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TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

A transdermal patch may be a medicated adhesive patch that is placed on the skin to deliver a particular dose of medication through the skin and into the blood. Often, this promotes healing to an injured area of the body. A plus of a transdermal drug delivery route over alternative forms of medication delivery like oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, sometimes through either a porous membrane covering a reservoir of medication or through body heat melting skinny layers of medication embedded within the adhesive. Transdermal drug delivery offers controlled release of the drug into the patient, it permits a gradual blood level profile, leading to reduced general aspect effects and, sometimes, improved efficacy over alternative dosage forms. The main objective of transdermal drug delivery system is to deliver medication into circulation through skin at predetermined rate with minimal inter and intrapatient variations.

Keywords: Topical, Reservoir, Transdermal, Epidermis

INTRODUCTION:

Throughout the past few years, interest within the development of novel drug delivery systems for existing drug molecules has been revived. The event of a unique delivery system for existing drug molecules not solely improves the drug's performance in terms of effectiveness and safety however additionally improves patient compliance and overall therapeutic profit to a big extent. Transdermal Drug Delivery System (TDDS) are defined as self contained, distinct dose forms which are also called as "patches" once patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the circulation. TDDS are dosage forms designed to deliver a therapeutically effective quantity of drug across a patient's skin.

The main objective of transdermal drug delivery system is to deliver drugs into circulation through skin at planned rate with least inter and intra patient variation. Presently transdermal delivery is one among the foremost promising ways for drug application. It reduces the load that the oral route normally places on the alimentary tract and liver. It enhances patient compliances and minimizes harmful facet effects of a drug caused from temporary over dose and is convenience in transdermal delivered drugs that need just only once weakly application.

That will improve bioavailability, a lot of uniform plasma levels, longer length of action leading to reduction in dosing frequency, reduced facet effects and improved medical care because of maintenance of plasma levels up to the tip of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. Transdermal delivery not solely provides controlled, constant administration of drugs, however additionally permits continuous input of medicine with short biological half lives and eliminates periodic entry into circulation, which regularly causes undesirable facet effects. Many necessary benefits of transdermal drug delivery are limitations of hepatic first pass

metabolism, improvement of therapeutic effectuality and maintenance of steady plasma level of drug.The developments of TDDS may be a multidisciplinary activity that encompasses elementary practicability studies ranging from the choice of drug molecule to the demonstration of sufficient drug flux in an ex vivo and in vivo model followed by fabrication of a drug delivery system that meets all the tight desires that are specific to the drug molecule (physicochemical, stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most vital economy.

The first transdermal system, Transderm SCOP was approved by FDA in 1979 for the prevention of nausea and expulsion related to travel. Most transdermal patches are designed to release the active ingredient at a zero order rate for a period of many hours to days following application to the skin. This can be particularly advantageous for prophylactic medical care in chronic conditions. The proof of transdermal drug absorption could also be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites within the excrement and through the clinical response of the patient to the administered drug medical care.

Transdermal route and drug delivery prospects

Skin:

The largest organ:

The skin is the largest organ of the body that covers a surface area of approximately 2 sq.m. and receives about one third of the blood circulation through the body. It is a porosity barrier against the percutaneous absorption of assorted chemical and biological agents. It is one amongst the foremost without delay obtainable organs of the body with a thickness of few millimeters (2.97 0.28 mm) that,

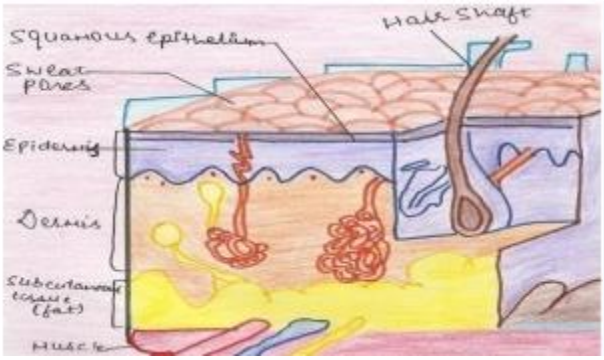
- ✓ Separates the underlying blood circulation network from the outside environment.
- ✓ Serves as a barrier against physical, chemical and microbiological attacks.
- ✓ Acts as a thermostat in maintaining temperature.
- ✓ Plays role within the regulation of blood pressure.
- ✓ Protects against the penetration of ultraviolet rays.
- ✓ Skin may be a major factor in determining the various drug delivery aspects like permeation and absorption of drug across the dermis. The diffusional resistance of the skin is greatly keen about its anatomy and ultrastructure.

Anatomy of Skin:

The structure of human skin will be categorised into four main layers

- ✓ The epidermis
- ✓ The viable epidermis
- ✓ A non-viable epidermis (Stratum horny layer)
- ✓ The overlying dermis

The innermost subcutaneous fat layer (Hypodermis)

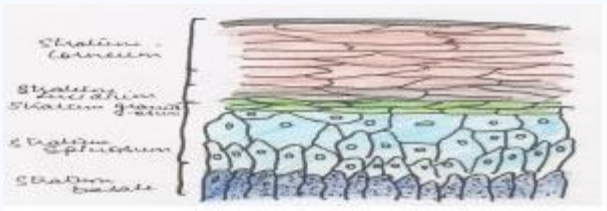


SCHEMATIC REPRESENTATION OF SKIN AND ITS APPENDAGES

The Epidermis:

The cuticle could be a frequently self-renewing, stratified squamous epithelial tissue covering the whole outer surface of the body and primarily composed of 2 parts: the living or viable cells of the stratum basale (viable epidermis) and therefore the dead cells of the stratum corneum commonly referred to as the horny layer.
Viable epidermis is mainly classified into four distinct layers

- ✓ Stratum lucidum
- ✓ Stratum granulosu
- ✓ Stratum spinosu
- ✓ Stratum basale

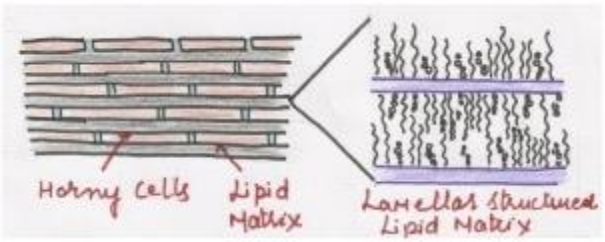


SCHEMATIC REPRESENTATION OF ANATOMY OF EPIDERMIS

Stratum corneum:

This is the outmost layer of skin conjointly known as as horny layer. It is the rate limiting barrier that restricts the inward and outward movement of chemical substances. The barrier nature of the horny layer depends critically on its constituents: 75-80% proteins, 5-15% lipids, and 5-10% ondansetron material on a dry weight basis.

Stratum corneum is roughly 10mm thick once dry however swells to many times once absolutely hydrous. It is versatile however comparatively impermeable. The design of stratum could also be sculptural as a wall-like structure with macromolecule bricks and supermolecule mortar. It consists of horny skin cells (corneocytes) that are connected via desmosomes (protein-rich appendages of the cell membrane). The corneocytes are embedded in a lipid matrix that plays a significant role in determining the porousness of substance across the skin.



SCHEMATIC REPRESENTATION OF MICROSTRUCTURE OF STRATUM CORNEUM

Viable epidermis:

This is settled below the corneum and varies in thickness from 0.06 mm on the eyelids to 0.8mm on the palms. Going inwards, it consists of varied layers as stratum lucidum, stratum granulosum, stratum spinosum, and also the stratum basale. Within the basale layer, cellular division of the cells perpetually renews the stratum and this proliferation compensates the loss of dead horny cells from the skin surface. As the cells made by the basale layer move outward, they itself alter morphologically and histochemically, undergoing keratinisation to make the outmost layer of corneum.

SCHEMATIC REPRESENTATION OF DIFFERENT LAYERS OF EPIDERMIS

Dermis:

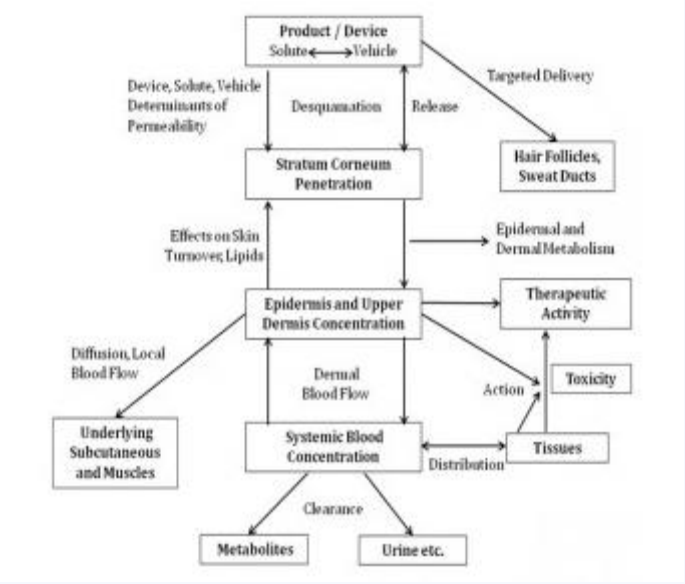
Dermis is that the layer of skin simply below the cuticle that is three to five mm thick layer and consists of a matrix of connective tissues, that contains blood vessels, humour vessels, and nerves. The cutaneous blood supply has essential function in regulation of blood heat. It conjointly provides nutrients and oxygen to the skin, whereas removing toxins and waste merchandise. Capillaries reach to inside 0.2 mm of skin surface and supply sink conditions for many molecules penetrating the skin barrier. The blood offer therefore keeps the dermal concentration of permeate terribly low, and therefore the ensuing concentration distinction across the cuticle provides the essential drive for transdermal permeation. In terms of transdermal drug delivery, this layer is usually viewed as essentially gelled water, and therefore provides a borderline barrier to the delivery of most polar medication, though the dermal barrier is also vital once delivering extremely lipophillic molecules.

Hypodermis:

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It is a fat cargo deck. This layer helps to manage temperature, provides organic process support and mechanical protection. It carries principal blood vessels and nerves to skin and will contain sensory pressure organs. For transdermal drug delivery, drug must penetrate through all 3 layers and reach in circulation.

Percutaneous absorption:

Before a locally applied drug will act either locally or systemically, it should penetrate through horny layer. Percutaneous absorption is outlined as penetration of drugs into numerous layers of skin and permeation across the skin into circulation. Percutaneous absorption of drug molecules is of explicit importance in transdermal drug delivery system as a result of the drug must be absorbed to an adequate extent and rate to achieve and maintain uniform, systemic, therapeutic levels throughout the period of use. Normally once drug molecule cross the stratum tissue layer barrier, passage into deeper dermal layers and general uptake happens comparatively quickly and simply.



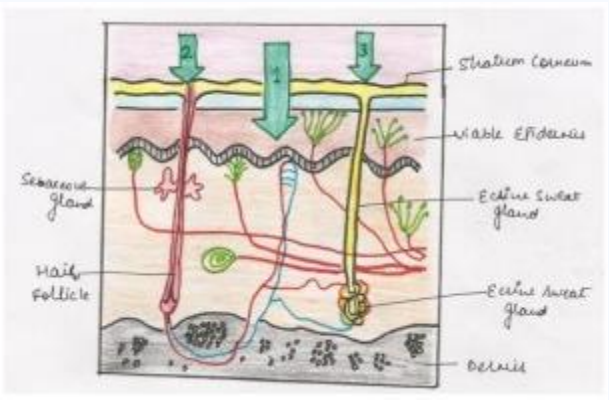
SCHEMATIC REPRESENTATION OF PERCUTANEOUS PERMEATION

The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the circulation could be a multistep method that involves:

- ✓ Dissolution within and release from the formulation
- ✓ Partitioning into the skin's outmost layer, the stratum corneum (SC)
- ✓ Diffusion through the SC, mainly via a lipidic intercellular pathway.
- ✓ Partitioning from the SC into the aqueous viable epidermis, diffusion through the viable epidermis and into the upper dermis, uptake into the papillary dermis (capillary system) and into the microcirculation.

Routes of drug penetration through skin:

In the method of transcutaneous permeation, a drug molecule might go through the stratum itself or might get diffuse through shunts, notably those offered by the comparatively widely distributed hair follicles and eccrine glands. Within the initial transient diffusion stage, drug molecules might penetrate the skin along the hair follicles or sweat ducts and so absorbed through the follicular epithelium and also the sebaceous glands. Once a gradual state has been reached the diffusion through the intact corneum becomes the first pathway for transdermal permeation



POSSIBLE MACRO ROUTES FOR DRUG PENETRATION 1) INTACT HORNY LAYER, 2) HAIR FOLLICLES AND 3) ECCRINE SWEAT GLANDS

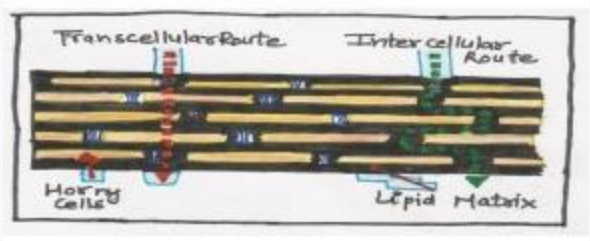
For any molecules applied to the skin, 2 main routes of skin permeation is defined:

Transepidermal route

Transfollicular route

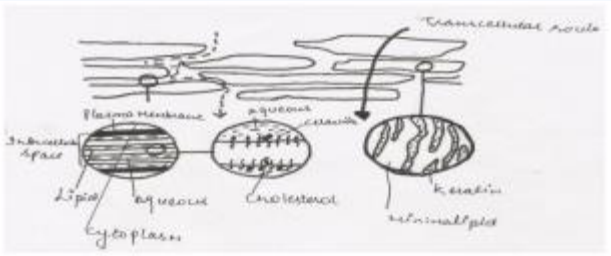
Transepidermal route:

In transepidermal transport, molecules cross the intact stratum corneum. Two potential micro-routes of entry exist, the transcellular (or intracellular) and the intercellular pathway.



SCHEMATIC REPRESENTATION OF TRANSEPIDERMAL ROUTE

Both polar and non-polar substances diffuse via transcellular and intercellular routes by totally different mechanisms. The polar molecules in the main diffuse through the polar pathway consisting of "bound water" within the hydrous corneum whereas the non-polar molecules dissolve and diffuse through the non-aqueous lipid matrix of the corneum. Therefore the principal pathway taken by a penetrant is set in the main by the partition constant (log K). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophillic permeants (octanol/water log K > 2) traverse the corneum via the intercellular route. Most molecules pass the corneum by each routes.



POSSIBLE MICRO ROUTES FOR DRUG PENETRATION ACROSS HUMAN SKIN INTERCELLULAR OR TRANSCELLULAR.

Transfollicular route (Shunt pathway):
This route includes transport via the sweat glands and also the hair follicles with their associated oily glands. Though these routes supply high porousness, they are thought-about to be of minor importance due to their comparatively tiny space, approximately 0.1% area of the entire skin. This route looks to be most vital for ions and enormous polar molecules that hardly permeate through the horny layer.

Barrier functions of the skin:
The top layer of skin is most important function in maintaining the effectiveness of the barrier. Here the individual cells overlie one another and area unit tightly packed, preventing bacterium from entry and maintaining the water holding properties of the skin. Horny layer principally consists of the keratinized dead cell and water content is additionally less as compared to the other skin elements. Lipids are secreted by the cells from the bottom layer of the skin to the highest. These lipid molecules link up and form a troublesome connective network, in effect acting as the mortar between the bricks of a wall.

Basic Principles of transdermal permeation:
Transdermal permeation is predicated on passive diffusion. Skin is the most intensive and readily accessible organ of the body as solely a fraction of millimetre of tissue separates its surface from the underlying capillary network. The discharge of a therapeutic agent from a formulation applied to the skin surface and its transport to the circulation could be a multistep method, which incorporates

1) Diffusion of drug from drug to the rate controlling membrane.

2) Dissolution at intervals and release from the formulation.

3) Natural action by horny layer and penetration through viable epidermis.

4) Uptake of drug by capillary network within the dermal outgrowth layer.

5) Effect on the target organ.

6) Partitioning into the skin's outer layer, the horny layer.

7) Diffusion through the horny layer, principal via a lipidic intercellular pathway.

Properties that influence transdermal delivery:

1. Release of the medication from the vehicle
2. Penetration through the skin barrier.
3. Activation of the pharmacological response.

Advantages of transdermal drug delivery:

- ✓ Transdermal drug delivery permits the shunning of duct absorption with its associated pitfalls of enzymatic and pH scale associated deactivation.
- ✓ Avoidance of first pass metabolism.
- ✓ The lack of peaks in plasma concentration will cut back the danger of aspect effects, therefore medicine that need comparatively consistent plasma levels are excellent candidate for transdermal drug delivery.
- ✓ As a substitute for oral route.
- ✓ The patch additionally allow constant dosing instead of the peaks and valley in medication level related to orally administered medication.
  Rapid notifications of medication within the event of emergency as well as the capability to terminate drug effects quickly via patch removal.
- ✓ Avoidance of gastro intestinal incompatibility.
- ✓ Convenience particularly notable in patches that need just one occasion weekly application, such an easy dosing regimen will aid in patient adherence to drug medical care.
- ✓ Minimizing undesirable aspect effects.
- ✓ Provide utilization of drug with short biological half lives, narrow therapeutic window.
- ✓ Avoiding in drug fluctuation drug levels.
- ✓ Inter and intra patient variation.
- ✓ Termination of therapy is easy at any point of time.
- ✓ Provide quality for self administration.
- ✓ They are non invasive, avoiding the inconvenience of parentral medical care.
- ✓ The activity of medicine having a short half life is extended through the reservoir of drug within the therapeutic delivery system and its controlled release.
- ✓ It is of great advantages in patients who are sick or unconscious.

- ✓ Transdermal patches are better way to deliver substances that are broken down by the abdomen aids, not well absorbed from the gut, or extensively degraded by the liver.
- ✓ Transdermal patches are cost effective.

Disadvantages of transdermal drug delivery:

- ✓ Transdermal drug delivery system cannot deliver ionic drugs.
- ✓ It cannot reach high drug levels in blood.
- ✓ It cannot develop for medication of huge molecular size.
- ✓ It cannot deliver drugs in a very pulsatile fashion.
- ✓ It cannot develop if drug or formulation causes irritation to skin.
- ✓ Possibility of local irritation at site of application.
- ✓ May cause allergic reaction.
- ✓ Sufficient aqueous and lipid solubility, a log P (octanol/ water) between one and three is needed for permeate to cross stratum corneum and underlying aqueous layer.
- ✓ Only potent drugs are appropriate candidates for transdermal patch owing to the natural limits of drug entry imposed by the skin's impermeability.
- ✓ Long time adherence is tough.

Factors affecting transdermal permeation

Biological factor:

Skin conditions:

The intact skin itself acts as barrier however several agents like acids, alkali cross the barrier cells and penetrates through the skin, many solvents open the advanced dense structure of corneum Solvents like alcohol, chloroform take away lipide fraction, forming artificial shunts through that drug molecules will pass simply.

Skin age:

It is seen that the skin of adults and young ones are more permeable than the older ones however there is no dramatic distinction .Children shows noxious effects owing to the larger surface area per unit body weight .Thus potent steroids, boric acid, bactericide have made severe facet effects.

Blood Supply:

Changes in peripheral circulation will have an effect on transdermal absorption.

Regional skin site:

Thickness of skin, nature of stratum and density of appendages vary site to site. These factors have an effect on penetration.

Skin metabolism:

Skin metabolizes steroids, hormones, chemical carcinogens and a few medicine. Thus skin metabolism determines effectivity of drug permeated through the skin.

Species differences:

The skin thickness, density of appendages and keratinization of skin vary species to species, thus affects the penetration.

Physicochemical factors:

Skin hydration:

In contact with water the permeableness of skin will increase considerably. Hydration is most significant issue increasing the permeation of skin. Therefore use of humectant is done in transdermal delivery.

Temperature and pH:

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

Diffusion coefficient:

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

Drug concentration:

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

Partition coefficient:

The best partition constant (K) is needed for good action. Drugs with high K are not able to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

Molecular size and shape:

Drug absorption is reciprocally associated with mass, small molecules penetrate quicker than large ones.

Environmental factors:

Sunlight:

Due to daylight the walls of blood vessels become thinner resulting in bruising with omly minor trauma in sun-exposed areas. Conjointly pigmentation: the foremost noticeable sun-induced pigment change may be a freckle or solar lentigo.

Cold Season:

Often result in itchy, dry skin. Skin responds by increasing oil production to compensate for the weather's drying effects. A decent moisturizer can facilitate ease symptoms of dry skin. Also, drinking millions of water will keep your skin hydrous and looking bright.

Air Pollution:

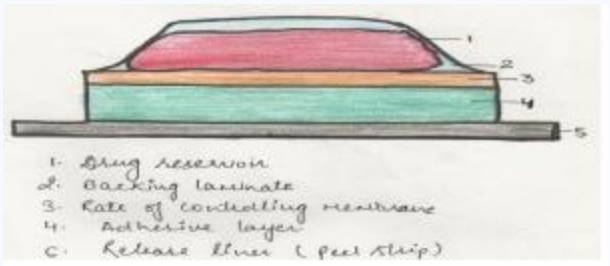
Dust will clog pores and increase microorganism on the face and surface of skin, each of that result in disease of the skin or spots. This affects drug delivery through the skin. Invisible chemical pollutants within the air will interfere with skin's natural protection system, breaking down the natural skin's oils that ordinarily trap moisture in skin and keep it supple.

Effect of heat on transdermal patch:

Heat induced high absorption of transdermal delivered drugs. Patient ought to be suggested to avoid exposing the patch application site to external heat supply like heated water baggage, predicament bottles. Even high temperature might also increase the transdermally delivered drugs. During this case the patch ought to be removed straight off.Transdermal drug patches are stored in their original packing and confine a cool, dry place till they are ready to use.

Formulation of transdermal drug delivery system:

Various elements of a transdermal drug delivery system are shown in below figure



SCHEMATIC REPRESENTATION OF COMPONENTS OF TDDS

Drug substance:

For successfully developing a transdermal drug delivery system, the drug ought to be choosen with guardianship. The subsequent are some of the desirable properties of a drug for transdermal delivery.

Physicochemical properties:

- ✓ The drug ought to have a relative molecular mass less than 1000 Daltons.
- ✓ The drug ought to have affinity for each lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conductive to successful drug delivery via the skin.
- ✓ The drug ought to have low melting point.
- ✓ Along with these properties the drug ought to be potent, having short half life and be non-irritating.

Biological Properties:

- ✓ Drug ought to be terribly potent ,i.e. it ought to be effective in few mg/day
- ✓ The drug ought to have short biological half life.
- ✓ The drug should not be irritant and non allergic to human skin.
- ✓ The drug ought to be stable once contact with the skin.
- ✓ They should not stimulate an immune reaction to the skin.
- ✓ Tolerance to the drug should not develop under near zero order release profile of transdermal delivery.
- ✓ Dose is less than 50 mg per day, and ideally less than 10 mg per day.
- ✓ The drug should not get irreversibly bound within the subcutaneous tissue.

- ✓ The drug should not get extensively metabolized within the skin.

Polymer matrix:
Polymers are the backbone of transdermal drug delivery system. System for transdermal delivery are made-up as multi layered polymeric laminates in ehich a drug reservoir or a drug polymer matrix is sandwitched between two polymeric layers, an outer imperviable backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive, or rate controlled membrane.

Ideal properties of a polymer to be employed in a transdermal system:

- ✓ Molecular weight, chemical practicality of the polymer ought to be such that the particular drug diffuses properly and gets discharged through it.
- ✓ The polymer ought to be stable.
- ✓ The polymer ought to be nontoxic
- ✓ The polymer ought to be simply of factory-made
- ✓ The polymer ought to be cheap
- ✓ The polymer and its deaggration product should be non virulent or non-antagonistic to the host.
- ✓ Large amounts of the chemical agent are incorporated into it.

Some ordinarily used chemical compound for TDD are shown in below table

USEFUL POLYMERS FOR TRANSDERMAL DEVICES

Natural Polymers	Synthetic Elastomers	Synthetic Polymers
Cellulose derivatives	Polybutadiene	Polyvinylalcohol
Arabino Galactan	Hydrinrubber	Polyethylene
Zein	Polysiloxane	Polyviny Chloride
Gelatin	Acrylonitrile	Polyacrylates
Proteins	Neoprene	Polyamide
Shellac	Chloroprene	Acetal copolymer
Strarch	Silicon rubber	Polysyrene

Penetration Enhancers:
These are compounds that promote the skin permeableness by altering the skin as barrier to the flux of a desired penetrate

Ideal properties of penetration enhancers:

- ✓ Controlled and reversible enhancing action
- ✓ Chemical and physical compatibility with drug and different pharmaceutical excipients
- ✓ Should not cause loss of body fluids, electrolytes or different endogenous materials
- ✓ Non toxic, non allergic, non irritating
- ✓ Pharmacological immobility
- ✓ Ability to act specifically for certain period Odorless, colorless, economical and cosmetically acceptable.

Some ordinarily used absorption enhancers for TDD shown in below Table

TYPES OF ABSORPTION ENHANCERS

Class	Examples	Mechanism	Transport Pathway
Surfactants	Na-lauryl sulfate Polyoxyethylene-9-laurylether, Bile salts: Na-deoxycholate Na-glycocholate Na-taurocholate	Transcellular Paracellular	Phospholipid acyl chain perturbation Reduction mucus viscosity, Peptidase inhibition
Fatty acids	Oleic acid, Short fatty acids	Transcellular Paracellular	Phospholipid acyl chain perturbation
Cyclodextrins	a-, b- and g cyclodextrins, Methylated b cyclodextrins	Transcelular Paracellular	Inclusion of membrane compounds
Chelating agents	EDTA, Polyacrylates	Transcellular Paracellular	Complexation of Ca^{2+} opening of tight junctions
Positively charged polymer	Chitosan salts, Trimethyl chitosan	Paracellular	Ionic interactions with negatively charged groups of glycocalix

Different excipients:

Various solvents like chloroform, methanol, acetone, isopropananol, and methylene chloride, are used to prepare drug reservoir. Additionally plasticizers like dibutylpthalate, propanediol are added to supply physical property to the transdermal patch.

Pressure sensitive adhesive:

A Pressure Sensitive Adhesive (PSA) may be a material that helps in maintaining an intimate contact between stratum system and also the skin surface. It ought to adhere with less than applied finger pressure, be sharply and permanentaly tachy, exert a robust holding force. Additionally, it ought to be removable from the graceful surface without leaving a residue e.g.: polyacrylamates, polyacrylates, polyisobutylene, polymer based adhesive. The choice of an adhesive relies on varied factors, as well as the patch style and drug formulation. PSA ought to be physicochemical and biologically compatible and will not alter drug unharness. The PSA may be positioned on the face of the device or within the back of the device and lengthening peripherally.

Backing laminates:

While planning a backing layer the consideration of chemical resistance and excipients may compatible as a result of the prolonged contact between the backing layer and also the excipients, drug or penetration enhancer through the layer. They must an occasional moisture vapour transmission rate. They have to have optimal elasticity, flexibility and durability. eg: metallic element vapour coated layer, a plastic film and heat real layer.

Release liner:

During storage release liner prevents the loss of drug that has migrated into the adhesive layer and contamination. However, because the liner is in intimate contact with the delivery system, it ought to suits specific necessities concerning chemical inertness and permeation to the drug, penetration enhancer and water.

Major transdermal systems:

Drug in adhesive system:

Single layer drug in adhesive:

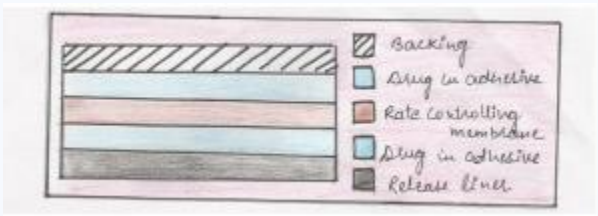
The adhesive layer of this technique contains the drug. In this type of patch the adhesive layer not solely serves to stick the entire various layers along, beside system to the skin, however is additionally responsible for releasing of the drug. The rate of release of drug from this kind of

system depends on the diffusion across the skin. The adhesive layer is enclosed by a temporary linear and a backing layer.

SINGLE LAYER ADHESIVE TRANSDERMAL DELIVERY SYSTEM

Multi layer drug in adhesion:

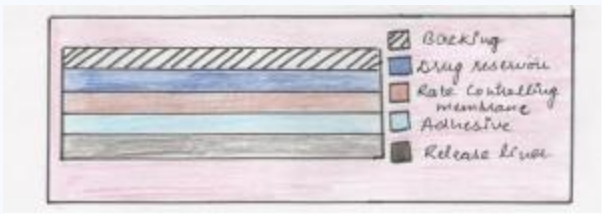
The multi-layer drug-in adhesive patch is analogous to the single-layer system therein each adhesive layers are responsible for the releasing of the drug. One of the layer is for immediate release of the drug and alternative layer is for control release of drug from the reservoir. The multi layer patch conjointly encompasses a temporary linear layer and a permanent backing.



MULTILAYERED DRUG IN ADHESIVE TRANSDERMAL SYSTEM

Reservoir:

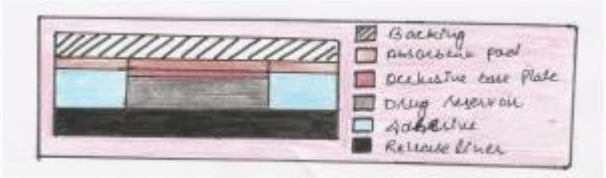
Unlike the single layer and multilayer drug in adhesive systems the reservoir transdermal system encompasses a separate drug layer. The drug layer may be a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is additionally backed by the backing layer. In this type of system the rate of release is zero order.



SCHEMATIC REPRESENTATION OF RESERVOIR TRANSDERMAL DELIVERY SYSTEM

Matrix:

The Matrix system design contains a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlying it. These form of patches are called monolithic device.



SCHEMATIC REPRESENTATION OF MATRIX TRANSDERMAL DELIVERY SYSTEM

Vapour Patch:

In this type of patch the adhesive layer not solely serves to adhere the varied layers along however conjointly to release vapour. The vapour patches are new on the market and that they unleash essential oils for up to 6 hours. The vapour patches unleash essential oils and are utilized in cases of decongestion mainly. Different vapour patches on the market are controlled

vapour patches that improve the standard of sleep. Vapour patches that cut back the number of cigarette that one smokes in a mouth are also available on the market.

Varied strategies for preparation of transdermal drug delivery system:

Asymmetric TPX membrane method:
A prototype patch will be fabricated by a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter used as the backing membrane. Drug sample is distributed into the pouch-shaped membrane, coated by a TPX asymmetric membrane, and sealed by an adhesive.

Asymmetric TPX membrane preparation
These are fabricated by using the dry/wet inversion method. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°c to create a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardener knife. At that time the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed directly in coagulation bath [maintain the temperature at 25°C]. After ten minutes of immersion, the membrane will be removed, air dry in a very circulation oven at 50°C for 12 hrs].

Circular teflon mould method:
Solutions containing polymers in varied ratios are utilized in an organic solvent. Calculated quantity of drug is dissolved in half the quantity of same organic solvent. Enhancers in numerous concentrations are dissolved within the other half of the organic solvent and then added. Di-N-butylphthalate is added as a plasticiser into drug polymer solution. The full contents are to be stirred for 12 h and so poured into a circular teflon mould. The moulds are placed on a leveled surface and covered with an inverted funnel to manage solvent vaporization in a very streamline flow hood model with speed of air 1/2 m /sec. The solvent is allowed to evaporate for 24 h. Before analysis the dried films are to be stored for an additional 24 h at 25±0.5 °C in desiccators containing silica gel before to eliminate aging effects. These styles of films are to be evaluated within one week of their preparation.

Mercury substrate method:
In this technique drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 min to provide a homogenised dispersion and poured in to a leveled mercury surface. Then the solution is roofed with inverted funnel to regulate solvent evaporation.

By using "IPM membranes" method:
In this technique drug is dispersed in a mixture of water and antifreeze containing carbomer 940polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutral and made viscous by the addition of triethanolamine. Buffer pH 7.4 is utilized in order to get solution gel, if the drug solubility in aqueous solution is incredibly poor. The formed gel are going to be incorporated within the IPM membrane.

By using "EVAC membranes" method:
In order to organize the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes is used as rate management membranes. If the drug is not soluble in water, propylene glycol is employed for the preparation of gel. Drug is dissolved in propylene glycol, carbopol organic compound will be added to the above solution and neutralized by using 5%w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the desired space. A rate controlling membrane are going to be placed over the gel and also the edges are going to be sealed by heat to get a leak proof device.

Aluminium backed adhesive film method:
Transdermal drug delivery system could manufacture unstable matrices if the loading dose is larger than 10 mg. Aluminium backed adhesive film technique is a suitable one for preparation of same, chloroform is alternative of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material are going to be superimposed to the drug solution and dissolved. A custammade aluminium former is lined with aluminium foil and also the ends blanked off with tight-fitting cork blocks.

Preparation of TDDS by using proliposomes:
The proliposomes are prepared by carrier technique using film deposition technique. From the earlier reference drug and lecithin within the ratio of 1:2 is used as an optimized ratio. The proliposomes are prepared by taking 5mg of mannitol powder in a 100ml spherical bottom

flask that is kept at 60-70 °C temperature and also the flask is revolved at 80-90 rpm and dried the mannitol at vacuum for 30 min. After drying, the temperature of the water tub is adjusted to 20- 30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture. Aliquot of 0.5 ml of the organic solution is introduced into the round-bottomed flask at 37°C containing mannitol after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and later drug loaded mannitol powders (proliposomes) are placed in desiccators over night and so sieved through a 100 mesh. The collected powder is transferred in to a glass bottle and stored at the freeze temperature till characterization.

By using free film method:

Free film of cellulose ester is prepared by casting on mercury surface. A polymer solution 2% w/w is ready by using chloroform. Plasticizers are incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring that is placed over the mercury surface in a glass petri dish. The speed of evaporation of the solvent is controlled by putting an inverted funnel over the petridish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film are going to be separated out and keep between the sheets of paper in desiccators till use. Free films of various thickness is ready by changing the volume of the polymer solution .

Desirable options for transdermal patches:

- Composition comparatively invariant in use.
- System size cheap.
- Defined web site for application.
- Application technique extremely reproducible.
- Delivery is zero order.
- Delivery is economical.

Conditions during which patches are used:

- When the patient has intolerable aspect effects (including constipation) and who is unable to oral medication (dysphagia) and is requesting an alternate technique of drug delivery.
- Where the pain management could be improved by reliable administration. This could be helpful in patients with psychological feature impairment or those who for alternative reasons do not seem to be able to self-medicate with their physiological state.
- It can be often utilized in combination with alternative improvement methods to produce synergistic effects.

Conditions during which patches do not seem to be used:

- Cure for acute pain is needed.
- Where rapid dose volumetric analysis is needed.
- Where demand of dose is equal to or less than 30 mg/24 hrs.

Evaluation of transdermal patches:

The transdermal patches are often characterised in terms of following parameters

- ✓ Physicochemical evaluation
- ✓ In vitro evaluation
- ✓ In vivo evaluation

Physicochemical evaluation:

Transdermal patches are often physicochemically evaluated in terms of these parameters:

- ✓ **Thickness:**
  The thickness of transdermal film is determined by motion magnifier, dial gauge, screw gauge or micrometer at totally different points of the film.

- ✓ **Uniformity of weight:**

Weight variation is studied by individually weighing ten arbitrarily designated patches and calculating the average weight. The individual weight must not deviate considerably from the average weight.

- ✓ **Drug content determination:**
  An accurately weighed portion of film (about 100 mg) is dissolved in 100ml of appropriate solvent in which drug is soluble so the solution is jolted incessantly for 24 h in shaker setup. Then the entire solution is sonicated. When sonication and consequent filtration, drug in solution is estimated spectrophotometrically by applicable dilution.

- ✓ **Content uniformity test:**
  10 patches are designated and content is decided 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% to125% of the specified value, then stratum patches pass the test of content uniformity. However if three patches have content within the range of 75% to 125%, then further twenty patches are tested for drug content. If these twenty patches have range from 85% to 115%, then the stratum patches pass the test.

- ✓ **Moisture content:**
  The ready films area weighed severally and kept in desiccators containing salt at room temperature for 24 h. The films are weighed once more when a such interval till they show a constant weight. The percent moisture content is calculated using 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 till a constant weight is achieved. % moisture uptake is calculated as given below.

  % Moisture uptake = Final weight – Initial weight X 100

- ✓ **Flatness:**
  A transdermal patch ought to possess a sleek surface and should not constrict with time. This could be incontestable with flatness study. For flatness determination, one strip is cut from the centre and two from either side of patches. The length of every strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is like 100 percent flatness.

  % constriction = I1 – I2 X 100

  I2 = Final length of every strip

  I1 = Initial length of every strip

✓ **Folding Endurance:**

Evaluation of folding endurance involves determining the folding capability of the films subjected to frequent extreme conditions of folding. Folding endurance is decided by repeatedly folding the film at a similar place till it break. The number of times the films may be folded at a similar place without breaking is folding endurance value.

✓ **Tensile Strength:**

To determine tensile strength, polymeric films area unit sandwiched singly by corked linear iron plates. One finish of the films is kept fixed with the assistance of an iron screen and alternative finish is connected to a freely movable thread over a pulley-block. The weights are added bit by bit to the pan hooked up with the hanging finish of the thread. A pointer on the thread is employed to measure the elongation of the film. The load simply enough to break the film is noted.

✓ **Tack properties:**

It is the flexibility of the polymer to adhere to substrate with very little contact pressure. Tack relies on relative molecular mass and composition of polymer as well as on the use of tackifying resins in polymer.

✓ **Thumb tack test:**

The force needed to get rid of thumb from adhesive is a measure of tack.

✓ **Rolling ball test:**

This test involves measurement of the gap that chrome steel ball travels along an upward facing adhesive. The less tacky the adhesive, the more the ball can travel.

✓ **Quick stick (Peel tack) test:**

The peel force needed 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.

✓ **Probe tack test:**

Force needed to probe away from an adhesive at a hard and fast rate is recorded as tack.

In vitro release studies:

Transdermal patches may be in vitro evaluated in terms of Franz diffusion cell. The cell consists of two compartments: donor and receptor. The receptor compartment contains a volume of 5-12ml and effective surface area of 1-5 cm2. The diffusion buffer is incessantly stirred at 600rpm by a magnetic bar. The temperature within the bulk of the solution is maintained by current regulated water through a water jacket that surrounds the receptor compartment. The drug content is analyzed using appropriate methodology, maintenance of sink condition is important.

In vivo Studies:

Transdermal patches may be in vivo evaluated in terms of in vivo evaluations are true depiction of the drug performance. The variables that cannot be taken into consideration throughout in vitro studies may be totally explored throughout in vivo studies. In vivo analysis of TDDS may be carried out using animal models human volunteers.

Animal models:

Considerable time and resources are needed to hold out human studies, thus animal studies are most popular at small scale. The foremost common animal species used for evaluating transdermal drug delivery system are mouse, depilous rat, depilous dog, depilous macaque, rabbit, guinea pig etc. Varied experiments conducted ends up in a conclusion that depilous animals are most popular over furry animals in each in vitro and in vivo experiments. Macaque is one in all the foremost reliable models for in vivo evaluation of transdermal drug delivery in man.

Human model:

The final stage of the development of a transdermal device involves assortment of pharmacokinetic and pharmacodynamic information following application of the patch to human volunteers. Clinical trials are conducted to assess the effectiveness, risk concerned, facet effects, patient compliance etc. Phase I clinical trials are conducted to see principally safety in volunteers and phase II clinical trials determine short term safety and principally 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 finished marketed patches to discover adverse drug reactions. Although human studies need extensive resources best to assess the performance of the drug.

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