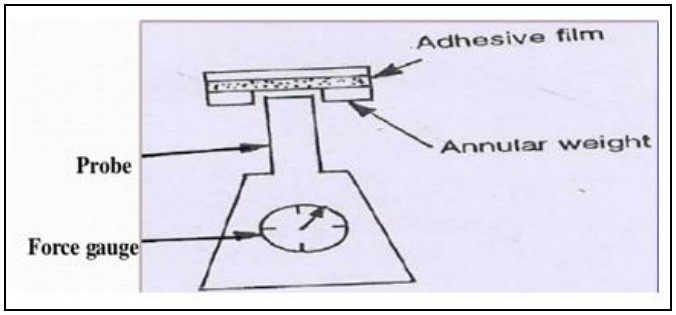

FIG. 10: PROBE TOUCHES THE ADHESIVE SURFACE AND BREAKS THE BOND AFTER THE CONTACT IS MEASURED

Shear Adhesion: Shear strength or creep compliance is thought of as a measure of the cohesive strength. This is a viscoelastic measurement that can be related to performance and processing. In the dynamic test, the TDDS is pulled from the test panel at a constant speed. Dwell time, speed, type of test panel, mode of failure and sample size should be noted, and the maximum force per unit width required to remove the TDDS from a specified area is usually reported. The relationship between shear force and the test area is curvilinear; the standard deviation increases with the width of the sample. In the static test, the TDDS sample is applied to a test panel that is at an angle 2º from the vertical, and the sample is subjected to a shearing force by means of a given weight (*e.g.,* 1000 g) suspended from the TDDS. Dwell time, weight used, type of test panel, mode of failure and sample size should be noted; the time taken for the TDDS sample to detach from the test panel is reported. One complication of shear testing is the stretching of the sample as it is being pulled. As with peel adhesion, industrial tape methods call for the use of a stainless steel test panel, but a substrate that is similar to human skin needs to be chosen. When the transdermal system is pulled from stainless steel, considerable stretching and deformation of the transdermal system may be seen. Some methods call for reinforcing the transdermal system by applying tape to the patch backing as represented in **Fig. 12**.

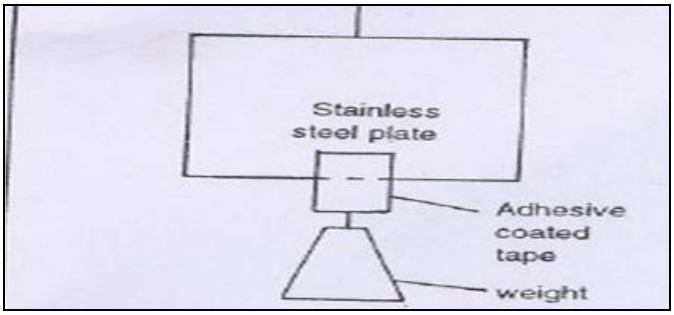

FIG. 11: COHESIVE STRENGTH OF AN ADHESIVE POLYMER TO MEASURE SHEAR ADHESION STRENGTH

An *in-vitro* Adhesion Technique: An *in-vitro* peel and the session test that predicts adhesion to human skin has not been developed. Skin is a variable material, and the test panels and probes used for testing adhesion properties are poor models of skin. The lack of *in-vivo/in-vitro* correlation may be attributed to the differences in the surface energy between the TDDS and skin versus the TDDS and a stainless steel test panel. The surface energy of

clean skin (27dyn/cm) is lower than those of stainless steel (500dyn/cm), polyethylene (31dyn/cm), polymethacrylate (39dyn/cm) and polystyrene (33dyn/cm). The *in-vitro* conditions do not necessarily represent the performance of the TDDS under *in-vivo* conditions. Skin is subject to moisture: either internal (perspiration) or external (washing), conditions that are difficult to duplicate for *in-vitro* testing. Also, *in-vivo* moisture conditions are greatly influenced by environmental factors such as heat, humidity, and exercise.

Changes to these factors may be caused by common activities such as bathing, showering, sunbathing, sauna, whirlpool, dressing, light exercise, strenuous exercise that produces a heavy sweat and swimming. Currently, *in-vivo* adhesion performance is usually based on subjective observations. The performance may be estimated by a scoring system based on patch lift. Adhesion to the skin is scored from 0 to 4, in which 0 indicates that the patch did not lift and 4 indicates that the patch fell off the skin. The condition of the skin before application of the TDDS is usually not stated [15, 16].

Kinetics of Transdermal Permeation: Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic systems. Transdermal permeation of a drug involves the following steps:

1. Sorption by stratum corneum.
2. Penetration of drug through the viable epidermis.
3. Uptake of the drug by the capillary network in the dermal papillary layer.

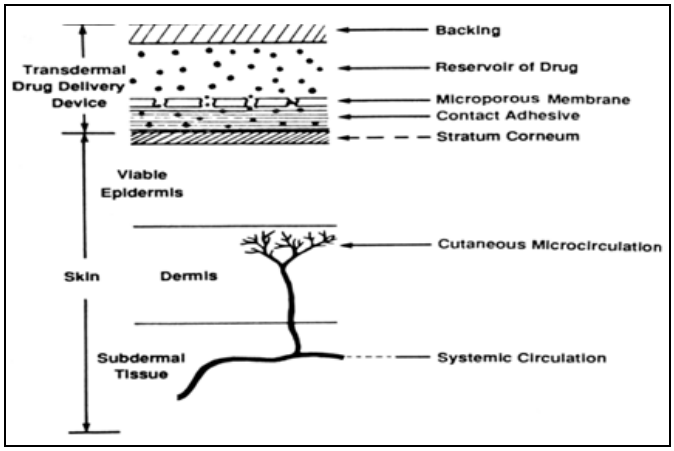

FIG. 12: TRANSDERMAL PATCH PERMEATION THROUGH THE SKIN INTO THE SYSTEMIC CIRCULATION

As mentioned in **Fig. 13**. This permeation can be possible only if the drug possesses certain physiochemical properties. The rate of permeation across the skin is given by:

$$Q = Ps (Cd – Cr)$$

Cd and Cr are the concentration of the skin penetrant, Ps is the overall permeability coefficient.

Where, Cd and Cr are the surface of stratum corneum and in the receptor compartment, *i.e.* on body respectively. Ps is the overall permeability coefficient of the skin tissue to the penetrant are. The relationship gives this permeability coefficient:

$$Ks\ Dss\ Ps = - hs$$

Ks is the partition coefficient, Dss is the apparent diffusivity, Ps is the permeability coefficient.

Where, Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum, Dss is the apparent diffusivity for the steady-state diffusion of the penetrant molecule through a thickness of skin tissues, and hs is the overall thickness of skin tissues. As Ks, Dss and hs are constant under given conditions the permeability coefficient Ps for a skin penetrant can be considered to be constant. From the equation it is clear that a constant rate of drug permeation can be obtained only when Cd >> Cr, *i.e.* the drug concentration at the surface of the stratum corneum Cd is consistently and substantially greater than the drug concentration in the body Cr. The equation becomes:

$$Q = Ps\ Cd$$

And the rate of skin permeation is constantly provided the magnitude of Cd remains fairly constant throughout skin permeation. For keeping Cd constant, the drug should be released from the device at a rate Rr, *i.e.* either constant or greater than the rate of skin uptake Ra, *i.e.* Rr >> Ra. Since, Rr >> Ra, the drug concentration on the skin surface Cd is maintained at a level equal to or greater than the equilibrium solubility of the drug in the stratum corneum Cs, *i.e.* Cd>>Cs. Therefore, the maximum rate of skin permeation is obtained and is given by the equation:

$$(dQ/dt)m = PSCs$$

From the above equation, it can be seen that the maximum rate of skin permeation depends upon the skin permeability coefficient Ps and is equilibrium solubility in the stratum corneum Cs. Thus skin permeation appears to be stratum corneum limited [17, 18, 19, 20].

Factors Affecting Transdermal Permeation:

Physicochemical Properties of the Penetrant Molecules Partition Coefficient:

- A lipid or water partition coefficient of 1 or greater is generally required for optimal transdermal permeability.
- It may be altered by chemical modification without affecting the pharmacological activity of the drug.

pH Conditions:

- Applications of solutions are whose pH values are very high or very low can be a destructive activity to the skin.
- With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species sand their transdermal permeability.

Penetrant Concentration:

- Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux.
- At content traction higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug constitution for a prolonged period [20, 2,, 22].

***In-vitro* Skin Permeation Studies:** The animals were sacrificed using anesthetic ether. of the entire abdominal skin in the water at 60°C for 45 sec, followed by careful removal of the epidermis The hair of the test animals was carefully trimmed short with a pair of scissors and the full thickness skin was removed from the abdominal region. The epidermis was prepared surgically by the heat separation technique, which involved soaking. *In-vitro* permeation study is done in the diffusion cell. Full-thickness abdominal skin of male Wister rats of weights 200 to 250 g is taken. The hair of the test animals was carefully trimmed short with a pair of scissors, and the full thickness skin was removed from the abdominal region. The epidermis was prepared surgically by the heat separation technique, which involved soaking of the entire abdominal skin in the water at 60 °C for 45 sec, followed by careful removal of the epidermis. The epidermis was washed with water and used for permeability studies. The permeation studies were performed for different formulations across female rat skin in a modified Keshary-Chein diffusion cell at 32 ± 0.5 °C. The diameter of the donor compartment cell provided an effective constant area of 3.14 cm^2. The films with an area of 3.14 cm^2 were applied to the skin using adhesive tape (cellophane) as the backing layer.

It is equilibrated for an hour in dissolution on medium. The phosphate buffer pH 7.4 (20 ml) was used as the receptor compartment medium, to ensure sink conditions and stability of the drug. This whole assembly was kept on a magnetic stirrer, and the solution was stirred continuously using a magnetic bead. The samples were withdrawn at different time intervals and replaced with an equal volume of diffusion medium. The samples were analyzed spectrophotometrically at 274 nm. To ascertain whether the components of the skin or other excipients of the film interfered in the drug analysis; a blank experiment (films without drug) was run, using the skin as a barrier membrane, with phosphate buffer saline pH 7.4. When the solution was analyzed at 274 nm for any interfering constituents, the released constituents amounted to an average of 0.04 ± 0.02%. [23, 24, 25,]

Care Taken While Applying Transdermal Patch: Prepare and clean the skin to remove any dirt, lotions, oils, or powders, clean the skin using warm water alone or with a clean soap. Avoid scented soaps or soaps that contain lotion. Dry the skin with a clean towel and paper towel. Open the package carefully by using scissors; avoid tearing or cutting the patch. Take the patch out of the packaging. Remove the protective liner on the patch as directed by the patch. Be careful not to touch the sticky side of the patch. If the patch's protective liner contains two parts, first peel off one part of the liner. Apply the exposed sticky part of the patch to the skin and press down. Next, peel back the second part of the liner and press the entire patch down. Place the patch, sticky side down, onto the clean area of skin, using the palm of your hand, press down on the patch to make sure

that patch is firmly attached to your skin. Use your fingers to press along the edges of the patch. The patch should be smooth with no bumps or folds as represented in **Fig. 14**. [26]

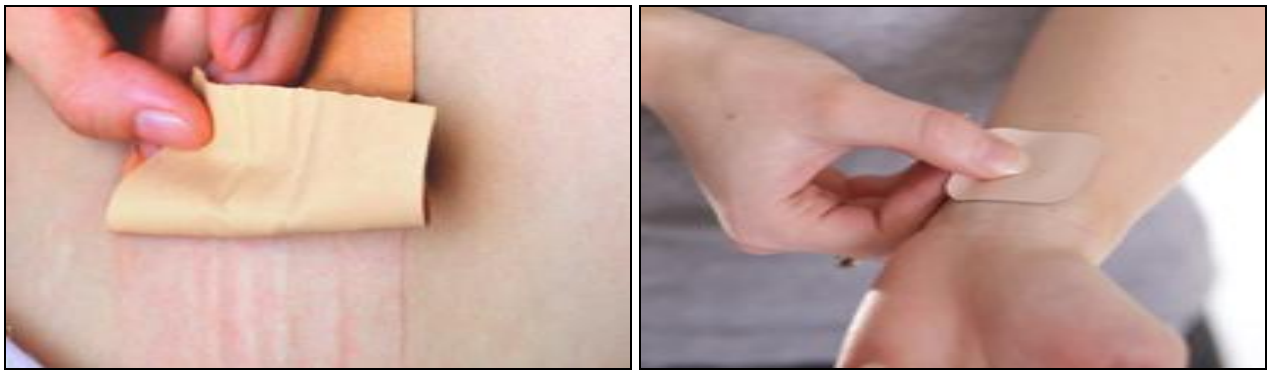

FIG. 13: THE PATCH SHOULD BE SMOOTH WITH NO BUMPS AS APPLIED TO THE SKIN WITH TAKING CARE

Skin Irritation Study: Healthy rabbits of the average weight of 1.2 to 1.5 kg are taken, and skin irritation and sensitization testing are performed. The dorsal surface 50 cm^2 areas of the rabbit are cleaned, hairs are removed from the clean dorsal surface by shaving and cleaning the surface by the rectified spirit, and the representative formulations is applied over the skin. The patch is removed after 24 h, and the skin is observed and classified into 5 grades based on the severity of skin injury.

a. pustule filled with fatty compounds and other product of sebaceous origin. The exposure of the unprotected skin to UV light (from sunlight or artificial sources) can result in toxic responses. These include short-term, generally reversible effects such as sunburn (erythema) and tanning (enhanced pigment darkening) as well to as long-term, generally irreversible effects such as premature skin aging (actinic elastosis) and development of the skin cancer.

b. Photosensitization related to xenobiotic exposure Xenobiotics localized within the skin can interact with light and produces an adverse reaction in the skin in many ways. These include phototoxicity, photoallergy depigmentation, induction of endogenous photosensitizers and induction of photosensitive disease states. The skin is the most common site of cancer in humans. Both benign and malignant tumors may be derived from viable keratinocytes and melanocytes of the epidermis, and rarely from skin appendages, blood vessels, peripheral nerves and lymphoid tissue of the dermis. Histologically, basal cell and squamous cell carcinomas that develop from keratinocytes account for 60% and 30% for all the skin cancers respectively [4]. Acne-like eruptions. These reactions are initiated by the proliferation of the epithelium of sebaceous glands and formation of keratin cyst resulting in the development of a pustule filled with fatty compounds and other product of sebaceous origin as mentioned in **Fig. 15**. [27]

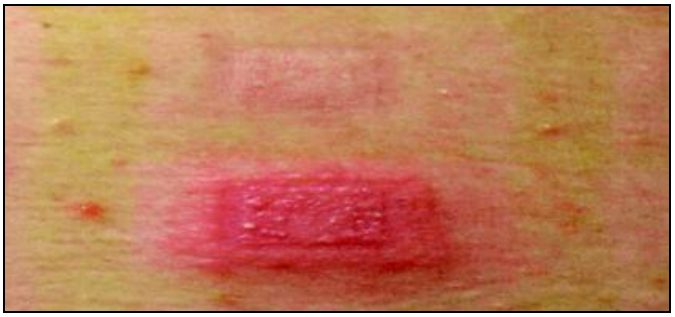

FIG. 14: SKIN IRRITATION PICTURE CAUSED BY EDEMA AND ERYTHEMA

Transdermal Market: The market for transdermal products has been in the significant upward trend that is likely to continue for the foreseeable future. An increasing number of TDDS products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDDS products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDDS products globally. **Table 1** gives detail information about 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[28].

Future of Transdermal Drug Delivery System: Future aspects in Drug delivery system include liposomes, niosomes, and microemulsion. The aim of this development is to improve the delivery of a

drug that has low inherent solubility in most of the classical formulation excipients. A wide range of potential drugs for delivery like steroids, antifungal, antibacterial, interferon, methotrexate, local anesthetics are formulated. The market for transdermal patches has been estimated to increase in the future and has recently experienced annual growth of a rate of 25%.

TABLE 1: INFORMATION ABOUT THE DIFFERENT DRUGS WHICH ARE ADMINISTRATED INDICATING WITH THE MARKETED NAMES

Product Name	Drug	Manufacturer	Indication
Alora	Estradiol	There tech /protocol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism males
Catapres-TTS	Clonidine	Alza/Boehringer Ingelheim	Hypertension
Climaderm	Estradiol	Ethical holdings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals Berlex Labs	Post menstrual syndrome
Combi Patch	Estradiol/norethindrone	Noven Inc/Aventis	Hormone replacement therapy
Diponit	Fentanyl	Alza/janssen pharmaceutical	Moderate or severe pain
Estraderm	Estrogen	Ethical holdings/Solvay health care	Postmenstrual syndrome
For matrix	Estrogen	Ethical holidays/Solvay Healthcare Ltd.	Postmenstrual syndrome
Fempatch	Estradiol	Parke-davis	Post menstrual syndrome
Habitual	Nicotine	Novartis	Smoking cessation
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nicoderm	Nicotine	Alza/Glaxo SmithKline	Smoking cessation
Nicotrol	Nicotine	Cygnus lnc/Mc Neil consumer products	Smoking cessation
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nitro dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Nuvelle TS	Estrogen/Progesterone	Ethical holding/Schering	Hormone replacement therapy
Ortho-Evra	Norelgestromin/estradiol	Ortho-McNeil Pharmaceuticals	Birth control
Prostep	Nicotine	Elan Corp/Lederle Labs	Smoking cessation
Testoderm TTS	Testosterone	Alza	Hypogonadism
Transdem scop	Scopalamine	Alza/Norvatis	Motion sickness
Transderm nitro	Nitroglycerin	Alza/Norvatis	Angina pectoris
Vivelle	Estradiol	Noven Pharmaceuticals/Norvatis	Post menstrual syndrome

Transdermal delivery of analgesics is likely to continue to increase in popularity as there are further improvements in design. Research is being performed to increase safety and efficacy. To improve practical matters such as the experience for the wearer of the patch, and also to provide more precise drug delivery associated with increased duration of action. Other potential improvements include improved transdermal technology that utilizes mechanical energy to increase drug flux across the skin either by altering the skin barrier or increasing the energy of the drug molecules.

After the successful design of patches using iontophoresis, various modes of 'active' transdermal technologies are being investigated for different drugs. These include electroporation (short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (uses low-frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (uses heat to make the skin more permeable and to increase the energy of drug molecules). Magnetic energy, magnetophoresis, has been investigated as a means to increase drug flux across the skin. The transdermal patch may be an underutilized tool for the management of acute and chronic pain. With improved delivery and a wider range of analgesics, we expect the popularity and applicability of this modality to deliver drugs to increase.

In the current scenario, transdermal route of drug delivery system in comparison with oral treatment as the most successful innovative research area in new drug delivery system, with around 40% of the drug delivery candidate products under clinical trials related to the transdermal or dermal system. The transdermal drug delivery systems have been designed as an alternative, safest and easy route for systemic drug delivery [29]. The systemic drug administration though skin holds several advantages such as maintaining constant drug level in blood plasma, less number of side effects, and improvement of bioavailability by circumvention of hepatic first-pass metabolism and increase

patient compliance concerning drug regime used for treatment. In recent times, skin considered as the safest port for drug administration, to provide continuous drug release into the systemic circulation.

CONCLUSION: This article provides valuable information regarding the transdermal drug delivery systems as a reference for the research scientists who are involved in the transdermal drug delivery system. Transdermal drug delivery made an important contribution to the medical practice and it delivers a specified amount of medication through the skin into the bloodstream. An advantage of a transdermal drug delivery route over other types of medication delivery is that the patch provides a controlled release of the medication into the patient, usually either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The drug delivery overcomes challenges associated with current popular drug delivery; thus it shows a promising future.

ACKNOWLEDGEMENT: The authors are thankful to Prof. Kedam Thyagaraju, Principal of SVU College of Pharmaceutical Sciences, SV University, Tirupathi.

CONFLICT OF INTEREST: The authors declare no conflict of interest

REFERENCES:

1. Jawale NR, Bhangale CD, Chaudhari MA and Deshmukh TA: Physical approach to transdermal drug delivery. A review, Journal of Drug Delivery and Therapeutics 2017; 7(3): 28-35.
2. Saidin NM, Anuar NK and Affandi MM: JAPS 2018; 8(03): 141-157.
3. Saini S, Baghel S, Chauhan and Agrawal S: Recent development in Penetration Enhancers and Techniques in Transdermal Drug Delivery System. Journal of Advanced Pharmaceutical Education and Research 2014; 4(1): 31-40.
4. Prakash D, Singh AP, Katiyar NS, Pathak K, Pathak D and Arti: Penetration enhancers – The adjuvants in transdermal drug delivery. World Journal of Pharmacy and Pharmaceutical Sciences 2016; 5(5): 353-357.
5. Bavaskar K, Jain A, Patil M and Kalamkar R: The impact of penetration enhancers on transdermal drug delivery system: physical and chemical approach. International Journal of Pharma Research & Review 2015; 4(7): 14-24.
6. Herman A and Herman AP: Essential oils and their constituents as a skin penetration enhancer for transdermal drug delivery: a review Journal of Pharmacy and Pharmacology 2014; 47(4): 473-85.
7. Wang FL, Ji HM, Zhu JY, Xu GJ, Guan YZ and Chen YJ: Penetration enhancement effect of turpentine oil on transdermal film of ketorolac. Tropical Journal of Pharmaceutical Research 2015; 14(8): 1341-48.
8. Mbah CJ and Nandi CO: Transdermal delivery of Gabapentin: Effect of cosolvent and microemulsion on permeation through rat skin. Pharmacology & Pharmacy 2014; 5: 471-78.
9. Erawati T, Soeratri W, Rosita N, Rukmanajati W and Rahma H: The influence of sesame oil addition on the arbutin release and penetration in carbomer gel base. International Journal of Pharma Research and Health Sciences 2014; 2(3): 241-45.
10. Swati L, Satish K and Surfraj S: Transdermal drug delivery system: a tool for novel drug delivery system: an overview. World Journal of Pharmaceutical Research 2014; 3(2): 1892-08.
11. Kesarwani A, Yadav AK, Singh S, Gautam H, Singh HN, Sharma A and Yadav C: Theoretical aspects of transdermal drug delivery system. Bulletin of Pharmaceutical Research 2013; 3(2): 78-89.
12. Pandey S, Badola A, Bhatt GK and Kothiyal P: An overview on transdermal drug delivery system. International Journal of Pharmaceutical and Chemical Sciences 2013; 2(3): 1171-80.
13. Lincy J: Review of transdermal drug delivery system. International Journal of Pharma Research and Health Sciences 2014; 2(4): 261-72.
14. Hafeez A, Jain U, Singh J, Maurya A and Rana L: Advances in transdermal drug delivery system: an overview Journal of Scientific and Innovative Research 2013; 2(3): 695-09.
15. Gaikwad AK: Transdermal drug delivery system: Formulation aspects and evaluation. International Journal of PharmTech Research 2013; 3(4): 2140-48.
16. Saini N and Bajaj A: Review article recent trend on transdermal drug delivery system and advancements in drug delivery through skin. International Journal of Research in Pharmaceutical and Biosciences 2014; 4(1): 5-14.
17. Sharma A, Saini S and Rana AC: Transdermal drug delivery system: a review. International Journal of Research in Pharmaceutical and Biomedical Sciences 2013; 4(1): 286-92.
18. Rana R, Saroha K, Handa U, Kumar A and Nanda S: Transdermal Patches as a tool for permeation of drug through skin. Journal of Chemical and Pharmaceutical Research 2016, 8(5): 471-481.
19. Kitz-Miller JP, Barnett CJ, Steiner NS, Stoicea N, Kamar N, Luzum JA, Mikulik E and Bergese SD: Buprenorphine: revisiting the efficacy of the transdermal delivery system. Ther Deliv 2015; 6(4): 419-422.
20. Sathitkarnmanee T, Tribuddharat S, Noiphitak K, Theerapongpakdee S, Pongjanyakul S, Huntula Y and Thananun M: Transdermal fentanyl patch for postoperative analgesia in total knee arthroplasty: a randomized, double-blind controlled trial. J Pain Res 2014; 7: 449-454.
21. Brown .B and Jones SA: Hyaluronic acid: a unique topical vehicle for localized drug delivery of drugs to the skin. JV 2000; 19: 308-18.
22. Tsai JC, Guy RH, Thornfeldt CR, Gaow N, Feingold KR and Elias PM: Metabolic approaches to enhance transdermal drug delivery. Jour Pharm Sci 1998; 85: 643-48.
23. Berner B and John VA: Pharmacokinetic characterization of Transdermal delivery systems. Jour Clinical Pharmacokinetics 1994; 26(2): 121-34.
24. Baker W and Heller J: Material selection for transdermal delivery systems, in transdermal drug delivery:

Developmental Issues and Research Initiatives, J Hadgraft and R. H. Guys, Eds. Marcel Dekker, Inc., New York 1989: 293-311.
25. Wiechers J: Use of chemical penetration enhancers in Transdermal drug delivery-possibilities and difficulties. Acta Pharm 1992: 4: 123.
26. Yamamoto T, Katakabe K, Akiyoshi K, Kan K and Asano T: Topical application of glibenclamide lowers blood glucose levels in rats. Diabetes Res Clin Pract 1990; 8: 19-22.
27. Al-Khamis K, Davis SS and Hadgraft J: Microviscosity and drug release from topical gel formulations. Pharm Res 1986; 3: 214-217.
28. Anon. Transdermal delivery systems-general drug release standards. Pharmacopeial Forum 1980; 14: 3860-3865.
29. Mayorga P, Puisieux F and Couarraze G. Formulation study of a Transdermal delivery system of primaquine. Int J Pharm 1996; 132: 71-79.

How to cite this article:
Paul AD, Prasanthi C, Sumiya N, Prasad PV and Kumar JV: Permeation enhancers compatible with transdermal drug delivery systems overcoming the skin barrier functions: current and future prospects. Int J Pharm Sci & Res 2019; 10(5): 2143-55. doi: 10.13040/IJPSR. 0975-8232.10(5).2143-55.