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From Patch to Practice: An Overview of Transdermal Drug Delivery Systems

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ABSTRACT

The human skin is a readily accessible surface for drug delivery. The skin of an average adult body receives about one-third of the blood circulating through the body. Over the past decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The human skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeter of the skin area. It is one of the most readily accessible organs of the human body. There is considerable interest in the skin as a site of drug application both for local and systemic effect. However, the skin, particularly the stratum corneum, poses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. 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 have been mostly limited to refinements of the materials used. The present review article explores the overall study on transdermal drug delivery system (TDDS) which leads to novel drug delivery system (NDDS). A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered in this method. A wide variety of pharmaceuticals are now available in transdermal patch form. A transdermal drug delivery system was introduced to overcome the difficulties of drug delivery through oral route. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific form of drug.

KEYWORDS:

Transdermal drug delivery system, bioavailability, Iontophoresis, Electroporation, ultrasound, microscopic projection

INTRODUCTION [1, 2, 3]

Optimum therapeutic outcomes require not only proper drug selection but also effective drug delivery. The human skin is a readily accessible surface for drug delivery. Over the past three decades developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The pharmacological response, both the desired therapeutic effect and the undesired adverse effect, of a drug is dependent on the concentration of the drug at the site of action, which in turn depends upon the dosage form and the extent of absorption of the drug at the site of action1. Tablets and injections have been the traditional way to take medications; new options are becoming increasingly popular. One highly successful alternative delivery method is the transdermal. The skin of an average adult body covers a surface of approximately 2 m^2 and receives about one-third of the blood circulating through the body. They deliver a drug into the body through transdermal layer of skin, it is necessary to understand about the skin.

Anatomy and physiology of skin:

Human skin comprises of three distinct but mutually dependent tissues:

A) The stratified, vascular, cellular epidermis,
B) Underlying dermis of connective tissues and
C) Hypodermis.

Epidermis

The multilayered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Table 1 gives thickness, water permeability and diffusivity of water through epidermis. It consists of the outer stratum corneum and viable epidermis.

Stratum corneum

This is the outermost layer of skin also called as Horney layer. It is approximately 10mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. The architecture of Horney layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein "bricks" embedded in lipid "mortar." The lipids are arranged in multiple bilayers. There is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bilayer form.

Viable epidermis

This is situated beneath the stratum corneum and varies in thickness from 0.06mm on the eyelids to 0.8mm on the palms. Going inwards, it consists of various layers such as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. In the Basale layer, mitosis of the cells constantly renews the epidermis, and this proliferation compensates the loss of dead Horney cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemical, undergoing keratinization to form the outermost layer of stratum corneum.

Dermis

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

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanical protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs.

For transdermal drug delivery, drug must penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.

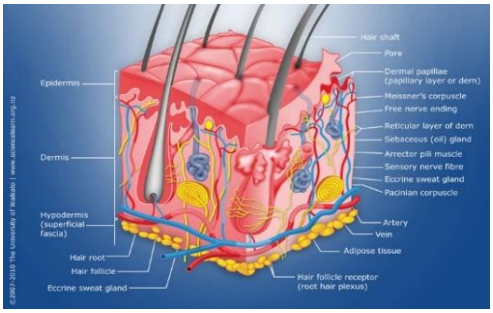

Figure 1: Anatomy and Physiology of skin

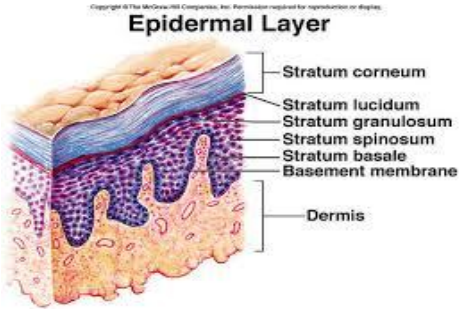

Figure 2: Layers of skin

History of Transdermal Drug Delivery[4,5]

Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion sickness. It was a three-day patch that delivered scopolamine. In 1981, patches for nitroglycerin were approved, and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, scopolamine, and testosterone.

There are also combination patches for contraception, as well as hormone replacement. Depending on the drug, the patches generally last from one to seven days. Transdermal patch (Skin patch) uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream.

Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch. Drugs administered through skin patches include: -

- Scopolamine (for motion sickness),
- Nicotine (for quitting smoking),
- Estrogen (for menopause and to prevent osteoporosis after menopause),
- Nitroglycerin (for angina)
- Lidocaine to relieve the pain of shingles (herpes zoster).

Molecules of insulin and many other substances, however, are too large to pass through the skin. Patches applied to the skin to eliminate the need for vascular access by syringe or the use of pumps. The major advantages provided by transdermal drug delivery include the following:

- Improved bioavailability,
- More uniform plasma levels,
- Longer duration of action resulting in a reduction in dosing frequency,
- Reduced side effects
- Improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms.

Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first pass drug degradation effects. Patches can also reduce side effects.

Transdermal Patches[6,7,8,9,10,11]

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream.

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types such as oral, topical, etc. is that it provides a controlled release of the medicament into the patient. A disadvantage to development, however, stems from the fact that the skin is a very effective barrier. A wide variety of pharmaceuticals can be delivered by transdermal patches. At the forefront of innovation, Aveva and Nitto Denko produced the first and only marketed transdermal patch using a revolutionary gel matrix adhesive system for an unequaled balance of adhesion reliability and gentleness. Because the gel matrix adhesive doesn't cause a disruption of the stratum corneum (skin) during removal, these patches can be removed and reapplied with minimal skin irritation and a desirable patient experience is achieved.

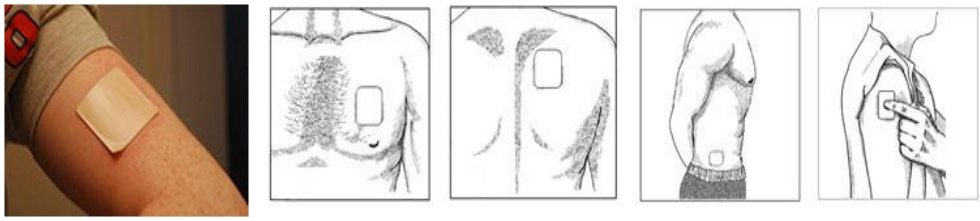

Figure 3: Transdermal patches

One of the most successful advancements in transdermal drug delivery systems, our crystal reservoir technology has resulted in smaller patches with a more controlled and sustained drug release. This efficient drug delivery technology may minimize the amount of active pharmaceutical ingredients required.

This efficient way of releasing a drug is based on the over saturation of an adhesive polymer with medication, thus forcing a partial crystallization of the drug. The presence of both molecular solute and solid crystal forms allows for a considerably higher concentration and consistent supply of drug in each patch. As the skin absorbs the molecular solute, crystals re-dissolve to maintain maximum thermodynamic activity at the site of contact. This technology is employed in the commercial production of the world's only Asthma Patch, which is sold in Japan and is one of the most successful patches in the world.

The transdermal (through the skin) drug delivery approach serves to illustrate "Fuzzy Front End" problems encountered with all the other new drug delivery approaches. For centuries, topical products (creams, gels, lotions, etc.) have been used to treat local skin disorders. The idea of using the skin as a route for systemic drug delivery, however, is of recent origin. The further idea of incorporating drugs in a "patch" that supplies them by transdermal means is even more recent. The most important issue in the development of new transdermal drug delivery systems is to modulate the transport of penetrates through the skin on demand. Skin patches hold promise for transdermal administration of a broad scope of medical treatments.

Patches control the release of drugs and avoid peaks and valleys associated with multiple-dose oral medication, combining extended duration of delivery with patient comfort, while significantly enhancing patient compliance. Patch delivery is easier than injection and eliminates the risk of infection. A number of drugs may be administered transdermal. Transdermal drug absorption significantly alters drug kinetics. Success depends on a variety of biological physiological, biochemical, and biophysical factors including the following:

a) Body site of application
b) Thickness, composition and integrity of the stratum corneum epidermis (a skin layer)
c) Size and structure of the molecule (related to molecular weight), which is an indicator of diffusivity)
d) Permeability of the membrane in the transdermal drug delivery system
e) State of skin hydration
f) pH and other physicochemical drug properties
g) Drug metabolism.
h) Lipid solubility
i) Degree of partitioning of the drug and associated components into the skin
j) Depot (reservoir) of/for drug in skin
k) Alteration of blood flow in the skin by additives and body temperature.

Advantages of transdermal patches[12,13,14]

The advantages of transdermal delivery are obvious even delivery of a therapeutic level of drug is painless, the patient does not need to inject himself, there are no bulky delivery devices to manage or dangerous needles to dispose of, and there are few or no gastrointestinal effects from the drug itself. Peak plasma levels of the drug are reduced, leading to decreased side effects. In addition, transdermal delivery is useful for those drugs that have a high first pass effect through the liver, have poor oral uptake, need frequent administration, or that interact with stomach acid. The first pass effect results in the destruction of a significant amount of the drug. Drugs absorbed through the skin, however, enter the general circulation directly avoiding the liver, with less total drug absorption occurring.

- Topical patches are a painless, noninvasive way to deliver substances directly into the body.
- Topical patches are a better way to deliver substances that are broken down by stomach acids, not well absorbed from the gut, or extensively degraded by the liver.
- Topical patches over a controlled, steady delivery of medication over long periods of time.
- Topical patches have fewer side effects than oral medications or supplements.
- Topical patches are easier to use and remember.
- Topical patches over an alternative to people who cannot or prefer not to take medications or supplements orally.
- Topical patches are cost effective. People prefer topical patches.

Limitations[12,13,14]

- TDDS cannot deliver ionic drugs.
- TDDS cannot achieve high drug levels in blood/plasma.
- It cannot develop for drugs of large molecular size.
- TDDS cannot deliver drugs in a pulsatile fashion.
- TDDS cannot develop if drug or formulation causes irritation to skin.

Popular Uses[5]

- The highest selling transdermal patch in the United States is the nicotine patch which releases nicotine in controlled doses to help with cessation of tobacco smoking. The first commercially available vapor patch to reduce smoking was approved in Europe in 2007.
- Two opioid medications used to provide round the clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans).
- Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis.
- Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evraor Evra).
- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.
- The antihypertensive drug Clonidine is available in transdermal patch form under the brandname Catapres TTS.
- Emsam, a transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant approved for use in the U.S. in March 2006.

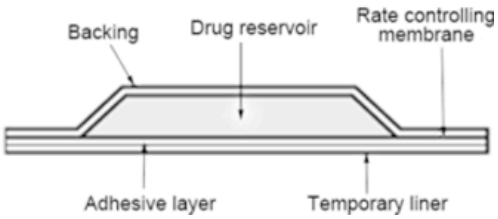

Figure 4: Layers of transdermal patch

Adverse Events

In 2005, the FDA announced that they were investigating reports of death and other serious adverse events related to narcotic overdose in patients using Duragesic, the fentanyl transdermal patch for pain control. The Duragesic product label was subsequently updated to add safety information in June 2005. In 2008, two manufacturers of the Fentanyl patch, Alza Pharmaceuticals (a division of major medical manufacturer Johnson & Johnson) and Sandoz, subsequently issued a recall of their versions of the patch due to a manufacturing defect that allowed the gel containing the medication to leak out of its pouch too quickly, which could result in overdose and death. As of 2010, Sandoz no longer uses gel in its transdermal fentanyl patch instead, Sandoz branded fentanyl patches use a matrix/adhesive suspension (where the medication is blended with the adhesive instead of held in a separate pouch with a porous membrane), similar to other fentanyl patch manufacturers such as Mylan and Janssen.

In 2007, Shire and Noven Pharmaceuticals, manufacturers of the Daytrana ADHD patch, announced a voluntary recall of several lots of the patch due to problems with separating the patch from its protective release liner. Since then, no further problems with either the patch or its protective packaging have been reported.

In 2009, the FDA announced a public health advisory warning of the risk of burns during MRI scans from transdermal drug patches with metallic backings. Patients should be advised to remove any medicated patch prior to an MRI scan and replace it with a new patch after the scan is complete. Skin burns have occurred with metal containing transdermal patches at the time of shock therapy from external as well as internal cardioverter defibrillators (ICD).

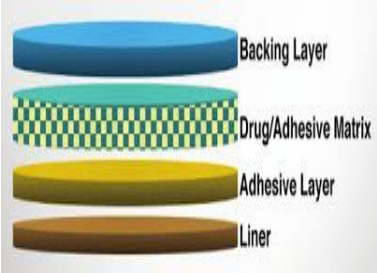

Figure 5: Backing layer, Adhesive layer, Liner.

The main components to a transdermal patch are Liner Protects the patch during storage. The liner is removed prior to use. Drug solution in direct contact with release liner. Adhesive Serves to adhere the components of the patch together along with adhering the patch to the skin. Membrane Controls the release of the drug from the reservoir and multilayer patches. Backing Protects the patch from the outer environment. Conditions in which Transdermal patches are used when:

- When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.
- Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia.
- It can be used in combination with other enhancement strategies to produce synergistic effects.

Conditions in which Transdermal patches are not used the use of transdermal patch is not suitable when:

(1) Cure for acute pain is required.
(2) Where rapid dose titration is required.
(3) Where the requirement of dose is equal to or less than30 mg/24 hrs.

Factors affecting transdermal bioavailability Two major factors affect the bioavailability of the drug via transdermal routes:

(1) Physiological factors
(2) Formulation factors

Physiological factors include.

(1) Stratum corneum layer of the skin
(2) Anatomic site of application on the body
(3) Skin condition and disease
(4) Age of the patient
(5) Skin metabolism
(6) Desquamation (peeling or flaking of the surface of the skin)
(7) Skin irritation and sensitization

Formulation factors include.

(1) Physical chemistry of transport
(2) Vehicles and membrane used.
(3) Penetration enhancers used.
(4) Method of application
(5) Device used.

Care taken while applying transdermal patch:

(1) The part of the skin where the patch is to be applied should be properly cleaned.
(2) Patch should not be cut because cutting the patch destroys the drug delivery system.
(3) Before applying a new patch, it should be made sure that the old patch is removed from the site.
(4) Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch.

(5) The patch should be applied accurately to the site of administration.

Figure 6: Handling of patches

Mechanism of Action of Transdermal Patch

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

1. Iontophoresis[15]

Iontophoresis passes a few mill amperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Mainly used of pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test. Iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia.

2. Electroporation[16,17,18]

Electroporation is a method of application of short, high voltage electrical pulses to the skin. After electroporation, the permeability of the skin for diffusion of drugs is increased by 4 orders of magnitude. Electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve free stratum corneum.

Electroporation has also been shown to disrupt lipid bilayer structures in the skin. Although the electric field applied for milliseconds during electroporation provides an electrophoretic driving force, diffusion through long-lived electropores can persist for up to hours, such that transdermal transport can be increased by orders of magnitude for small model drugs, peptides, vaccines and DNA. Recently, electroporation was shown to deliver a model peptide vaccine into the skin of mice to generate a strong cytotoxic T lymphocyte response.

3.Application by ultrasound

Application of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis. Katz et al. reported on the use of low frequency sonophoresis for topical delivery of EMLA cream.

4. Use of microscopic projection

Transdermal patches with microscopic projections called *microneedles* were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 μm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in development of cutaneous vaccines for tetanus and influenza.

Various other methods are also used for the application of transdermal patches like thermal poration, magnetophoretic, and photomechanical waves. However, these methods are in their early stage of development and require further detailed studying.

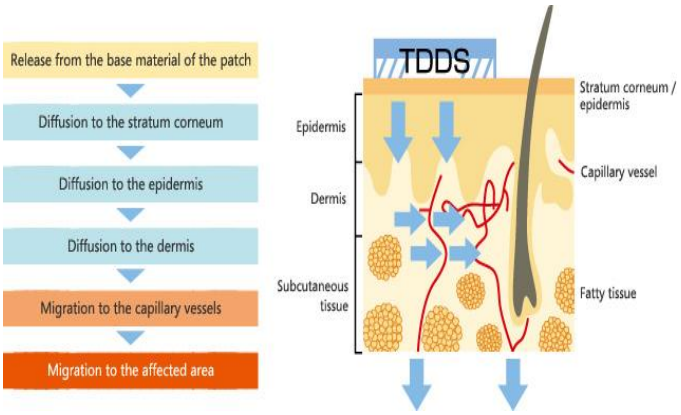

Figure 7: Mechanism of TDDS

Types of Transdermal Patch[19,20,21,22]

1. **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.

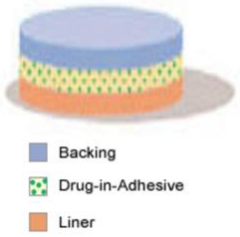

Figure 8: Single layer drug

2. Multilayer Drug in Adhesive

The multilayer 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 multilayer 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 line layer and a permanent backing.

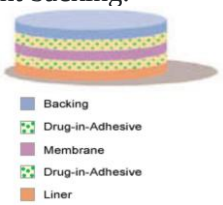

Figure 9: Multilayer drug adhesive

3. Reservoir

Unlike the Single layer and Multilayer 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.

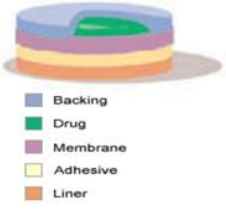

Figure 10: Reservoir

4. Matrix

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

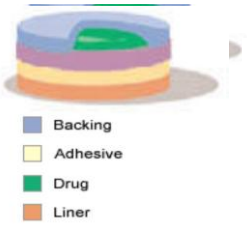

Figure 11: Matrix

5. 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.

Patch Technology for Protein Delivery[24,25,40]

Transdermal delivery of large proteins is a novel and exciting delivery method. There is no commercial technology currently available that incorporates proteins into transdermal patches. Trans Pharma uses its unique printed patch technology for transdermal delivery of proteins thereby complementing its Via Derm delivery technology. Such printed patches contain accurate doses of proteins in dry state. It is postulated that the highly water-soluble proteins are dissolved by the interstitial fluid that is secreted from the skin through the RF-Micro Channels, forming a highly concentrated protein solution in situ. The delivery of the dissolved molecules is then carried out, via the RF-Micro Channels, into the viable tissues of the skin, diffusing across a steep concentration gradient. This brings about a high delivery rate, as well as a peak blood profile of the drug resembling that of a subcutaneous injection. The protein patches do not contain any enhancers to facilitate the delivery process, thereby insuring an easier development process and regulatory pathway. Trans Pharma has adapted a manufacturing dispensing technology, widely used in the diagnostics industry, to successfully manufacture the printed patches. This manufacturing method enables complete and flexible control of drug load on the patch, control of patch size and shape, as well as high manufacturing yield with minimal protein losses. In addition, it was found that this manufacturing method fully retains the biological activity of the protein drug. Printed patches were used in studies in which human growth hormone (hGH), insulin, and Teriparatide (PTH1-34) were delivered in animals (guineapigs and pigs) and humans.

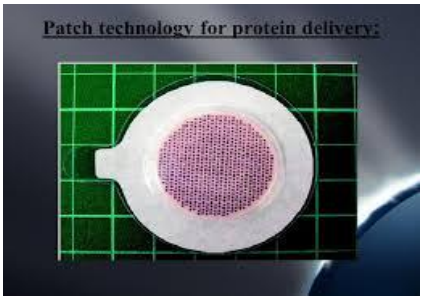

Figure 12: Protein delivery patch

Maximizing Transdermal Drug Delivery [29,30]

This drug delivery system is available since many years. Previously, the most frequent systems for applications were topical ointments and creams for various dermatological disorders. Here, various drugs are applied to your skin for providing systemic treatment. This system comprises of various topically monitored drug formulations that can deliver active components into general circulation. This

system is formulated for providing controlled uninterrupted drug delivery through skin for systemic circulation and distribution in the body. Due to the relative and impermeability property of skin, transdermal drug delivery system doubles the protection barricade to avert intrusion by microbes and prevents loss of physiological substances including water. Drug delivery technologies are now receiving considerable attention from pharmaceutical companies The main purpose of developing alternative drug delivery technologies is to increase efficiency and safety of drug delivery and provide more convenience for the patient. Substantial research conducted during the past several years has led to the development of technologies that meet the requisite criteria for delivering the drug through a non-invasive route. One of such technologies is transdermal drug delivery. Transdermal drug delivery is the non-invasive delivery of medications from the surface of the skin - the largest and most accessible organ of the human body - through its layers, to the circulatory system. Medication delivery is carried out by a patch that is attached to the body surface. Transdermal patch is a medicated adhesive pad that is designed to release the active ingredient at a constant rate over a period of several hours to days after application to the skin. It is also called skin patch. A skin patch uses a special membrane to control the rate at which the drug contained within the patch can pass through the skin and into the bloodstream.

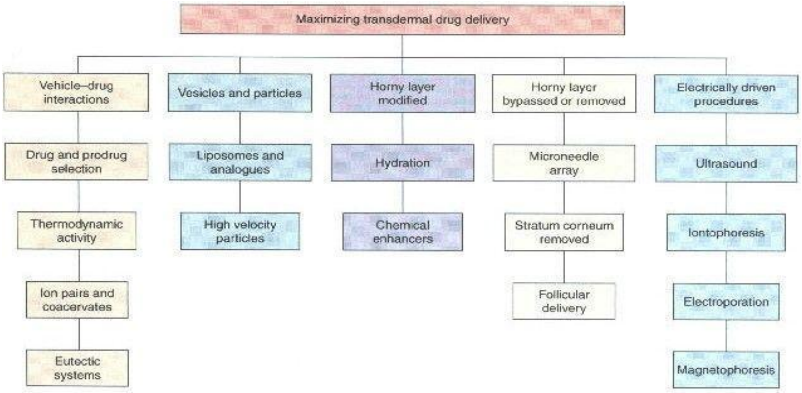

Figure 13: Maximizing drug delivery.

Evaluation Of Transdermal Patches

- Physicochemical evaluation
- *In vitro* evaluation
- *In vivo* evaluation

1.Physicochemical Evaluation[14,8,11]:

Thickness:

The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight:

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

Drug content determination:

An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, the drug in solution is estimated spectrophotometrically by appropriate dilution.

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 an additional 20 patches are tested for drug content.

If these 20 patches have a range from 85% to 115%, then the transdermal patches pass the test.

Moisture content:

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

% Moisture content = Initial weight –Final weight x 100

Moisture Uptake:

Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.

% Moisture Uptake = Final Weight –Initial Weight x 100

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 center 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.

% Constriction = I_1-I_2 x 100

I_1 = Initial length of each strip; I_2 = Final length of each strip

Folding Endurance:

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same time place until it breaks. The number of times the films could be folded at the same place without breaking is folding endurance value.

Tensile Strength:

To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the film is kept fixed with the help of an iron screen and the 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.

Tensile strength= F/a x b (1+L/l)

F is the force required to break
a is width of film.
b is thickness of film
L is length of film
l is elongation of film at break point.

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.

Thumb tack test:

The force required to remove thumb from adhesive is a measure of tack.

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.

Quick stick (Peel tack) test:

The peel force required to break 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.

Probe tack test:

Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

2. *In vitro* release studies:[29]

The Paddle over Disc: (USP apparatus 5/ Ph Eur 2.9.4.1)

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 medium at 32 ±5°C.

The Cylinder modified USP Basket:(USP apparatus 6 / Ph Eur 2.9.4.3)

This method is like the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32 ±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 (Ph Eur 2.9.4.2) may be used.

***In vitro* permeation studies:** [30,31,32]

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 keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophilic side in contact with receptor fluid. The receiver compartment is maintained at a 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 an 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 cm^2 per sec. Horizontal type skin permeation system: this has been widely used for the evaluation of drug permeation across skin. The cell is divided into receptor and donor compartments with a low solution volume (3.5ml) for each compartment and a small membrane area (0.64 cm^2). They are continuously stirred by a matched set of star-head magnets, which are rotated at a speed of 600rpm. The system is controlled by thermostatic water through a water jacket surrounding the two compartments.

Franz diffusion cell:

The cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 5-12mlmand effective surface area of 1-5 cm2. The diffusion buffer is continuously stirred at 600rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds the receptor compartment.

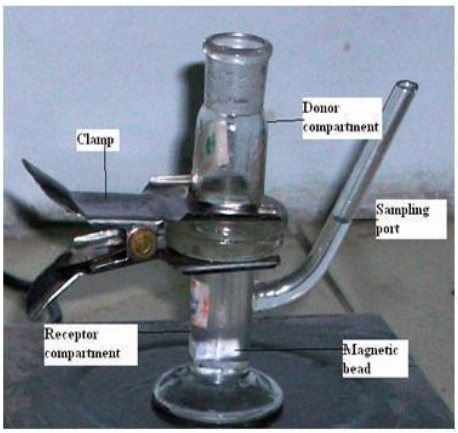

Figure 14: Schematic diagram of Franz diffusion cell

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 aloe appropriate loading of the applied compound and a low volume (0.3ml) receiving chamber that ensures rapid removal of penetrant at relatively low pumping rates.

In vivo Studies:

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be considered during in vitro studies can be fully explored during in vivo studies. *In vivo* evaluation of TDDS can be carried out using animal models human volunteers.

Animal models:

Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and *in vivo* experiments. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man.

Human models:

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources, they are the best to assess the performance of the drug.

List Of Marketed Products[39]

MARKETED PRODUCT

DRUG	BRAND NAME	MANUFACTURER
Nicotine	Nicoderm	gsk
Nicotine	Habitraol	Novartis
Nitroglycerine	Transderm nitro	Novartis
Insulin	SonoDerm	Imarx
Testosterone	Testoderm	Alza Corporation
Diclofenac diethyl amine	NuPatch 100	Zudus Cadilla

Figure 15: Marketed product

Scientific Studies[33,34,35]

Structure of the skin barrier

The skin is the largest human organ and consists of three functional layers: epidermis, dermis, and subcutaneous tissue. It has a wide variety of functions. One major task of the skin is to protect the organism from water loss and mechanical, chemical, and physical influences. The protective properties are provided by the outermost layer of the skin, the epidermis. Although its thickness measures on average only 0.1 mm (from 0.02 mm on the face up to 5 mm on the soles of the feet) it is specially structured to fulfill this challenging task. Out of the five layers of the epidermis, it is mainly the upper most layer (horny layer; stratum corneum) which forms the permeability barrier. The stratum corneum consists of horny skin cells (corneocytes) which are connected via desmosomes (protein-rich appendages of the cell membrane). The corneocyte is embedded in a lipid matrix. Thus, the structure of the stratum corneum can be roughly described by a “brick and mortar” model.

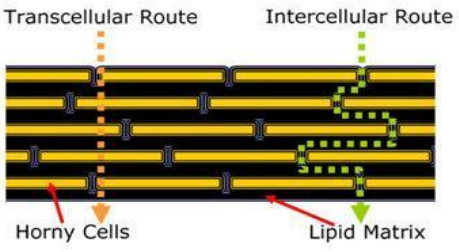

Figure 16: Skin barrier

Routes of penetration

Illustrates the possible pathway for a penetrant to cross the skin barrier. Accordingly, a molecule may use two diffusional routes to penetrate normal intact human skin: the appendageal route and the transepidermal route. The appendageal route comprises transport via the sweet glands and the hair follicles with their associated sebaceous glands. The routes circumvent penetration through the stratum corneum and are therefore known as shunt routes. Although these routes offer high permeability, they are of minor importance because of their relatively small area, approximately 0.1 % of the total skin area. The appendageal route seems to be most important for ions and large polar molecules which hardly permeate the stratum corneum.

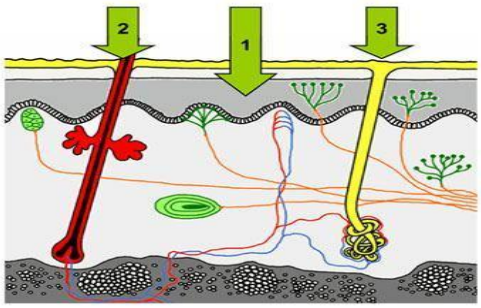

Figure 17: Route of penetration

Material And Methods

Preparation of transdermal patch containing drug and polymer matrix

- Matrix type transdermal patches compose of different ratio of metoprolol, Polyvinyl pyrrolidone (PVP), Ethyl cellulose, Glycerin and PEG400 where prepared by solvent evaporation techniques using bangles. The bottom of the bangle was wrapped with aluminum foil on which backing membrane was cast by pouring 5% w/v aqueous PVA solution followed by drying at 50°C for 8hrs.
- Drug matrix was prepared by dissolving requisite amount of drug (Propranolol) and EC in methanol. To this solution PEG400 (40% w/w of polymer composition) was added and stirred.
- The uniform dispersion obtained was cast on PVA backing membrane and dried at room temperature for 24hrs.
- The dry films were removed and wrapped in aluminum foil and kept in a desiccator until used, which is shoe in figure no.7.
- The prepared films were stuck to adhesive layer of bandage which was purchased from local market.

Figure 18: Making of patches

Evaluation Of Transdermal Patches[36,37,38]

Calibration Curve

1. Stock solution 100µg/ml was prepared in phosphate buffer pH 7.2.

***In vitro* skin permeation studies with polymeric matrix**

The *in vitro* skin permeation of Propranolol Hydrochloride from various transdermal patches using locally fabricated Franz type of diffusion cell. The diffusion cell consists of two parts; the upper part that is donor compartment and contain active ingredient and the carrier patch; the bottom part contains the receptor solution, the water jacket for temperature control, and the sampling port. The effective

permeation area of the diffusion cell and receptor and cell volume was $1cm^2$ and 20ml, respectively. The temperature was maintained at 37 ± 2^0C. The receptor compartment contained 20ml of phosphate buffer IP PH 7.2 stirred by magnetic stirrer. Permeability studies were carried out across rat skin. Sample 5ml were withdrawn and replace with the same volume of fresh receptor solution, to the sampling port of the diffusion cell predetermine time intervals till 6hrs.the absorbance of withdrawn samples were measured at 280nm for Propranolol Hydrochloride. Find out the %Cumulative Drug release of each formulation. Plot the graph between %Cumulative Drug release v/s time, which is present in figure no.10 (A, B, C). The experiments were done in triplicates, simultaneously blanks were also run, and the average value reported. (Franz TJ., 1991).

Thickness:

The thickness of the patch was determined by using vernier calipers, recording mean of 6 determinations.

Figure 20: Diffusion study of prepared TDS

Future Aspects [23,24,25,26,27,28]

Transdermal drug delivery is theoretically ideal for many injected and orally delivered drugs, but many drugs cannot pass through the skin because of skin's low permeability. Pharmaceutical companies develop new adhesives, molecular absorption enhancers, and penetration enhancers that will enhance skin permeability and thus greatly expand the range of drugs that can be delivered transdermal. Two of the better-known technologies that can help achieve significant skin permeation enhancement are iontophoresis and phonophoresis (sonophoresis). Iontophoresis involves passing a direct electrical current between two electrodes on the skin surface. Phonophoresis uses ultrasonic frequencies to help transfer high molecular weight drugs through the skin. A newer and potentially more promising technology is micro needle-enhanced delivery. These systems use an array of tiny needle-like structures to open pores in the stratum corneum and facilitate drug transport. The structures are small enough that they do not reach the nerve endings, so there is no sensation of pain. These systems have been reported to greatly enhance (up to 100,000-fold) the permeation of macromolecules through skin.

Conclusion:

Transdermal drug delivery is a painless, convenient, and potentially effective way to deliver regular doses of many medications. Unfortunately, from the perspective of transdermal technology, the skin is impermeable to all but the smallest of molecules. In particular, the upper layer of skin, known as the stratum corneum, presents the most formidable barrier. If the stratum corneum could be pierced or temporarily made more permeable, this would allow more rapid transmission of larger molecules such as the insulin molecule Wide range of drugs can be delivered improved drug uptake Minimal complications and side effects Low cost and Easy to use Flexibility and consistency in dosing. One of the major advantages of transdermal drug delivery is the steady delivery of drug, resulting in consistent drug levels. Another advantage is the convenience of weekly or bi-weekly application resulting in improved patient compliance. Transdermal delivery of a drug product which is currently approved as oral dosage form, allows for the avoidance of first pass metabolism by the liver and the delivery of a more even level of the therapeutic agent over the course of 24hours. Dermal patches are the most common form of transdermal delivery of drugs. To obtain FDA approval of a transdermal delivered drug, it is critical to involve the Food and Drug Administration (FDA) early in the development process. During recent years, transdermal drug delivery systems have shown a tremendous potential for their

ever-increasing role in health care. This has been mainly attributed to the favorable properties of lack of first pass metabolism effects of liver, better patient compliance, steady release profile and lowered pill burden.

Several transdermal drug delivery systems (TDDS) have recently been developed aiming to achieve the objective of systemic medication through application to the intact skin. The intensity of interest in the potential bio-medical application of transdermal controlled drug administration is demonstrated in the increasing research activities in a number of health care institutions in the development of various types of transdermal therapeutic systems (TTS) for long term continuous infusion of therapeutic agents including anti-hypertensive's, anti-anginal, antihistamine, anti-inflammatory, analgesic drugs etc.

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