TRANSDERMAL DRUG DELIVERY SYSTEM: A PAINLESS METHOD FOR HEALTHY SKIN - A REVIEW

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***Abstract*: Now a day about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such character's transdermal drug delivery system was emerged. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. This review article provides an overview of TDDS, its advantages over conventional dosage forms, drug delivery routes across human skin, permeation enhancers, and various components of transdermal patches, types of transdermal patches, methods of preparation and its methods of evaluation.**

***Keywords*: TDDS, Topical drug delivery, Systemic blood circulation, Skin, Transdermal patches.**

INTRODUCTION

First transdermal patch approved in 1979 by FDA was of Scopolamine for motion sickness. Second patch approved in 1981 was of Nitro-glycerine. Now a day's several patches are available in market for transdermal use. Some of them are: Clonidine, Testosterone, Fentanyl, Nicotine, Hormones etc. these patches usually applied from 1to7 days depending upon various conditions. Oral route is most commonly used route for drug delivery, but due to some major shortcomings such as poor B.A., first pass effect and the ability to create fluctuation of drug level in blood.

Topical or Transdermal delivery of anti-analgesic drugs has gained prominence in recent years, owing to its ability to provide concentrated and highly localized pain relief directly to a specific area of the body, unlike oral drug delivery which often causes side-effects as it winds its way through the gastrointestinal tract. However, in spite of its benefits like targeted and concentrated drug delivery, the transdermal application of hydrophobic drugs is significantly limited by the outermost layer of human skin (stratum corneum).

Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus, various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Trans mucosal delivery systems etc. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. The first Transdermal system, Transderm-SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel, particularly by sea. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy.

The advantages of delivering drugs through the skin include:

1. Hepatic first pass metabolism, salivary metabolism and intestinal metabolism are avoided.
2. The ease of usage makes it possible for patients to self-administer these systems.
3. In case of an emergency, removing the patch at any point of time during therapy can instantly stop drug input.
4. Since the composition of skin structurally and biologically is the same in almost all the humans, there is minimal inter and intra patient variation.
5. Drugs showing gastrointestinal irritation and absorption can be suitably administered through the skin.
6. Continuous, non-invasive infusion can be achieved for drugs with short biological half-lives, which would otherwise require frequent dosing.
7. Due to reduced frequency of dosing there is better patient compliance.
8. Therapeutic failures associated with irregularities in the dosing with conventional therapies can be avoided.
9. The adverse effects are minimized due to a steady and optimum blood concentration time profile.
10. The risks, pain and inconvenience associated with parenteral therapy are evaded.
11. The release is more prolonged than oral sustained drug delivery systems.

The following are some of the disadvantages of the transdermal delivery system;

1. There is possibility of skin irritation due to the one or many of the formulation components.
2. Binding of drug to skin may result in dose dumping.

3. It can be used only for chronic conditions where drug therapy is desired for a long period of time including hypertension, angina and diabetes.
4. Lag time is variable and can vary from several hours to days for different drug candidates.
5. Cutaneous metabolism will affect therapeutic performance of the system.
6. Transdermal therapy is feasible for certain potent drugs only.
7. Transdermal therapy is not feasible for ionic drugs. 8. It cannot deliver drug in pulsatile fashion.

SELECTION OF DRUG CANDIDATE FOR TRANSDERMAL DELIVERY

The transdermal route of administration cannot be employed for a large number of drugs. Judicious choice of the drug substance is the most important decision in the successful development of a transdermal system.
The drug candidate should have following ideas characteristics:

Adequate skin permeability

- Drugs with low molecular weight
- Drugs with low melting point
- Drugs with moderate oil and water solubility

Adequate skin acceptability

- Non-irritating drugs
- Non-metabolizing drugs Adequate clinical need
- Need to prolong administration
- Need to reduce side effects on target tissues
- Need to increase patient compliance.

STRUCTURE OF SKIN:

The skin can be considered to have four distinct layers of tissues including non-viable epidermis (stratum corneum), viable epidermis, viable dermis and hypodermis (subcutaneous connective tissue). The epidermis is the relatively thin, tough, outer layer of the skin. The epidermis has keratinocytes. They originate from cells in the deepest layer of the epidermis called the basal layer. New keratinocytes slowly migrate up toward the surface of the epidermis. Stratum corneum (non-viable epidermis) is the www.wjpps.com 2202 Nawazish et al. World Journal of Pharmacy and Pharmaceutical Sciences outermost portion of the epidermis, relatively waterproof and, when undamaged, prevents most bacteria, viruses, and other foreign substances from entering the body. The epidermis also protects the internal organs, muscles, nerves, and blood vessels against trauma. The outer keratin layer of the epidermis (stratum corneum) is much thicker. Viable Epidermis layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50-100 µm. The structure of the cells in the viable epidermis is physiochemically similar to other living tissues. Cells are held together by tonofibrils. The water content is about 90%. The dermis, the skin's next layer, is a thick layer of fibrous and elastic tissue (made mostly of collagen, elastin and fibrillin) that gives the skin its flexibility and strength. The dermis contains nerve endings, sweat glands and oil glands, hair follicles, and blood vessels. The subcutaneous tissue also known as hypodermis is not actually accepted as a true part of the structured connective tissue. It is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels. Most investigators consider the drug permeating through the skin enter the circulatory system before reaching the hypodermis where the fatty tissue serve as a depot of the drug.

EPIDERMIS

In a typical part of the epidermis there are number of different strata in which the cells have distinct anatomical features. From below, the first stratum is the basal layer or layer of Malpighi. Its cells are mostly polygonal in shape, the deepest tending to a cylindrical columnar form, and the most superficial becoming somewhat flattened. Active mitotic proliferation takes place in the deeper layers, the development of new cells leading to a gradual displacement of the older cells towards the surface. Hence, this stratum is also called stratum germinatum. The epidermis is quiet avascular, and between the cells of stratum germinatum there are fine intercellular channels which probably allow the transmission of nutrient fluids derived from capillary blood vessels in the adjacent dermis. These channels are bridged across by delicate protoplasmic threads connecting one cell with another. The stratum germinatum, therefore, appears to be syncytium of cells.

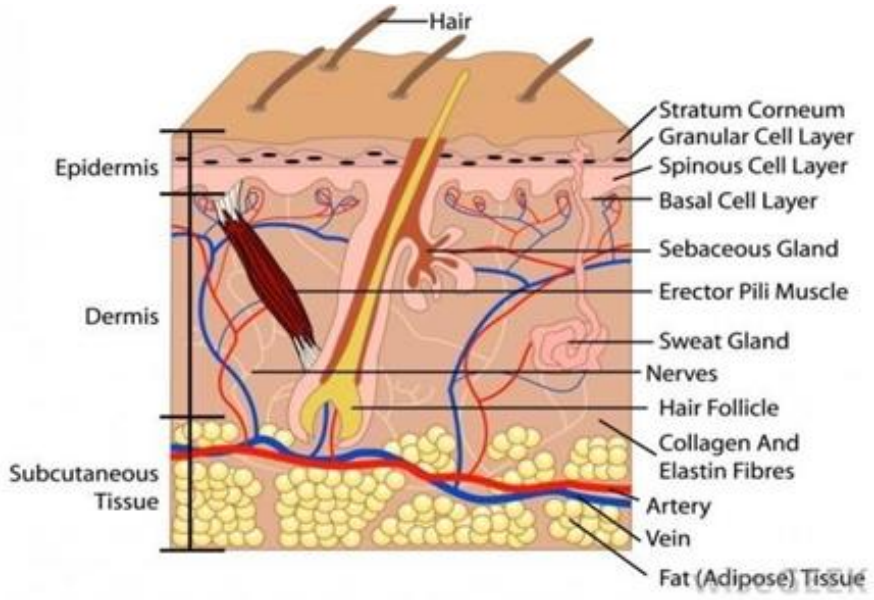

Figure 1: Transverse section of human skin

DERMIS

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 in superficial levels. Dermis contains fine plexuses of blood vessels, lymphatics and nerves, hair follicles, sweat glands and sebaceous glands.[31, 32] the thicker the epidermis; therefore, the more prominent are the papillae.

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 humectants 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 them3

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

Chloroform, methanol's damage the skin cells and promotes 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. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors 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.

PATHWAYS OF DRUG ABSORPTION THROUGH THE SKIN
The drug can be absorbed by various pathways through the skin depending on the physicochemical properties of the drug. Both lipophilic and hydrophilic drugs are absorbed from different routes. The upper stratum corneum of the skin opposes the absorption of drug but presence of various absorption routes facilitates the entry of drug and transport of drug to the systemic circulation. Various drug absorption routes (figure 1) are as follows:

Trans follicular route
Trans follicular route is the shortest pathway that drug has to follow to reach the systemic circulation that provides a large area for diffusion of drugs. Skin has various sweat glands, oil glands, hair follicles and pores opening to the outer surface of the skin via their ducts. These ducts offer a continuous channel across the stratum corneum for drug transport but various factors like secretion from glands, content and amount of secretion etc., affect the transport of drugs through this route. However Trans appendage route occupies only 0.1% of total skin surface and therefore contributes a little.[1]

Transcellular route
Drug delivering through this route passes from corneocytes which has highly hydrated keratin creating hydrophilic pathway. Corneocytes are surrounded by lipids connecting these cells. So a drug requires a number of partitioning and diffusion steps. It is the most widely used route by various types of drugs. In transcellular route drug passes through the matrix (cytoplasm) of the cells. This route is suitable for hydrophilic drugs. The drug passes through the corneocytes of stratum corneum. The highly hydrated keratin provide aqueous pathway to the hydrophilic drugs. A number of partitioning and diffusion steps are needed to pass the drug through the cell matrix12

Intercellular route
As name indicates in intercellular pathway the drug diffuses through the continuous lipid matrix present between the cells. The barrier property of this route is due tortuous structure formed by corneocytes and the drug has to pass through the alternating lipid and aqueous domain by partitioning into the lipid bilayer and diffusing to the inner side. It has been found that water has to travel 50 times more by this route so; it is suitable mainly for uncharged lipophilic drugs.[35]

APPROACHES TO DEVELOPMENT TRANSDERMAL THERAPEUTIC SYSTEMS
Various technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of a drugs. These technologies can be classified into two major categories as follows.

Rate-programmed transdermal DDS
1. Membrane permeation-controlled systems
2. Adhesive dispersion-type systems.
3. Matrix diffusion-controlled systems.
4. Micro reservoir type or micro sealed dissolution controlled systems.

Physical stimuli-activated transdermal DDS

1. Structure based
1. Microneedles
2. Macro flux
3. MDTS

2. Electrically based
1. Iontophoresis
2. Ultrasound
3. Photochemical waves
4. Electroporation
5. Electroosmosis

3. Velocity based
1. Powder jet
2. Needle free injection

COMPONENTS OF TRANSDERMAL PATCH:
The basic components of transdermal patch consists of polymer matrix / Drug reservoir, active ingredient (drug), permeation enhancers, pressure sensitive adhesive (PSA), backing laminates, release liner, and other excipients like plasticizers and solvents.

1. Polymer matrix
Polymers are the backbone of a transdermal drug delivery system. Systems for transdermal delivery are fabricated as multilayered polymeric laminates in which a drug reservoir or a drug–polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane. Polymer selection and design must be considered when striving to meet the diverse criteria for the fabrication of effective transdermal delivery systems. The main challenge is in the design of a polymer matrix,

followed by optimization of the drug loaded matrix not only in terms of release properties, but also with respect to its adhesion cohesion balance, physicochemical properties, compatibility and stability with other components of the system as well as with skin.
The polymers utilized for TDDS can be classified as
(1) Natural polymers includes cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc,
(2) Synthetic elastomers includes polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butyl rubber etc,
(3) Synthetic polymers includes polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc. The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropyl methylcellulose are used as matrix formers for TDDS. Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membrane.

2. Drug
The most important criteria for TDDS are that the drug should possess the right physicochemical and pharmacokinetic properties. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half-life which causes non- compliance due to frequent dosing. For example, drugs like rivastigmine for Alzheimer's and Parkinson dementia, rotigotine for Parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS.

3. Permeation enhancers
To increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug permeation enhancers interact with structural components of stratum corneum i.e., proteins or lipids. The enhancement in absorption of oil soluble drugs is apparently due to the partial leaching of the epidermal lipids by the chemical enhancers, resulting in the improvement of the skin conditions for wetting and for trans-epidermal and trans-follicular permeation. The miscibility and solution properties of the enhancers used could be responsible for the enhanced transdermal permeation of water soluble drugs.

4. Pressure sensitive adhesive (PSA)
A PSA maintains an intimate contact between patch and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently techy, and exert a strong holding force. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. PSA should be physiochemically and biologically compatible and should not alter drug release. The PSA can be positioned on the face of the device (as in reservoir system) or in the back of the device and extending peripherally (as in case of matrix system).

5. Backing laminate
The primary function of the backing laminate is to provide support. Backing layer should be chemical resistant and excipients compatible because the prolonged contact between the backing layer and the excipients may cause the additives to leach out or may lead to diffusion of excipients, drug or permeation enhancer through the layer. They should have a low moisture vapour transmission rate. They must have optimal elasticity, flexibility, and tensile strength. Examples of some backing materials are aluminium vapour coated layer, plastic film (polyethylene, polyvinyl chloride, polyester) and heat seal layer.

6. Release liner
During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. The release liner is composed of a base layer which may be non-occlusive (paper fabric) or occlusive (polyethylene and polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metalized laminate.

7. Other excipients
Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

TYPES OF TRANSDERMAL PATCHES
Single layer drug in adhesive
In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.
a) Multi -layer drug in adhesive
This type is also similar to the single layer but it contains an immediate drug-release-layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.
b) Vapour patch
The patch containing the adhesive layer not only serves to adhere the various surfaces together but also serves as to release the vapour. The vapour patches are new to the market, commonly used for releasing the essential oils in decongestion. Various other types of vapour patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

c) Reservoir system

In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix.

d) Matrix system

i. Drug-in-adhesive system

This type of patch is formulated by mixing the drug with adhesive polymer to form drug reservoir. It then followed by spreading on an impervious backing layer by solvent casting or melting method. The top of the reservoir is protected by an unmediated adhesive polymer layers. It may further be categorized into single-layer and multi-layer drug-in-adhesive. The system is considered to be compatible with a wide variety of drugs. Moreover the system is competent to deliver more than one drug in a single patch. It offers advantages in reduced size and thickness and improved conformability to the application site, helping drive patient preference.

ii. Matrix-dispersion system

The drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. It is then altered into a medicated disc with the definite shape and thickness. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

e) Micro reservoir system

The system consists of microscopic spheres of drug reservoirs which releases drug at a zero order rate for maintaining constant drug levels. Micro reservoir system is a combination of reservoir and matrix-dispersion system. The aqueous solution of water soluble polymer is mixed with drug to form a reservoir. It is then followed by dispersing the solution homogeneously using high shear mechanical force in a lipophilic polymer to form thousands of microscopic drug reservoirs. Cross linking agents are added to stabilize the thermodynamically unstable dispersion by in-situ cross-linking the polymer.

EVALUATION PARAMETERS FOR TDDS PATCH

Physical appearance

The prepared patches were physically examined for colour, clarity and surface texture. Thickness of the patch The thickness of the drug loaded patch is measured in different points by using a digital micrometre and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch. Patch will have an equal thickness at every point. The variation of thickness within the patch and patch to patch can be calculated.

Weight uniformity

The patches are dried at 60°C before weighing. The weight uniformity of the patch is measured by cutting and weighing the 1 cm 2 piece of 3 patches and then calculating the weight variation. The mean of the 3 is taken as the weight of the patch. The individual weight should not deviate significantly from average weight.

Folding endurance:

A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. 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

Individually weighed patches are kept in the desiccators having fused calcium chloride at room temperature for 24 hrs.

Drug content

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples. Flatness test 38-39 Flatness test is performed to determine the smoothness of the film. Three strips of the film one from the centre and two from the both sides of the film are to be cut and measured length wise. Variation in length is measured by finding out percent constriction. Zero percent constriction is considered equivalent to 100% flatness.

Thumb tack test

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

Shear Adhesion test

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung 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 take for removal, greater is the shear strength.

Peel Adhesion test

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. 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 force required for tape removed is measured. Peel adhesion is the force required to remove an adhesive coating from a test substrate. Adhesive should provide adequate contact of the device with the skin and should not damage the skin on removal. Peel adhesion properties are affected by the molecular wt. of the adhesive polymer, the type and amount of additives, and polymer composition. It is tested by measuring the force required to pull a single coated tape, applied to a substrate, at a 180 angle.

Rolling ball tack test

In this test a steel ball of 7/16 inch in diameter is rolled down an inclined having horizontally placed patch facing adhesive surface upward. The ball rolls down and runs horizontal distance on the patch. The distance run by the ball gives the tack property of the adhesive patch.

Quick Stick (peel-tack) test

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

Uniformity of dosage unit test

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2m membrane filter and analyzed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.

Polariscope examination

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

Skin Irritation study

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

A NOVEL APPROACH IN TRANSDERMAL DRUG DELIVERY: MICRO FABRICATED MICRO NEEDLES

The development of more sophisticated drugs has demanded the need for more sophisticated methods to deliver those drugs. Conventional drug delivery techniques using pills and injections are often not suitable for Transdermal protein based, DNA-based, and other therapeutic compounds produced by modern biotechnology. An attractive alternative method of delivery involves drug administration across the skin. This approach avoids degradation in the gastrointestinal tract and first-pass effects of the liver associated with oral delivery as well as the pain and inconvenience of intravenous injection.

Despite its many potential advantages, transdermal drug delivery is severely limited by the poor permeability of human skin; most drugs do not cross skin at therapeutically relevant rates. A number of methods have been developed to increase rates of transdermal transport with varied levels of success. Chemical enhancers can increase permeability of skin to small molecules but also trigger skin irritation or other safety concerns which limit their use. Iontophoresis employs an electric field to drive ionized molecules across skin by electrophoresis and nonionized molecules by electroosmosis. Despite concerns about skin irritation, Iontophoresis may be useful to deliver some peptides and small proteins. Recently, physical methods to transiently increase skin permeability using electroporation and ultrasound have shown promise for delivery of both small drugs and macromolecules.

In this study, we present a novel approach to transdermal drug delivery which dramatically enhances transport of molecules across skin. We have used standard micro fabrication techniques to etch arrays of micron-size needles into silicon. When these microneedle arrays are inserted into the skin, they create conduits for transport across the stratum corneum, the outer layer of skin which forms the primary barrier to transport. Once a compound crosses the stratum corneum it can diffuse rapidly through deeper tissue and be taken up by the underlying capillaries for systemic administration. The design of microneedles which painlessly permeabilize skin is based on an understanding of skin anatomy. Human skin is made of three layers: stratum corneum, viable epidermis, and dermis. The outer 10-15 ím of skin, called stratum corneum, is a dead tissue that forms the primary barrier to drug transport. Below lies the viable epidermis (50-100 ím),a tissue containing living cells and nerves, but no blood vessels. Deeper still, the dermis forms the bulk of skin volume and contains living cells, nerves, and blood vessels. Therefore, microneedles which penetrate the skin just a little more than 10-15 ím should provide transport pathways across the stratum corneum, but do so painlessly since the microneedles do not reach nerves found in deeper tissue.

Microneedles were made using micro fabrication technology, which is the same technology used to make integrated circuits. An advantage of this approach is that micro fabrication readily makes structures of micron dimensions in a way that is easily scaled up for cheap and reproducible mass production. To adapt this technology for transdermal drug delivery, we created three-dimensional arrays of sharp-tipped microneedles of approximately 150 ím in length.

A deep reactive ion etching process was used to micro fabricate the needles for this study. In this process, a chromium masking material is deposited onto silicon wafers and patterned into dots which have a diameter approximately equal to the base of the desired microneedles. The wafers are then loaded into a reactive ion etcher and subjected to carefully controlled plasma based on fluorine/oxygen chemistries to etch very deep, high aspect ratio valleys into the silicon. Those regions protected by the metal mask remain and form the microneedles.

CONCLUSION

This article provide an valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who are involved in TDDS. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs.

To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system. Transdermal drug delivery represents one of the most rapidly advancing areas of novel drug delivery. Due to recent advances in technology and the ability to deliver the drug systemically without rupturing the skin membrane, transdermal route is becoming a widely accepted route of drug administration. TDDS are designed for controlled release of drug through the skin into systemic circulation maintaining consistent efficacy. It offers the delivery of drug at lowered dose that can save the recipient from the harm of large doses with improved bioavailability. This may be achieved by by-passing the hepatic first metabolism. Almost all major and minor pharmaceutical companies are developing TDDS.

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