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Transdermal Drug Delivery System: An Overview

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ABSTRACT

The drug delivery through the skin to achieve a systemic as well as local effect of a drug is known as Transdermal drug delivery system. Its main advantage includes controlled drug release with minimum side effects, improved bioavailability and many more. The human skin is readily accessible surface for drug delivery. For penetration of drug through the skin the stratum corneum is the main barrier. So to avoid the stratum corneum and to increase the flux through the skin membrane different techniques of penetration enhancement are used. This review mainly represents different factors affecting Transdermal bioavailability, technologies for developing Transdermal drug delivery system, different evaluation tests for Transdermal patches, different methods of preparation of TDDS, recent techniques for enhancing Transdermal drug delivery system.

Keywords: Transdermal drug delivery system [TDDS], Controlled release, Enhancement technique.

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INTRODUCTION

The most common route of drug administration is the oral route. This is because due to its advantage of easy administration as compared to other routes of administration. But it has some demerits like having poor bioavailability due to hepatic metabolism and its tendency to produce rapid blood level spikes (which includes both high and low) which leads to the need for both high or frequent dosing, which is expensive and troublesome. To overcome these hindrances there is need to develop new drug delivery system, which will improve the safety, therapeutic efficacy of the drug by delivering the drug to the specific site. Transdermal drug delivery system is the system in which medications are administered topically in the form of patches which when applied to the skin deliver the drug through the skin at a predetermined and controlled rate. These patches deliver the drug through the skin in predetermined and controlled manner in order to increase the therapeutic efficacy of the drug and reduce the side effects of the drug [1]. For effective TDDS the drug should easily penetrate the skin and easily reach the target site. The first Transdermal system was approved by FDA was Transderm-SCOP in 1979. This was approved by FDA for prevention of nausea and vomiting associated with ravel particularly by sea.[1]

Advantages/Merits of Transdermal Drug Delivery System

- It increases the therapeutic value of many drugs by avoiding the specific problems associated with the drugs like lower absorption, GI irritation, decomposition due to first pass hepatic effect.
- This route is suitable for administration of drugs that have very short half life, poor oral availability and narrow therapeutic window.
- It maintains constant and controlled blood levels for long period of time.
- Self administration is possible by this system.
- The termination of drug input can be done at any point of time by removing the patch.
- This simple method helps in improving the patient compliance and comfort by non invasive, painless and simple method of application.
- Transdermal medications deliver a steady infusion of drug over a long period of time. Adverse drug effects which are frequently associated with intermittent dosing can also be avoided.
- It helps in avoiding the first pass metabolism of drugs.
- Transdermal patches are cost effective.

Disadvantages/Demerits of Transdermal drug delivery system

- Drugs that have large molecular size makes absorption difficulty. So drug molecule should ideally be below 800-1000 daltons.
- The possibility of local irritation may develop at the site of application. Many problems like erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the formulation of patch
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.
- Transdermal drug delivery system cannot achieve high drug levels in blood/plasma.
- Many drugs with a hydrophilic structure having a low peneteration through the skin and slowly to be of therapeutic benefit. Drugs with a lipophillic character, however, are better suited for transdermal delivery. [2,3,4]

Structure of the skin barrier

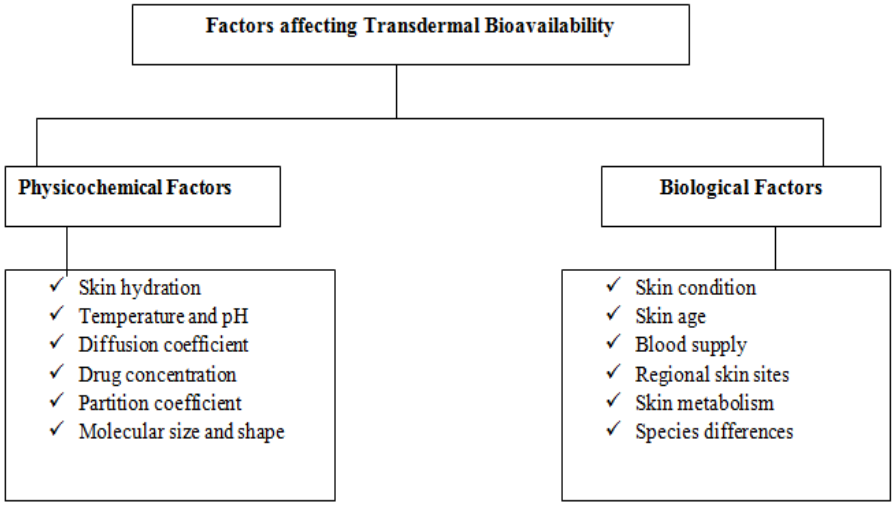
Skin is the largest human organ of our body composed of several layers: the stratum corneum (uppermost layer), the viable epidermis, the dermis and the lower layers of adipose tissue. The stratum corneum consists of flat, roughly hexagonally shaped, partly overlapping cells, with a thickness of 0.3µm and a diameter of 30µm. Just below the stratum corneum is the viable epidermis, which made of three layers: the stratum granulosum, spinosum and basale. It has a thickness of the cells ranging from 50-100µm. Below the viable epidermis dermis is present. Dermis thickness is about 2000-3000µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amorphous ground substance. For the past few decades, the transdermal route has been selected for delivery of certain drugs. However, its use is limited due to low permeability of the skin to many drugs [5-7].

Routes of Penetration

Transdermal drug delivery system is a most suitable system for a long-term treatment or for a multi dose treatment because different transdermal patches are prepared for a long period of time in a suitable dose proving treatment from a day to even up to seven days. To penetrate a molecule in the normal human intact skin there are two diffusion pathways: the appendageal and the transepidermal pathway. The appendageal route is for ions and large polar molecules and the transepidermal route is for the unionized molecules which can cross the intact layer. A molecule should have adequate lipophilicity and optimum molecular weight to penetrate in to the intact skin. Hydrophilic drugs partitioned preferentially via intracellular domains, whereas lipophillic

permeants (octanol/water log K > 2) partitioned the subcutaneous (SC) via intercellular route. Most of the molecules traverse the stratum corneum by both routes. The transport of various drug molecules through the skin, promptly restricted by the barrier properties of epidermis. To avoid these difficulties in permeation through SC, carriers\vesicles can be used as penetration enhancers for circumventing the SC barrier [8-10].

Factors affecting Transdermal Bioavailability



Physicochemical factors

Skin hydration

In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectant is done in transdermal delivery.

Temperature and pH

The permeation of drug increase ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

Diffusion coefficient

Penetration of drug depends on diffusion coefficient of drug. At a constant temperature, the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

Drug concentration

The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

Partition coefficient

The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

Molecular size and shape

Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

Biological factors

Skin condition

Acids and alkalis, many solvents like chloroform, methanol damage the skin cells and promote penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.

Skin age

The young skin is more permeable than older. Childrens are more sensitive for skin absorption of toxins. Thus, skin age is one of the factor affecting penetration of 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 significantly penetration.

Skin metabolism

Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.

Species differences

The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration.[11-12]

Components of TDDS

The main components of a transdermal patch are

Release Liner

Protects the patch during storage. The liner is removed prior to use.

Drug reservoir

The most important part of TDDS is drug reservoir. It consists of drug particles dissolved or dispersed in the matrix. To make the drug soluble, solvents and cosolvents are used. The effect of solvent and cosolvent should be considered while doing selection.

Adhesive

Serves to adhere the components of the patch together along with adhering the patch to the skin. The adhesive must possess sufficient adhesion property so that the TDDS should remain in place for a long time. Pressure sensitive adhesives are commonly used for transdermal patch to hold the skin. Commonly used adhesives are silicone adhesives, poly iso butylenes adhesives and poly acrylate based adhesives.

Membrane

Membrane controls the release of the drug from the reservoir and multi-layer patches. It may or may not contain rate-controlling membrane. It should be flexible enough not to split or crack on bending or stretching. Some of rate-controlling membranes are polyethylene sheets, ethylene vinyl acetate copolymer and cellulose acetate.

Backing

Protects the patch from the outer environment. The backing layer should be impermeable to drug and penetration enhancers. It serves a function of holding the entire system and protects drug reservoir from atmosphere. The commonly used backing materials are polyesters, aluminized polyethylene terepthalate and siliconized polyethylene terepthalate.[13-15]

Types of Transdermal Patch

Single-layer Drug-in-Adhesive

The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

Multi-layer Drug-in-Adhesive

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

Reservoir

Unlike the Single-layer and Multi-layer Drug-in adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

Vapour Patch

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

Microreservoir system

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

Matrix system

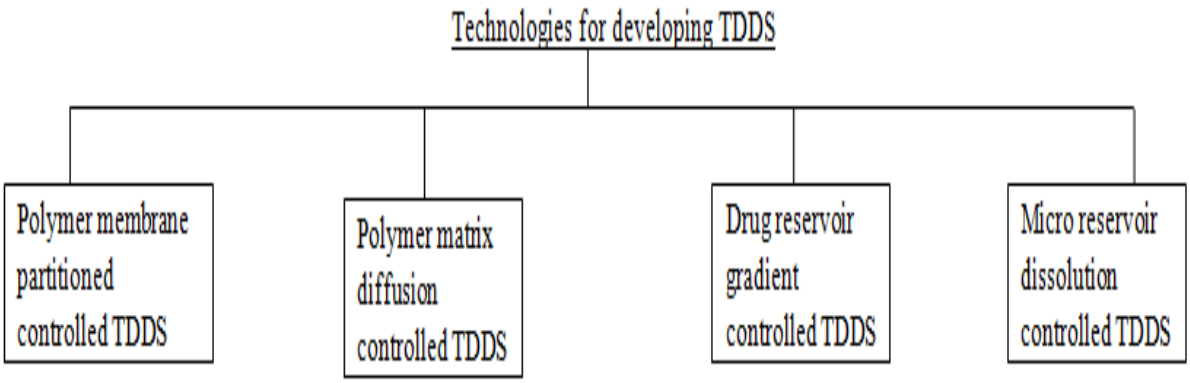
Drug-in-adhesive system

In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting (in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

Matrix-dispersion system

In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. 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. [16]

Technologies for developing Transdermal drug delivery systems



Polymer membrane partition-controlled TDD systems

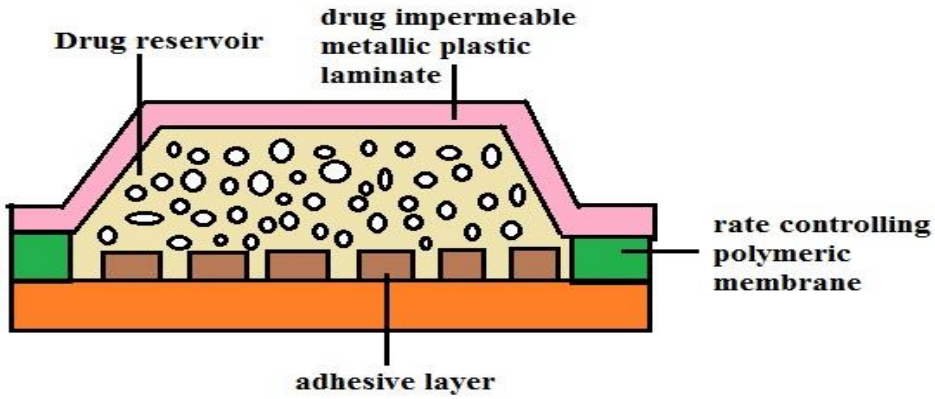


Figure 1: Polymer membrane partitioned controlled TDDS system.

In this type of systems, the drug reservoir is sandwiched between a drug-impermeable backing laminate and a rate controlling polymeric membrane. The drug is allowed to permeate only through the rate controlling membrane. The drug solids are homogeneously dispersed in a solid polymer matrix, suspended in an unleachable, viscous liquid medium e.g. silicone fluid to form a paste like suspension or dissolved in a releasable solvent e.g. alkyl alcohol to form a clear drug solution. The rate controlling membrane can be either a microporous or a nonporous polymeric membrane e.g. ethylene-vinyl acetate copolymer, with specific drug permeability. On the external surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic pressure sensitive adhesive polymer e.g. silicone adhesive may be applied to provide intimate contact of TDDS with the skin surface. Varying the composition of drug reservoir formulation, the permeability coefficient and thickness of rate controlling membrane can alter the drug release rate. e.g. Some FDA approved systems – Transderm- Nitro for angina pectoris, Transderm-Scop for motion sickness, Catapres-TTS system for hypertension. The intrinsic rate of drug release from this type of TDD system is defined by where, CR is drug concentration in reservoir compartment.

Km / r the partition coefficient for the interfacial partitioning of drug from the reservoir to the membrane. Ka / m the partition coefficient for the interfacial partitioning of drug from membrane to adhesive. Da diffusion coefficient in rate controlling membrane. Dm diffusion coefficient in adhesive layer. ha thickness of rate controlling membrane. hm thickness of adhesive layer.

Polymer matrix diffusion-controlled TDDS systems

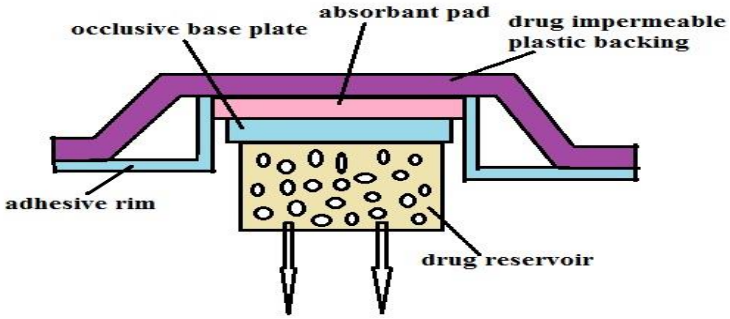


Figure 2: Polymer matrix diffusion controlled TDDS system.

In this system, the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix and then the medicated polymer formed is molded into medicated disks with defined surface area and thickness. This drug reservoir containing polymer disk is then mounted on occlusive baseplate in a compartment fabricated from a drug impermeable plastic backing. Instead of coating adhesive polymer directly on the surface of medicated disk, it is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disk. e.g. Nitro-Dur system and NTS system for angina pectoris. The rate of release from polymer matrix drug dispersion-type is where, Ld is drug loading dose initially dispersed in polymer matrix. CP is solubility of drug in polymer matrix. DP is diffusivity of drug in polymer matrix. Only drug dissolved in polymer matrix can diffuse, CP is practically equal to CR. Alternately, the polymer matrix drug dispersion type TDDS can be fabricated by directly dispersing drug in a pressure-sensitive adhesive polymer e.g. polyacrylate and then coating the drug-dispersed adhesive polymer by solvent casting or hot melt onto a flat sheet of drug-impermeable backing laminate to form a single layer of drug reservoir, this yields a thinner patch.eg. Minitran system, Nitro-Dur II system for angina pectoris.

Drug reservoir gradient-controlled TDD systems

Polymer matrix drug dispersion-type TDDS can be modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multilaminate adhesive layers. The drug release from this type of drug reservoir gradient-

controlledTDDS can be expressed. In this system, the thickness of diffusional path through which drug molecules diffuse increases with time i.e. ha (t). The drug loading level in the multilaminate adhesive layer is designed to increase proportionally i.e. Ld (ha) so as to compensate time dependent increase in diffusional path as a result of drug depletion due to release. Thus, theoretically this should increase a more constant drug release profile. eg. Deponit system containing nitroglycerinefor angina pectoris.

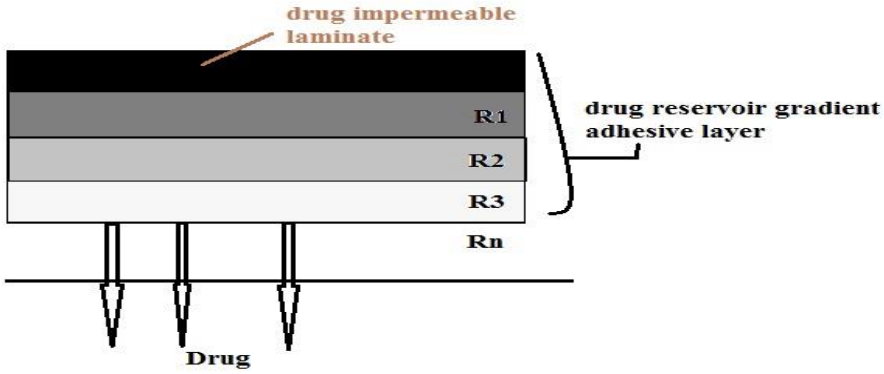


Figure 3: The cross sectional view of drug reservoir gradient controlled TDDS

Microreservoir dissolution-controlled TDD systems

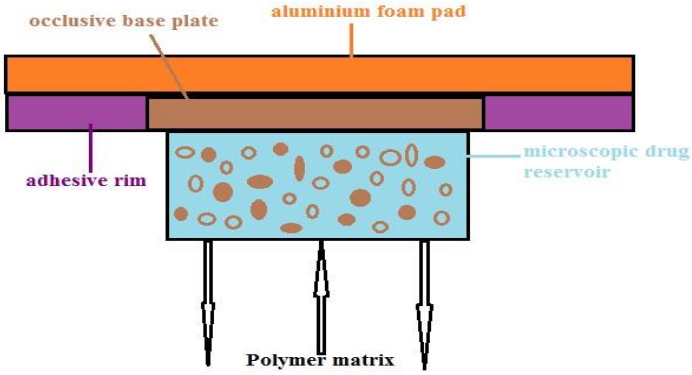


Figure 4: Cross sectional view of micro reservoir dissolution controlled TDDS

A hybrid of reservoir and matrix dispersion-type drug delivery systems, which contains dug reservoir formed by first suspending the drug solids in an aqueous solution of water-miscible drug solubilizer e.g. propylene glycol, then homogeneously dispersing the drug suspension with controlled aqueous solubility in a lipophilic polymer by high shear mechanical force to form thousands of unleachable microscopic drug reservoirs. This thermodynamically unstable system is quickly stabilized by immediately cross-linking the polymer chains in situ, which produces a medicated polymer disk with a constant surface area and a fixed thickness. Medicated disk is mounted at the center of an adhesive pad. eg. Nitrodisk system for angina pectoris. [12, 17, 18]

Method of Preparation of TDDS

Circular Teflon mould method

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

By using IPM membranes method

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

Asymmetric TPX membrane method

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

By using EVAC membranes" method

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

Mercury substrate method

In this method drug is dissolved in polymer solution along with plasticizer. The above solution is

to be stirred for 10-15 minutes to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation.

By using free film method

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the Petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccators until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

Aluminium backed adhesive film method

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custam made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

Preparation of TDDS by using Proliposomes

The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°c temperature and the flask is rotated at 80-90rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders proliposomes) are placed in a desiccator over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization. [19-27]

Evaluation of Transdermal Patches

Thickness of the patch

The thickness of the drug loaded patch can be measured in different points by using a digital

micrometer to determine thickness of the prepared patch.

Weight uniformity

The prepared patches are dried at 60°C for 4 h before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weight.

Folding endurance

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

Percentage moisture content

The prepared films are weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 h after which the films are reweighed and percentage moisture content is determined using below mentioned formula:

$$\% \text{ Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final Weight}} \times 100$$

Percentage moisture uptake

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

$$\% \text{ Moisture Uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial Weight}} \times 100$$

Drug content

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then, the solution is filtered through a filter medium and analyze the drug content with the suitable method such as UV or HPLC technique.

Polariscope examination

This test is performed to examine the drug crystals from transdermal patch by polariscope. A specific surface area of the piece is kept on the object slide and observed for the drug crystals to distinguish whether the drug is present as crystalline form or amorphous form in a patch.

Shear adhesion test

This test is performed to evaluate cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross-linking, type and amount of tackifier added. An

adhesive coated tape is applied onto a stainless steel plate; a specific weight is hung up from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time taken to pull the tape from plate, greater is the shear strength.

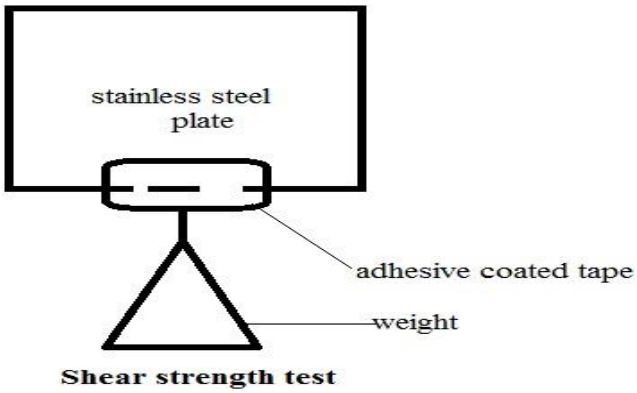


Figure 5: Shear strength test

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 the required to pull the tape is measured

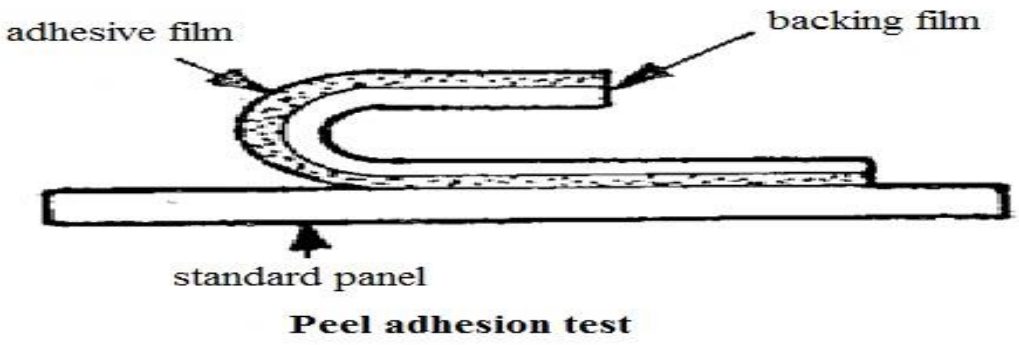


Figure 6: Peel adhesion test

Thumb tack test

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

Probe Tack test

In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the

probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.

Rolling ball tack test

This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

Flatness test

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

Percentage Elongation break test

The percentage elongation break is to be determined by noting the length just before the reak point, the percentage elongation can be determined from the below mentioned formula. Elongation percentage = L1-L2 ×100 L2 .Where, L1is the final length of each strip and L2 is theinitial length of each strip.

$$\% \text{ elongation} = \frac{L1 - L2}{L2} \times 100$$

Peel tack (Quick Stick)

In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required to break the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

Skin irritation study

Skin irritation and sensitizing testing is performed on healthy rabbits (average weight 1.2 to 1.5 kg). Clean the dorsal surface of the rabbit and remove the hair. Again, clean the shaved surface by rectified spirit and the test formulations are applied over the skin. The patch is removed after 24 h and the skin is observed and can be classified into 5 grades on the basis of the severity of skin injury.

***In vitro* release studies**

The Paddle over disc (USP apparatus 5)

This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains dissolution

medium at 32±0.5°C.

Franz diffusion cell

The in vitro diffusion study is carried out with the rat abdominal skin using Franz diffusion cell. The cylinder consists of two chambers, the donor and the receptor compartment. The donor compartment is open at the top and is exposed to atmosphere. The temperature is maintained at 37±0.5°C and receptor compartment is provided with sampling port. The diffusion medium used is phosphate buffer pH 7.4. The diffusion study is done to get an idea of permeation of drug through barrier from the transdermal system. In vitro studies are also done for TDDS development. Usually, two types of diffusion cells are used as horizontal and vertical. The Franz and Keshary Chien (K-C) type of diffusion cells are of horizontal type of cells. In this work, K-C type of diffusion cell was used. Diffusion cell generally comprises two compartments, one containing the active component (donor compartment) and the other containing receptor solution (receptor compartment), separated by barrier i.e. albino rat abdominal skin. The cell consists of sampling port and temperature maintaining jacket. The outlet and inlet is connected with latex tube so the jacket had stagnant water inside and heat was provided by hot plate. The stainless steel pin is used to stir the receptor solution using magnetic stirrer. The mice/rat abdominal skin is placed on receptor compartment and both compartments are held tight by clamps. Phosphate buffer pH 7.4 is used as receptor solution. The volume of diffusion cell can be 15 ml and content is stirred with bent stainless steel pin. The temperature is maintained at 37±2°C with the help of magnetic stirrer. The diffusion is carried out for 24 h and 1 ml sample is withdrawn at predetermined time intervals for 24 h. The same volume of phosphate buffer pH 7.4 is added to receptor compartment to maintain sink conditions and the samples are analyzed to find out amount of drug released from the sample solutions.

The cylinder modified USP basket (USP apparatus 6)

This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32±0.5°C.

The reciprocating disc (USP apparatus 7)

In this method, patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction cell method may be used.

***In vitro* permeation studies**

The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to

the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages. Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as Franz diffusion cell or K-C diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then, the amount of drug permeated per centimeter square at each time interval is calculated. Design of system, patch size, surface area of skin, thickness of skin and temperature etc. are some variables that may affect the release of drug. So permeation study involves preparation of skin, mounting of skin on permeation cell, setting of experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux i.e. drug permeated per cm2 per sec.

Horizontal-type skin permeation system

This has been widely used for the evaluation of drug permeation across skin. The cell is divided in receptor and donor compartments with a low solution volume (3.5 ml) for each compartment and a small membrane area (0.64 cm2). They are continuously stirred by matched set of star-head magnets, which are rotated at a speed of 600 rpm. The system is controlled by thermostated water through a water jacket surrounding the two compartments.

Flow-through diffusion cell

Flow through diffusion cells have the advantage that they can be used when the drug has lower solubility in the receptor compartment. This cell can be fully automated and connected directly to HPLC. They have large capacity donor chamber to allow appropriate loading of the compound and a low volume (0.3 ml) receiving chamber that ensures rapid removal of penetrant at relatively low pumping rates.

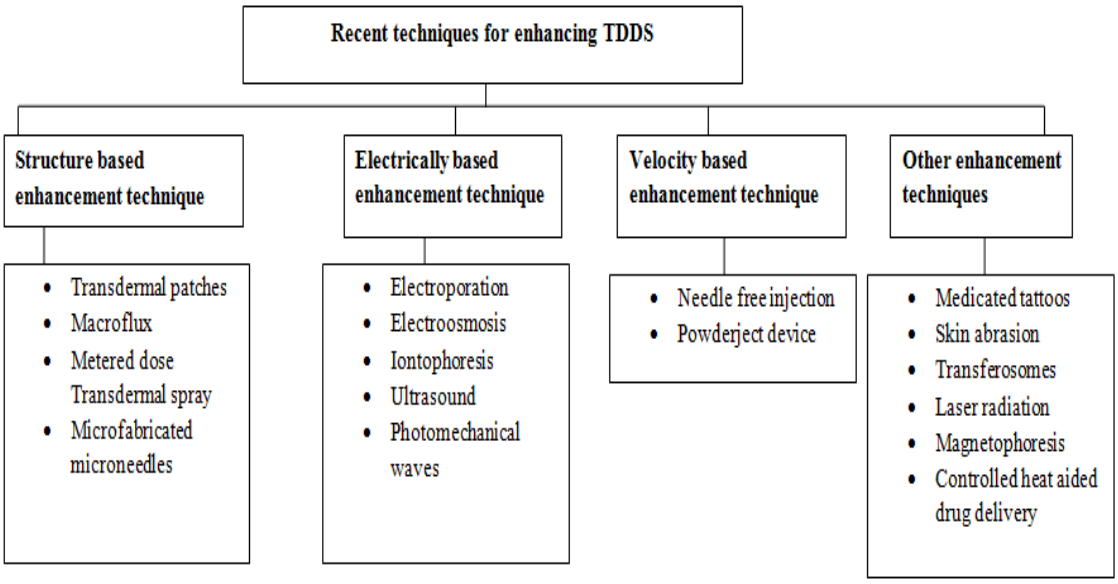
Stability studies

Stability studies are conducted according to the ICH guidelines at 40°C and 75% RH for 6 months. The samples are analyzed for the drug content. [17, 28-32]

Table 1: Examples of Marketed TDDS [17]

SR.NO	TDDS	Therapeutic agent	Design
1	Duragesic (Janssen)	Fentanyl	Four-layer patch
2	Testoderm (Alza)	Testosterone	Three-layer patch
3	Estraderm (Novartis)	Estradiol	Four-layer patch
4	Climara (Novartis)	Estradiol	Three-layer system
5	Vivelle (Novartis)	Estradiol	Three-layer system
6	Catapres-TTS (Boehringer Ingelheim)	Clonidine	Four-layer patch
7	Nicotrol (McNell Consumer)	Nicotine	Multilayer rectangular patch
8	Nicoderm CQ (Smithkline BeechamConsumer)	Nicotine	Multilayer rectangular patch
9	Prosstep (Lederie)	Nicotine	Multilayer round patch
10	Habitrol (Novartis Consumer)	Nicotine	Multilayer round patch

Recent Techniques for Enhancing Tdds



Recent Techniques for Enhancing TDDS

Structure-based enhancement techniques

Transdermal Patches

A transdermal patch or skin adhesive patch is that device which is loaded with drug candidate and usually applied on the skin to transport a specific dose of medication across the skin and into the blood circulation. The adhesive serves two functions: It is glue in nature that keeps the patch adhered to the skin, and it acts as the suspension that holds the drug. The problems associated with this is the concentration of the drug within the adhesive directly affects the "stickyness" of the adhesive so if the large quantities of drug is to be administered, either the size of the patch have to be increased or the patch needs to be reapplied again and again. Several pharmaceuticals usually

combined with substances, like alcohol, within the patch to improve their penetration via skin in order to improve absorption.

Components of Transdermal Patch

-Release liner

-Drug reservoir

-Adhesive

-Membrane

-Backing

Requirements for pressure-sensitive adhesives (PSAs)

Several classes of PSAs are used for skin contact application include acrylics, polyisobutylene and silicone polymers. The functional properties of PSAs such as tackyness, adhesive property, release force, and cohesive strength as well as adhesive formulations having attributes such as enhanced drug flux and skin friendliness. A PSA must be able to performance effectively under a wide range of temperatures, humidity levels, and application frequency (from 24 hrs for some products to one week for others). The effects of mechanical stresses (e.g., stretching) as well as skin irritation and sensitization also must be considered. The human studies of various commercially available transdermals are examined and reported to assess the relative performance capabilities of each type of transdermal design. Monolithic TTS was fabricated in PSAs- (a) terpolymer (PSA1) of 2-ethylhexyl acrylate, methyl methacrylate, and acrylic acid, (b) copolymer (PSA2) of 2-ethylhexyl acrylate, methyl methacrylate, acrylic acid, and vinyl acetate, and (c) Eudragit E100 pressure sensitive adhesive (PSA3). The transport of nicorandil via skin can be achieved by the skin permeation enhancer i.e. *N*-methyl-2-pyrrolidone (NMP) was investigated at different concentrations (5%) in PSAs.

Macroflux

These are devices having an area of around 8cm as well as 300 micro projections per cm2 with the length of individual micro projection less than 200Î¼m. Three types of macroflux have been designed. They include, Dry-Coated Macrofluxsystem-this is used for short period delivery that consists microprojection array coated with medicament that adhered to a elastic polymer adhesive backing.

Metered-Dose Transdermal Spray (Mdts)

It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come non volatile in nature, which consists the completely dissolved

medicament in solution . The use of MDTS reaches the sustained level and better permeation of the drug via skin. The MDTS has the following potential advantages:

- It improves delivery potential without skin irritation due to its non-occlusive nature.
- Increased acceptability.
- Dose flexibility
- Simple manufacture

Microfabricated Microneedles

These are the devices which are having the features of both the hypodermic needle and transdermal patch that can deliver the drug that transports the drug effectively across the memberane. The systems consists of a drug reservoir and a some projections (microneedles) extending from the reservoir, these helps in penetrating the stratum cornea and epidermis to deliver the drug.

Poke with patch approach

Involves piercing into the skin followed by application of the drug patch at the site of treatment.

Coat and poke approach

Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.

Biodegradable microneedles

Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.

Hollow microneedles

Involves injecting the drug through the needle with a hollow bore.

Electrically based enhancement Technique

Electroporation

It this method, short and high-voltage electrical pulses are applied to the skin thus the diffusion of drug is improved with the increasing permeability. The electrical pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea.

Electro-Osmosis

To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

Iontophoresis

It involves passing of current (few milliamperes) to skin limited to a certain area using the electrode remains in contact with the formulation which is to be administered. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anesthesia.

Ultrasound

In this technique, there is a mixing of drug substance with a coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier.

Photomechanical Waves

Photomechanical waves significantly led to the stratum cornea highly permeable to drug substance through a possible permeabilisation mechanism due to development of transient channels.

Velocity based enhancement technique

Needle-Free Injections

- Intraject
- Implaject
- Jet Syringe
- Iject
- Mini-ject

Powderject Device

The solid drug particles are propelled across the skin with the aid of high-speed gas flow. This consists of a gas canister that allows helium gas at high pressure to enter a chamber at the end of which drug cassette containing powdered drug between two polycarbonate membranes. After release, the instantaneous rupturation of both membranes usually seen that results in the gas to expand quickly which forms a strong motion like a wave that travels down the nozzle. This takes place at the speed of 600-900 m/s.

Other Enhancement Techniques

Medicated Tattoos

Med-Tats is a modification of temporary tattoo which contains an active drug substance for trandermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms.

Skin Abrasion

This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substance. In general, one approach is adopted to creates micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules is generally known as Microscissuining.

Transfersomes

This device penetrates the skin barrier along the skin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles.

Laser Radiation

This involves the exposure of the skin to the laser beam that results in the ablation of the stratum cornea without damaging the epidermis which remains in contact with it. Removal of the stratum cornea by this technique is considered to improve the delivery of lipophilic and hydrophilic drugs.

Magnetophoresis

The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength.

Controlled Heat Aided Drug Delivery (CHADD) System

It facilitates the transfer of drug substance to the blood circulation by applying heat to the skin that increases the temperature and ultimately led to increase in microcirculation and permeability in blood vessel. CHADD system consists of small unit that is used for heating purpose, placed on top of a conventional patch device. An oxidation reaction occurs within the unit which tends to form heat of limited intensity and duration. [19, 27, 33-42]

Table 2: Ideal Properties of TDDS: [43-44]

Sr.no	Properties	Comments
1	Shelf life	Up to 2 years
2	Particle size	Less than 40 cm^2
3	Dosing Frequency	Once in a day or once in a week
4	Aesthetic appeal	Clear or white colour
5	Packaging	Easy removal of release liner and minimum number of steps required to apply
6	Skin reaction	Non irritating and non sensitizing
7	Release	Consistent pharmacokinetic and Pharmacodynamic profile over time

General clinical considerations in the use of TDDS

The patient should be advised of the following general guidelines. The patient should be advised of

the importance of using the recommended site and rotating locations within the site. Rotating location is important to allow the skin to regain its normal permeability and to prevent skin irritation. TDDS should be applied to clean, dry skin relatively free of hair and not oily, inflamed, irritated, broken. Wet or moist skin can accelerate drug permeation time. Oily skin can impair the adhesion of patch. If hair is present at the site, it should be carefully cut, not wet shaved nor should a depilatory agent be used, since later can remove stratum corneum and affect the rate and extent of drug permeation. Use of skin lotion should be avoided at the application site, because lotions affect the hydration of skin and can alter partition coefficient of drug. Patient should not physically alter TDDS, since this destroys integrity of the system. The protecting backing should be removed with care not to touch fingertips. The TDDS should be pressed firmly against skin site with the heel of hand for about 10 seconds. A TDDS should be placed at a site that will not subject it to being rubbed off by clothing or movement. TDDS should be left on when showering, bathing or swimming. A TDDS should be worn for full period as stated in the product's instructions followed by removal and replacement with fresh system. The patient or caregiver should clean the hands after applying a TDDS. Patient should not rub eye or touch the mouth during handling of the system. If the patient exhibits sensitivity or intolerance to a TDDS or if undue skin irritation results, the patient should seek reevaluation. Upon removal, a used TDDS should be folded in its half with the adhesive layer together so that it cannot be reused. The used patch discarded in a manner safe to children and pets. [13, 45]

Future of transdermal therapy

Ten years ago, the nicotine patch had revolutionized smoking cessation; patients were being treated with nitroglycerin for angina, clonidine for hypertension, scopolamine for motion sickness and estradiol for estrogen deficiency, all through patches. At that time, biotech medicinal was still being developed. During the past decade, the number of drugs formulated in the patches has hardly increased, and there has been little change in the composition of the patch systems. Modifications are limited to the refinements of the materials to be used. The reason is the only a limited number of drugs fit the molecular weight, and potency requirements for transdermal absorption. Various patches are available from more than ten years, and they have a proven history. [7]

CONCLUSION

Transdermal drug delivery system is useful for topical and local actions of drugs. With the help of various enhancement technique the permeability of low permeable drugs can be increased. To optimize this drug delivery system greater understanding of different mechanisms of biological

interactions and the polymer are required. Transdermal drug delivey system have greater potentials they can be used for both hydrophilic and hydrophobic substances into promising deliverable drugs. Due to large advantage of TDDS and various permeation enhancers which would significantly increase the number of drugs suitable for TDDS. A lot of researchers are taking interests in TDDS. Transdermal drug delivery system would be a realistic practical application as the next generation of drug delivery system.

REFERENCES

1. Jain, N. K: Controlled and Novel Drug Delivery, CBS Publishers, and Distributors, 2002, 107.
2. Sharma N, Parashar B, Sharma S, Mahajan U:Blooming Pharma Industry with Transdermal Drug Delivery System. Indo Global J Pharm. Sci. 2012; 2(3): 262-278.
3. Keleb E, Sharma RK, Mosa EB, Aljahwi AZ: Transdermal Drug Delivery System- Design and Evaluation. Int. J. Adv. Pharm. Sci. 2010; 1:201-211.
4. Arunachalam A, Karthikeyan M, Kumar VD, Prathap M, Sethuraman S, Ashutoshkumar S,
5. Manidipa S: Transdermal Drug Delivery System: A Review. Current Pharma Res. 2010; 1(1):70-81.
6. IB Pathan, CM Setty: Trop J Pharma Res, 2009, 8(2), 173-179.
7. N Kanikkannan, K Kandimalla, SS Lamba, M Singh: Current Med Chem., 1999, 6, 593-608.
8. S Dey, B Mahanti, B Mazumder, A Malgope, SD Gupta: Der Pharmacis Sinica, 2011, 2(3), 94-106.
9. BC Nandy, SK Chourasia, S Roy, B Mazumdar, KC Meena, D Aujha, M Makhija, K Pathak. Der Pharmacia Sinica, 2011, 2(4), 203-217.
10. AC Williams, BW Barry: Drug Carrier Systems, 1992, 9, 305-353.
11. M Fartasch, ID Bassukas. TL Dipegen, Br J Dermatol, 1993, 128, 1-9.
12. Ortho Evra, simple, convenient way to get the medicine you need, [Internate] URL:http/www.orthoevra.com.
13. Zhou Y, Wu XY: Fine element analysis of diffusional drug release from complex matrix system, J control Rel 1997; 49: 277 – 288.
14. Chad RW: Development and Selection of Components for Transdermal Drug Delivery Systems, [Internate]. http://www.pharmainfo.net/jasmine-jose/transdermal-patches-innovative-technology
15. Hopp SM: Developing Custom Adhesive Systems for Transdermal Drug Delivery Products. Pharmaceutical Technology 2002, 30-36.

16. William A.C and Barry B.W,“ penetration enhancers ”,Advance Drug delivery Rev.2004;56:603-618.
17. Vyas SP, Khar RK: Controlled Drug Delivery: Concepts and Advances, first edition, Vallabh Prakashan, 2002, pp 411- 447.
18. Chein YW: Transdermal Drug Delivery, In : Swarbick J. editor, Novel Drug Delivery Systems, second edition, New York: Marcel Dekker, 2005, 50, pp 301 – 380.
19. Wiechers J: Use of chemical penetration enhancers in Transdermal drug delivery-possibilities and difficulties. Acta pharm. 1992: 4: 123.
20. Anon: Transdermal delivery systems-general drug release standards. Pharmacopeial Forum, 1980; 14: 3860-3865.
21. 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 pp. 293-311
22. Mayorga P, Puisieux F and Couarraze G: Formulation study of a Transdermal delivery system of primaquine. Int. J. pharm. 1996; 132: 71-79.
23. Yamamoto T, Katakabe k, Akiyoshi K, Kan K and Asano T: Topical application of glibenclamide lowers blood glucose levels in rats. Diabetesres. Clin. Pract. 1990; 8: 19-22.
24. Al- Khamis K, Davis S.S and Hadgraft J: Microviscosity and drug release from topical gel formulations. Pharm. Res. 1986; 3: 214-217.
25. Crawford R.R and Esmerian O.K: Effect of plasticizers on some physical properties of cellulose acetate phthalate films. J. Pharm. Sci. 1997; 60: 312- 314.
26. Deo M.R, Sant V.P,Parekh S.R, Khopade A.J and Banakar U.V: Proliposome-based Transdermal delivery of levonorgestrel. Jour. Biomat. Appl. 1997; 12: 77-88.
27. Yan-yu X, Yun- mei S, Zhi-Peng C and Qi-nerg P: Preparation of silymarin proliposomes; A new way to increase oral bioavailability of silymarin in beagle dogs. Int. pharm. 2006; 319: 162-168.
28. Shaila L, Pandey S and Udupa N: Design and evaluation of matrix type membrane controlled Transdermal drug delivery system of nicotin suitable for use in smoking cessation. Indian Journ. Pharm. Sci. 2006;68: 179-18.
29. Aarti N, Louk A.R.M.P, Russsel.O.P and Richard H.G: Mechanism of oleic acid induced skin permeation enhancement in vivo in humans. Jour. control. Release 1995; 37: 299-306.
30. Wade A and Weller P.J: Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical Publishing Association 1994; 362-366.
31. Lec S.T, Yac S.H, Kim S.W and Berner B: One way membrane for Transdermal drug delivery systems / system optimization. Int. J Pharm. 1991; 77: 231 - 237.

32. Singh J, Tripathi K.T and SakiaT.R: Effect of penetration enhancers on the invitro transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. Drug Dev.Ind. Pharm. 1993; 19: 1623-1628.
33. Loyd V. Allen Jr, Nicholas G. Popovich, Howard C: Ansel. Pharmaceutical dosage forms and drug delivery systems, 8th Edition., Wolter Kluwer Publishers,New Delhi, 2005 pp. 298-299.
34. Helier J, Trescony PV: Controlled drug release by polymer dissolution II, Enzyme mediated delivery device. J. Pharm. Sci. 1979, 68: 919.
35. http://www.pharmainfo.net/reviews/transdermal-drug-delivery-technology-revisited-recent-advances
36. Grossberg GT, Sadowsky C, Olin JT: Rivastigmine Transdermal System for the Treatment of Mild to Moderate Alzheimer's Disease. Int J ClinPract. 2010, 64(5): 651-660.
37. Venkatraman S, Gale R. Skin adhesives and skin adhesion: Transdermal drug delivery systems. Biomaterials 1998, 19(13): 1119-36
38. Tipre ND &Vavia RP: Formulation Optimization and Stability Study of Transdermal Therapeutic System of Nicorandil. Informa Healthcare 2002, 7(3):325-332.
39. Calhoun A Darlene et al: Recent Advances in Neonatal Pharmacotherapy: Transdermal Therapy in Neonates. Ann. Pharmacother. 2006, 40 (4): 710-719.
40. http://www.theiaforum.org/april2004.htm
41. Sugar IP, Neumann E: Stochastic model for electric field-induced membrane pores. Electroporation. Biophys. Chem.1984, 19(3): 211. 25.
42. http://berkeley.edu/news/media/releases/2007/02/12_IRE.shtml
43. Izumoto T, Aioi A, Uenoyana S, Kariyama K, Azuma M: Relationship between the transference of drug from a transdermal patch and physicochemical properties, Chem Pharm Bull (Tokyo)1992,40,456-458.
44. Gordon RA, Peterson TA: Four myths about transdermal drug delivery, Drug Delivery Technology 2003, 3, 1-7. [TDDS web page.]
45. Barry B: Transdermal Drug Delivery, In: Aulton M. E., editor, Pharmaceutics: The Science of Dosage Form Design, Churchill Livingstone Ltd., 2002, pp 499 – 533.