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Review Article

Transdermal drug delivery - A review

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ABSTRACT

Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. Transdermal drugs are self-contained, discrete dosage form. It delivers a drug through intact skin at a controlled rate into the systemic circulation. Delivery rate is controlled by the skin or membrane in the delivery system Transdermal drug delivery - an approach used to deliver drugs through the skin for therapeutic use as an alternative to oral, intravascular, subcutaneous and transmucosal routes. Various transdermal drug delivery technologies are described including the use of suitable formulations, carriers and penetration enhancers. The most commonly used transdermal system is the skin patch using various types of technologies. Several transdermal products and applications include hormone replacement therapy, management of pain, angina pectoris, smoking cessation and neurological disorders such as Parkinson's disease. Formulated to deliver the drug at optimized rate into the systemic circulation should adhere to the skin for the expected duration should not cause any skin irritation and/or sensitization, Enhancing bioavailability via bypassing first pass metabolism, Minimizing pharmaco-kinetic peaks and troughs.

Keywords: Transdermal drug delivery; transcutaneous permeation; percutaneous permeation; microporation; electroporation; iontophoresis; sonophoresis; microneedles

INTRODUCTION

Transdermal drug delivery is defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems (Jain N K, 2002). The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979. These patches administered scopolamine for motion sickness**.** Table 1 present advantages and disadvantages of transdermal drug delivery system.

Significance of problem

Drugs curing a diseased condition in one part of body can also have an adverse effect on some other part of the body. For instance, most of the drugs available in the market have some or the other side effect associated with using them. The side effects encountered are mainly with the liver, heart, lung, kidney, etc. Some of the oral medications have an adverse effect on the system; some make the patient feel drowsy, nauseated, and dizzy. The solution to gastrointestinal to get over all the side effects might not be available, but there are surely ways and means to reduce them. One way is use of transdermal drug delivery patches that target only the area that needs to be treated. Transdermal Drug Delivery systems are sometimes preferred over other methods of drug administration because they present lower risk to liver or gastrointestinal track over oral or any other form of drug administration, for instance in the case of estradiol patches, patient's are at lower risk of damaging liver compared to those who take estradiol tablets orally (Langer Robert, 2004). "The pharmacokinetics of a compound significantly affects its efficacy and safety. Transdermal delivery has the potential to yield more stable drug plasma levels and to bypass major organs involved in first-pass metabolism (Nitti, 2006).

Limitations for a drug substance to be incorporated into a transdermal delivery system are

1. Heavy drugs molecules (>500 Da) usually difficult to penetrate the stratum cornea.
2. Drugs with very low or high partition coefficient fail to reach blood circulation (Chandra- shekar NS, 2008).
3. Drugs that are highly melting can be given by this route due to their low solubility both in water and fat (Miller KJ, 2009).

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Table 1: Advantages and disadvantages of TDDS

Advantages	Disadvantages
• Self administration is possible and Continuous, sustained release of drug. • Avoids peak and trough drug levels and Longer, multiday dosing interval. • Avoids first-pass hepatic metabolism and enzymatic degradation by gastrointestinal tract (Brown L, 1988) • Less frequent dosing improves patient Compliance (Stevenson JC, 1999) • Alternate route for patients who are unable to take oral medications. • Dose delivery unaffected by vomiting or Diarrhea (Barry BW, 1983)	• Only small, lipophilic drugs can be delivered currently through the skin. • Drug molecule must be potent because patch size limits its amount that can be delivered (Potts RO, 2007) • Not suitable for high drug doses (Merkle HP, 1989) • Adhesion may vary with patch type and environmental conditions(Samisoe G, 2004) • Skin irritation and hypersensitivity reactions may occur. • The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

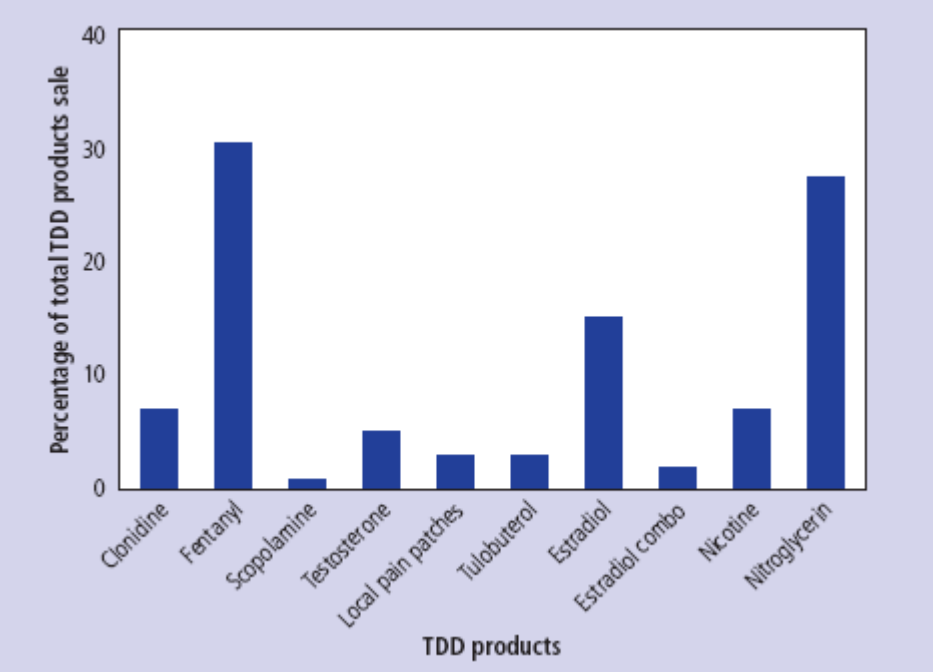

Figure 1: Graph of Transdermal Drug Delivery Products Vs. Percentage Total Sold Transdermal Drug Delivery Products

Transdermal drug delivery system market

Table 2 gives a list of companies in transdermal drug delivery systems with their current products and technologies in the market. 3M Pharmaceuticals is a leader in pioneering the technological components in transdermal drug delivery system and components made by 3M are used for manufacturing the complete spectrum of drugs delivered transdermally (Singh Somnath, 2005) Figure 1 shows a graph showing the range of transdermal drug delivery system currently sold in the market (Singh Somnath, 2005) On the X-axis are the drugs that are administered transdermally, while the Y-axis in the graph shows percentage of the total transdermal products that are being sold in the market.

Skin and drug permeation

For understanding the concept of TDDS, it is important to review the structural and biochemical features of human skin and those characteristics which contribute to the barrier function and the rate of drug access intothe body via skin **(**Jacob SW**,** 1970**)**.

Table 2: Commercial available transdermal therapeutic systems

Drug/Manufacturer	Type
Scopolamine (Alza/Ciba)	Reservoir
Nitroglycerin (Alza/Ciba)	Reservoir
Searle	Matrix
Isosrbide dinitrate (Nitro electric industrial)	Matrix
Estradiol (Ciba-Giegy)	Reservoir
Nicotine (ALZA)	Reservoir
Ciba-Giegy	Matrix
Park-Davis	Matrix

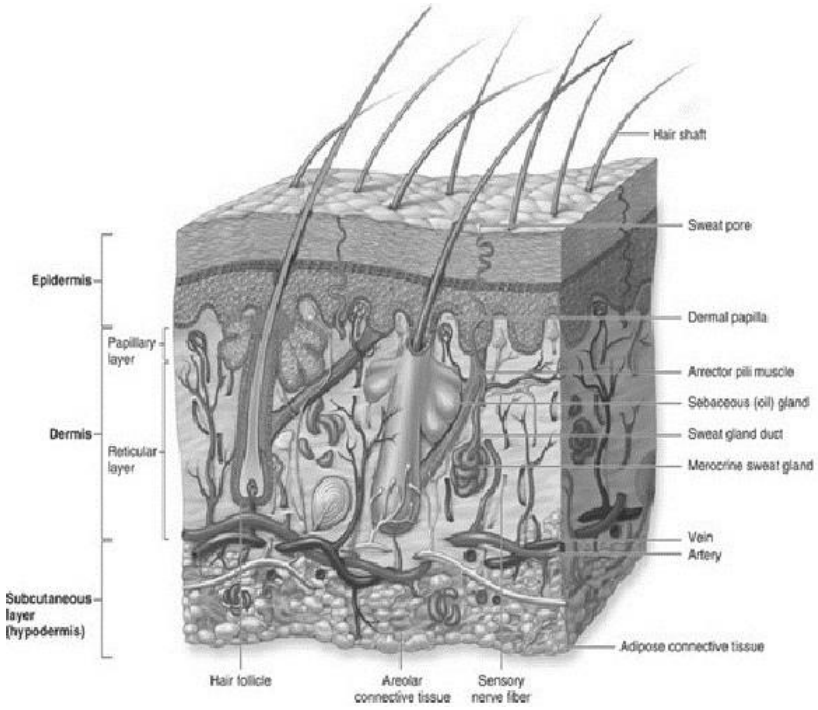

Figure 2: Schematic diagram of different layers of skin

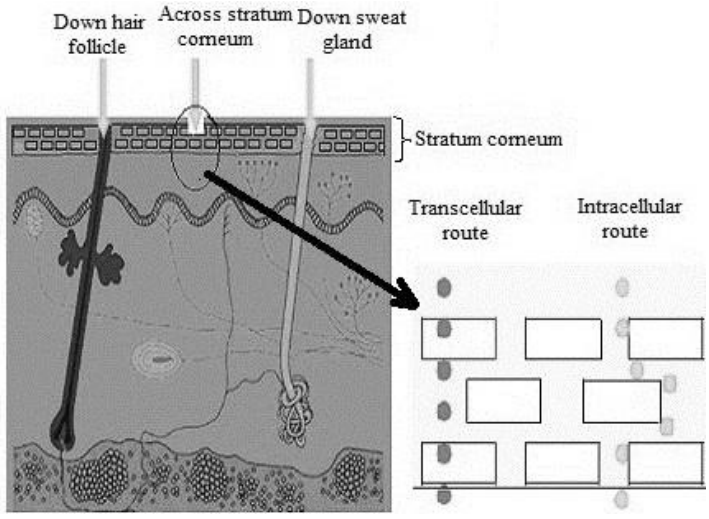

Figure 3: Drug penetration pathways across skin

Anatomically, the skin can be divided in to two layers: epidermis and dermis or corium (Figure 2). Some of the differences between epidermis and dermis layers of skin. The skin is one of the most extensive organs of the human body covering an area of about $2m^2$ in an average human adult. This multilayered organ receives approximately one third of all blood circulating through the body (Guy RH, 1987). Epidermis results from an active epithelial basal cell population and is approximately 150 micrometers thick. It is the outermost layer of the skin and the process of differentiation results in migration of cells from the basal layer towards the skin surface (Flynn GL, 1985). Below this layer are the other layers of the epidermis - the stratum lucidum, stratum granulosum, stratum spinosum and stratum germinativum. Together, these other layers constitute the viable epidermis (Jacob SW, 1970). Dermis is foundation of firm connective tissue upon which epidermis is laid and is of mesoderm origin. The dermis or corium consists of a dense felt work of connective tissue in which bundles of collagenous fibres predominate, mingled with a certain proportion of elastic tissue insuperficial levels. Dermis contains fine plexuses of blood vessels, lymphatics and nerves, hair follicles, sweat glands and sebaceous glands (Gros L, 1980).

Drug penetration pathways

There are critically three ways in which a drug molecule can cross the intact stratum corneum: via skin appendages (shunt routes); through the intercellular lipiddomains; or by a transcellular route (Figure 3). A particular drug is likely to permeate by a combination of these routes, with the relative contributions of these

pathways to the gross flux governed by the physico-chemical properties of the molecule (Hadgraft, 1989).

a) The appendgeal route

Skin appendages provide a continuous channel directly across the stratum corneum barrier. However, their influence on drug penetration is hindered by a number of factors. The surface area occupied by hair follicles and sweat ducts are small (typically 0.1% of skins surface area) therefore limiting the area available for direct contact of the applied drug formulation.

b) Transcellular route

Drugs entering the skin via the transcellular route pass through corneocytes. Corneocytes, containing highly hydrate keratin, provide an aqueous environment for which hydrophilic drugs can pass. The diffusion pathway for a drug via the transcellular route requires a number of partitioning and diffusion steps .

c) Intercellular route

The intercellular pathway involves drug diffusing through the continuous lipid matrix. This route is a significant obstacle for two reasons. (i) Recalling the 'bricks and mortar' model of the stratum corneum, the interdigitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which is in contrast to the relatively direct path of the transcellular route. (ii) The intercellular domain is a region of alternating structured bilayers. Consequently, a drug must sequentially partition into, and diffuse through repeated aqueous and lipid domains. This route is generally accepted as the most common path for small uncharged molecules penetrating the skin.

BASIC COMPONENTS OF TDDS

a) Drug

For successfully developing a TDDS, the drug should be chosen with great care. Some of the desirable properties of a drug and factors to be considered for transdermal delivery are shown in Table 3 & 4. These are some examples of drugs which are suitable for TDDS like Nicardipine hydrochloride, Captopril, Atenolol and metoprolol tartrate, Clonidine, Indapamide, Propranolol hydrochloride, Carvedilol, Verapamil hydrochloride and Nitrendipine (Kumar TS, 2010).

b) Release liner

During storage the patch is covered by a protective liner that is removed and discarded before the application of the patch to the skin. Since the liner is in intimate contact with the TDDS, the liner should be chemically inert (Miller KJ, 2009).

c) Backing

Backings are chosen for appearance, flexibility and need for occlusion. Examples of backings are polyester-film, polyethylene film and polyolefin film. Other considerations are the backing additives leaching out and diffusion of excipients, drug or enhancer through the backing (Miller KJ, 2009).

Table 3: Ideal properties of drug for TDDS

Parameters	Properties
Dose	Should be low (less than 20 mg/day)
Half-life	10/less (hrs)
Molecular weight	< 400 Da
Skin permeability coefficient	> 0.5×10-3 cm/h
Skin reaction	Non airritating and non-sensitizing
Oral bioavailability	Low

Table 4: Factors to be considered for transdermal dose calculation

Physicochemical	Pharmacokinetic	Biological
Solubility	Half-life	Skin toxicity
Crystallinity	Volume of distribution	Site of application
Molecular weight	Total body clearance	Allergic reaction
Polarity	Therapeutic plasma concentration	Skin metabolism
Melting point	Bioavailable factor	--

d) Overlay

A TDDS may include a drug-free adhesive coated film, foam or nonwoven component designed to be placed over a transdermal patch that has been applied onto the skin. This overlay secures the medicated patch to the skin of the patient (Lee M, 2002)

e) Membrane

A membrane may be sealed to the backing to form a pocket to enclose the drug-containing matrix or used as a single layer in the patch construction. The diffusion properties of the membrane are used to control availability of the drug and/or excipients to the skin. The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in a transdermal system:

(i) Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.

(ii) The polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product; and inexpensive.

(iii) The polymer and its degradation products must be non- toxic or non-antagonistic to the host (Sugibayashi K, 1994).

f) Enhancer and excipients

One long-standing approach for improving transdermal drug delivery uses penetration enhancers (also called sorption promoters or accelerants) which penetrate into skin to reversibly decrease the barrier resistance. (Ko CU, 1996) An enhancer may modulate the skin permeability in some fashion (Qvist MH, 2002) Some of the more desirable properties for penetration enhancers acting within skin have been given as (Barry BW, 1991).

- They should be non-toxic, non-irritating and non allergenic.
- They would ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body, i.e. should not bind to receptor sites.
- When removed from the skin, barrier properties should return both rapidly and fully.
- They should be cosmetically acceptable with an appropriate skin 'feel'

Some of the most widely studied permeation enhancers are Sulphoxide (DMSO), Fatty Acids (Oleic acid), Alcohol (Methanol), Glycol (Williams AC, 2009)

TDDS classification based on their technical sophistication

a) Rate pre-programmed drug delivery system

b) Activation modulated drug delivery system

c) Feedback regulated drug delivery system

d) Carrier based drug delivery system

A) Rate Pre Programmed Drug Delivery System

It involves the system design that deliver medicaments by controlling molecular diffusion of drug molecules across the skin barrier within or surrounding the delivery system **(**Kumar TS, 2010**)**.

(1) Polymer membrane permeation controlled drug delivery system

It involves the system in which the drug is enclosed within a drug reservoir. This is covered by the semi-permeable membrane of polymer that regulates the release and having a specific permeability. There are some potential development with process of membrane permeation are as microporous membrane permeation controlled gastrointestinal delivery device, gastric fluid resistance intestinal targeted controlled release gastrointestinal device and gel diffusion controlled drug delivery system (Weiner E, 1976)

(2) Polymer matrix diffusion controlled drug delivery system

It is developed by dispersing drug particles in carrier matrix (in a homogenous manner) that is rate controlling. For e.g. NitroDur – It is designed for application onto intact skin for 24 hrs that provide consistence transdermal infusion of nitroglycerine (Keith AD, 1983)

(3) Microreservoir partitioned controlled drug delivery system

It involves dispersion of micro particles of suspension of drug (aqueous in nature) in a polymer using high energy dispersion. e.g. Syncromate implant – Engineered to deliver subdermal administration of norgestomet (Karim A 1983)

B) Activation Modulated Drug Delivery System

This type of delivery system can be achieved by-

1-Physical means

i. Hydrodynamic pressure controlled drug delivery system.

ii. Vapour pressure activated drug delivery system.

iii. Hydration activated drug delivery system**.**

2-Chemical means

3-Biochemical means

C) Feedback Regulated Drug Delivery System

The release of the drug molecules from the transdermal system is facilitated by a agent that triggers the release of drug, such as biochemicals in the body and also regulated by its concentration through some feedback mechanism (Helier J, 1979).

i. Bio-erosion regulated drug delivery system.

ii. Bio-responsive drug delivery system.

D) Carrier Based Drug Delivery System

Colloidal particulates carrier system

This involves vesicular system like hydrogels, liposomes, niosomes, nanocapsules, nanoparticles, polymeric complexes, microspheres, nanoerythrosomes, transferosomes, dendrimers, aquasomes, etc.

Types of Transdermal drug delivery systems

Broadly speaking, most commercially available TDDS can be categorized as reservoir systems, matrix systems without a rate-controlling membrane or matrix systems with a rate-controlling membrane and microreservoir system (Tyle P, 2003)

(1) Reservoir systems

In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate-controlling membrane, which can be microporous or nonporous. In the drug reservoir compartment, the

drug can be in the form of a solution, suspension, or gel or dispersed in a solid polymer matrix. On the outer surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic adhesive polymer can be applied.

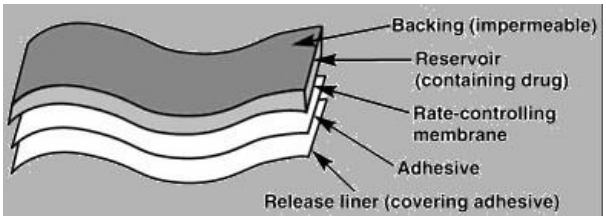

Figure 4: Reservoir systems

II) Matrix systems

i) Drug-in-adhesive system: The drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the (Rochazka AV, 2000) medicated polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesives)onto an impervious backing layer. On top of the reservoir, layers of unmedicated adhesive polymer are applied (Adgraft J, 2001).

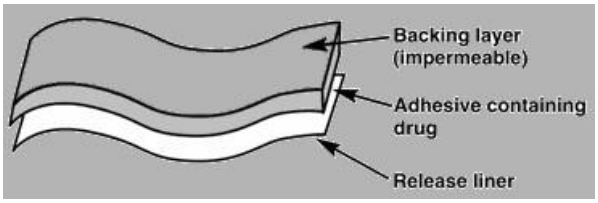

Figure 5: Matrix systems

ii) Matrix-dispersion system: The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk then is fixed onto 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 the circumference to form a strip of adhesive rim.

III) Microreservoir systems: This drug delivery system is a combination of reservoir and matrix-dispersion systems. 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 unleachable, microscopic spheres of drug reservoirs. The thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ.

Recent techniques for enhancing TDDS

A) Structure-Based Enhancement Techniques

1. Micro fabricated 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.

2. Microneedles

Microneedles are tiny and very sleek devices that are manufactured by the silicon etching technology and micro-mechanical system manufacturing (MEMS) technique, which do not penetrate deep enough into the skin to reach up to the nerve endings and thus there is no pain sensation during the microneedles insertion into the skin (Bora P, 2008).

3. 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 200µm. Three types of Macroflux have been designed. They include,

- Dry-Coated Macroflux system-this is used for short period delivery that consists microprojection array coated with medicament that adhered to a elastic polymer adhesive backing.
- D-TRANS Macroflux system-this is also for short duration administration that consists of a microprojection array combined with reservoir of drug.
- E-TRANS Macroflux system-this is for on demand delivery that involves a microprojection array combined with an electrotransport system

4. 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:

i. It improves delivery potential without skin irritation due to its non-occlusive nature.
ii. Increased acceptability.
iii. Dose flexibility
iv. Simple manufacture (Kumar R, 2007).

B) Electrically-based enhancement techniques

1. Iontophoresis

It involves passing of current (few milliamperes) to skin limited to a certain area using the electrode remains in contact (Calhoun A, 2006) 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 (theiaforum.org, 2004).

2. 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.

3. 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.

4. Electroporation

It this method short and high voltage electrical pulses (Kumar R, 2007) are applied to the skin thus the diffusion of drug is improved with the increasing permeability. The electrical (Neumann E, 1982) pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs (Sugar IP, 1984). For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea (berkeley.edu, 2007).

5. 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.

C) Velocity Based Enhancement Techniques

- Needle-Free Injections
- Intraject
- Implaject
- Jet Syringe
- Iject
- Mini-ject

2. 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.

D) Other Enhancement Techniques

1. 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.

2. 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.

3. 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 Micro scissuining.

4. 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 a 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.

5. 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.

Evaluation of Transdermal films

The evaluation of transdermal patches is done to assess the quality and reproducibility. Various evaluation tests includes

(I). Physico chemical studies: The physical parameters such as thickness, weight variation, folding endurance, tensile strength, water vapor transmission and drug content were determined (Pharmainfo.net).

(II). Microscopic studies: Distribution of drug and polymer in the film can be studied using scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double sided (Samanta MK, 2003) adhesive tape. The sections are then coated with gold palladium alloy using fine coat ion sputter to render them electrically

conductive. Then the sections are examined under scanning electron microscope (Verma PRP, 2000)

(III). Thickness: The thickness of film was measured by using electronic vernier calipers, Screw gauze, and micrometer with a least count of 0.01mm. Thickness was measured at five different points on the film and average of five readings was taken.

(IV). Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

(V). Folding endurance: It was determined by repeatedly folding the film at the same place until it breaks. The number of times of film could be folded at the same place without breaking cracking gave the value of folding endurance.

(VI). Drug content: Drug content was found out by dissolving patches each of 2 cm x 2 cm in suitable solvent in which drug get dissolved and place it in a shaker device for up to 24 hrs, after that place it in a sonicator and then allow it to filter and the filtrate was analysed spectroscopically.

(VII). Content uniformity test: 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

(VIII). Weight variation: Ten films are weighed and calculate the average weight, and weigh the individual weight .of films. The individual weight of film should not deviate from its mean weight.

(IX). Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation (Baichwal, MR, 1985)

$$\text{Tensile strength} = F/a.b\ (1+L/l)$$

(X). Moisture content: The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h (Bagyalakshmi J 2007). The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula:-

$$\%\ \text{Moisture content} = \text{Initial weight} - \text{Final weight} \times 100 / \text{Final weight}$$

(XI). Moisture Uptake: Weighed films are kept in a desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below (Gondaliya D, 2003)

(XII). Adhesive studies: The therapeutic efficacy of TDDS can be affected by the contact between the patch and the skin. The adhesion of adhesives capable of bonding to surfaces with the application of light pressure (Williams Adrian, 2003)

(XIV). Tack properties: It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer.

(a). Thumb tack test: The force required to remove thumb from adhesive is a measure of tack.

(b). Rolling ball test: This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

Principle: This tester employs rolling ball method, and tests the primary adhesive properties by testing the bond of measurable strength formed immediately after adhesive specimen and steel ball are brought into contact under low pressure.

(c). Quick stick (Peel tack) test: The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90◦ at the speed of 12 inch/min.

(XV). Shear strength properties or creep resistance: Shear strength is the measurement of the cohesive strength of an adhesive polymer i.e., device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate. Minghetti et al performed the test with an apparatus which was fabricated according to PSTC-7 (pressure sensitive tape council) specification.

(XVI). *In vitro* skin permeation and release kinetics studies: The design and development of transdermal drug delivery systems is greatly aided by in-vitro studies. In-vitro studies can help in investigating the mechanism of skin permeation of drug before it can be developed into a transdermal therapeutic system. The methodology used in the in-vitro study is relatively easy (Siewert M, 2003) to follow and generally affords the investigator better control over the experimental

conditions than is possible in-vitro. The assembly used for the in-vitro studies is shown in figure 4. The factors that require consideration when selecting an in vitro system include:

- The rate limiting process: Drug solubilization or diffusion in the vehicle, partitioning from the vehicle, diffusion through the test membrane or partitioning and removal by the receptor phase.
- The intrinsic diffusivity of the permeate and apparent diffusivity.
- The predominating route of diffusion during the experiment and the relative contents of drug binding and metabolism, occurring in the membrane, delivery and receptor phase.
- The predominating route of diffusion during the experimentation and the relative extents of drug binding.
- The intrinsic barrier potential of the membrane and the effects that vehicle components may have on retardative properties. Hydration of the membrane and the presence of penetration enhancers may be important here.

It is one chambered (vertical) type cell. Most widely used for in-vitro testing of TDDS. Many modifications have been made in the Franz diffusion cell design according to the requirement. Here skin is mounted on the plate above O ring. 20-70 ml phosphate buffer of pH 7.4 (physiological pH) is filled in reservoir compartment. Transdermal patch is applied on upper layer of skin. Diffusion medium in reservoir is stirred at particular rpm. Sampling is done at particular interval from reservoir compartment i.e. specified volume of fluid is withdrawn and is replaced by equivalent amount of the same fluid.

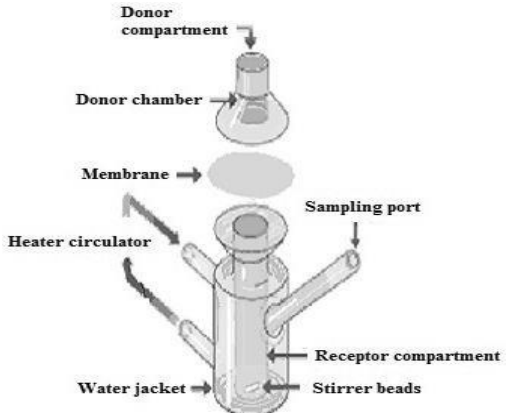

Figure 6: Franz Diffusion Cell

THE FUTURE OF TRANSDERMAL DRUG DELIVERY

The statical data showed a market of $ 12.7 billion in the year 2005 which is assumed to increase by $ 21.5 billion in the year 2010 and $ 31.5 billion in the year 2015. Almost all the pharmaceutical companies are developing TDDS. TDDS may be ideal for many injected as well as orally given drugs, but many drugs cannot penetrate the skin membrane effectively because of low permeability of skin barrier. Pharmaceutical companies are now developing new adhesives, substances that enhance molecular absorption as well as penetration that will ultimately affect skin permeation and greatly increase the list of drugs which can be delivered transdermally. Well known technologies that are iontophoresis and phonophoresis (sonophoresis) considered to acheive significant plasma concentration levels via skin membrane. A microoneedle technology is more promising for drug administered via skin. These systems use an arrangement of small needle-like structures to open pores in the stratum cornea and facilitate drug transport without any sensation of pain because these are not reachable to nerve endings. These systems are reported to greatly enhance the permeability of macromolecules across skin (permegear.com, 2003)

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