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TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Transdermal drug delivery systems are topically administered medicament. Transdermal patches deliver the drug for systemic effects at a predetermined & controlled rate. characterization of transdermal patch is use to check it is quality, size, time of onset & duration, adhesive property, thickness, weight of patch, moisture of content, uniformity and cutaneous toxicological studies. Drug delivery through the skin to achieve a systemic effect of a drug is commonly called as transdermal drug delivery & differs from traditional topical drug delivery. Topical administration of therapeutic agent offers much advantage over conventional oral & invasive method of drug delivery. An increasing number of TDD products continue to delivery real therapeutic benefit to patient around the world

INTRODUCTION

Dermis is also called as corium. it is the sensitive highly vascular part of skin located just below the stratum basal of epidermis. it is good to have a fine-grained & smooth skin with fine pores. a healthy skin is slightly moist, soft, flexible and slightly acidic in reaction. It serves the body in so many ways that it is one of largest organ of the body. Stratum corneum is the outermost layer of epidermis. it is an effective barrier against light , heat, bacteria, water & many chemicals. stratum lucidum are filled with keratin stratum corneum & consists of 3 to 5 layers of clear, flat, dead cells, lacking granules & nuclei. stratum basal is the inner most layer of epidermis. & is made up of dividing stem cells & melanocytes. epidermis is made up of keratinocytes.(1)

Transdermal drug delivery system are drug loaded adhesive patches which, when applied to the skin, deliver the therapeutic agent, at a controlled rate, through the skin to the skin to the systemic circulation & to the target organ.(2) Transdermal patch is also called as skin patch uses a special membrane to control the rate at which the liquid contained in the reservoir within the patch can pass through the skin and into the bloodstream.(4) Transdermal drug delivery system as compared to their corresponding oral or in injectable dosage forms counterparts.(2) Dermis & transdermal delivery of large molecule such as peptide, protein, & DNA has remained a significant challenge.(8) Transdermal route has vied with oral treatment as the most successful innovative research area in drug delivery, as oral treatment involves attainment & maintenance of drug concentration in the body within a therapeutically effective.(5) Transdermal drug delivery is an appealing alternative to minimize & avoid the limitation allied with oral & parenteral administration of drugs. later delivery systems, suffer from certain restrictions like peak and valley phenomenon that is they exhibit fluctuations in plasma drug levels & do not render sustained.(6) Transdermal patches have been useful in developing new application for therapeutics & for reducing first-pass drug-degradation effect.(4) To overcome these difficulties there was a need for the development of new drug delivery system, which can improve the therapeutic efficacy and safety of drug by more precise spatial & temporal placement within the body thereby reducing both the size and number of doses.(7) Today there exist a number of patches for drug such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, scopolamine, & 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.(4) In

the form of patches that deliver drugs for systemic effect at a predetermined and controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered patches work in a very simple way. A drug is applied in a relatively high dosage to the inside of patch, which is work on the skin for an extended period of time.(7) In TDD application, adhesives are used to maintain intimate contact between the patch & the skin surface. many classes of adhesives are available that might be considered for use with TDD patches, although in practice pressure sensitive adhesives are preferred. pressure sensitive adhesive are generally defined as materials that adhere to a substrate with light pressure & which leave no residual adhesive upon their removal.(7) The components of TDDS are liners, adherents, drug reservoirs, drug release membrane. That play important role in the imperative release of the drug through the skin. It is cosidered that a well designed TDDS can supply the drug at a rate, to sustain the required therapeutic plasma concentration without much fluctuation that may cause basic manifestation or therapeutic inefficacy lag time to reach steady state fluxes are in hours as the transport of most drug across the skin is very slow.(6) The degree of keratinization is largely under genetic control. however, intermitted pressure, or abrasion, stimulates production of keratinized cells. The zone of keratinization involves stratum granulosum, stratum lucidum & stratum corneum.(1)

Definition:- A transdermal patch or skin patch is a medicated adhesive patch that is places on the skin to deliver a specific dose of medication through the skin & into the bloodstream.

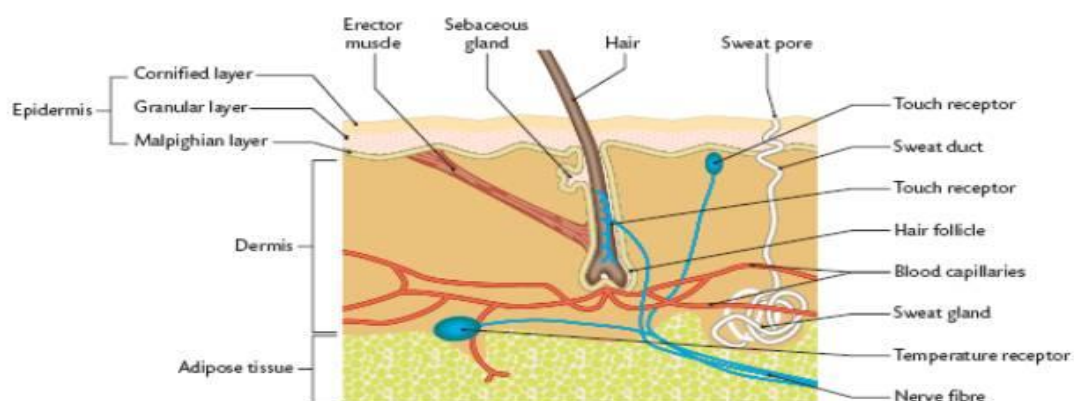


Fig.1: Structure of Skin

The Layers of Skin

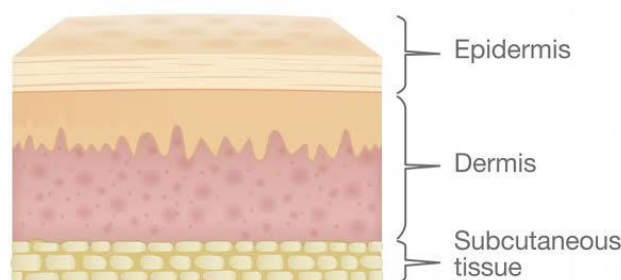


Fig.2: Structure of layers of Skin

Basic components of transdermal drug delivery system

1) Polymer matrix or matrices:-

Polymers are employed in skin preparation & it strengthens the foundation of TDDS. Polymer selection & design are of prime important in this system. The polymer should be stable, non reactive with the drug, easily manufactured & fabricated into desired product, & inexpensive. Polymers are utilized in TDDS in versatile manner including as rate controlled membranes, adhesives. The element way to control the release of a drug is to disperse through an inert polymeric matrix. the drug is physically blended with polymeric powder and the medicated polymer is then molded into a medicated disc with a defined surface area and controlled thickness. an inverse relationship is thus observed between the release rate and membrane thickness the diffusion properties of the membrane are used to ensure availability of the drug and excipients to the skin. The adhesive a vital component plays an intimate contact between the delivery system with the skin. The adhesion of TDDS is one of the critical factors to the safety, efficacy and quality of the product. It is related to drug delivery and therapeutic effect. It carries the drug which can either be dispersed or dissolved in the matrix or the compartment containing drug is separated from the adhesive layer by a diffusion controlling membrane. The development of new polymers which include hydrogen hydrophilic polymers, and polyurethanes. During storage the patch is covered by the protective liner that is removed and discarded before the application of the patch to the skin since the liner is in intimate contact with the TDDS. Other materials used for TDDS release liner include polyester foil and metalized laminate. Backings are chosen for appearance,

flexibility and need for occlusion. it causes the TDDS to lift and may possibly irritate the skin during long term use.

2) Drug:

Transdermal delivery of drugs has taken a surge of popularity nowadays. various physiochemical, pharmacokinetic & pharmacological properties of the drug are considered for TDS development. Transdermal delivery is limited to drugs used in low doses.

3) Penetration enhancer:-

These are compound with promote skin permeability by altering the skin as a barrier to the flux of a desired penetrate. Penetration enhancers are incorporate into a formulation to improve the diffusivity & solubility of drug through the skin that would reversibly reduce the barrier resistance of the skin. Desirable properties for penetration enhancer acting within the skin should be non-irritant, non-sensitizing, non phototoxic & non-comedogenic ideally work rapidly & the activity & duration of effect should be both predictable & reproducible. Have no pharmacological activity within the body.

4) Other excipients:-

Plasticizers have also been used in much formulation ranging from 5 to 20% (w/w dry basis) along with the brittleness & ductility of the film it is also responsible for adhesiveness of the film with other surface or membrane & improvement in strengths of film some of the example are glycerol or sorbitol.

5) Membrane:-

A membrane may be sealed to the backing to form a pocket to enclose the drug containing matrix or used as a single layer in the patch construction.

6) Permeation enhancer

7) Pressure sensitive adhesive

8) Backing laminates

9) Release liner



Fig. 3: Basic components of transdermal system

Limitation of TDDS

- 1) Clinical need is another area that has to be examined carefully before a along with a number of drug may be administered by transdermal route.
- 2) Heavy drugs molecules usually difficulty to penetrate the stratum cornea.
- 3) Drugs with very low or high partition coefficient fail to reach blood circulation.
- 4) Drugs that are highly melting can be given by this route due to their low solubility both in water & fat
- 5) Many approaches have been attempted to deliver medicament across skin barrier & enhance the efficacy. (2)

Parameters of TDDS

- 1) Hydration state of skin.
- 2) pH of the drug.
- 3) Drug metabolism by skin flora.
- 4) Lipid solubility.
- 5) Drug depot in skin.
- 6) Size of the molecule that is to be administered.
- 7) Thickness.
- 8) Integrity of the stratum cornea epidermidis. (2)

Approaches:

Several technologies have been successfully to provide a rate control over the release & the transdermal permeation of drugs.

1) Adhesive dispersion type system:-

The consist of drug impermeable backing membrane the drug reservoir which is prepared by directly dispersing the drug in an adhesive polymer & then spreading the medicated adhesive by solvent casting or hot melting onto a flat sheet of drug impermeable backing to form a thin drug reservoir layer.

2) Membrane permeation-controlled system:-

The drug reservoir is totally embedded in a compartment molded between a drug impermeable backing laminate and a rate controlling polymeric membrane. the drug molecule are permitted to release across the rate controlling membrane simply by diffusion process through the pores. the release rate from this type of TDS can be tailored by varying the

polymer composition, permeability coefficient & thickness of the rate controlling membrane & adhesive.

3) Matrix diffusion controlled system:-

The drug reservoirs are prepared homogeneously by dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then molded into a medicated disc with a defined surface area & controlled thickness. The dispersion of drug particles in polymer matrix can be accomplished by either homogeneously mixing the finely ground drug particles in polymer or a highly viscous base polymer followed by cross linking of the polymer chains or homogeneously blending drug solids with a rubbery polymer at an elevated temperature and under vacuum. The polymer disc which contains drug reservoir is fixed onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. (6)

Circulation of Skin

Blood supply towards skin serves two main purposes- It provides nutrient flow & regulates heat loss. Most blood supply to the skin is controlled neurogenically & not metabolically.

The local cooling of the skin causes local reflex vasoconstriction even in the absence of a change in core temperature. Also application of local heat causes local vasodilatation. The skin is greatly under control of the autonomic nervous system. The sympathetic vasoconstriction can reduce the total flow of blood through the skin to less than 20 ml/min. The inhibition of this sympathetic vasoconstriction due to heat, results in a widespread passive vasodilatation. The skin is well-supplied with lymph vessels that drain lymph & transmit the fluid to the deeper lymphatic system, returning the lymph to veins. (3)

Drug acting on skin

1) Demulcents

Inert substances which soothe inflamed skin by preventing contact with air/irritants in the surrounding. Propylene glycol is a clear, viscous liquid, miscible with water as well as some oils that are used in cosmetics. Glycerin is a clear, sweet, viscous liquid. Undiluted glycerin has a dehydrating property, produces a warm sensation & irritates mucous membranes. To dry skin and cracked lips (50% water) it acts as an emollient.

2) Emollient

Bland oily substances which soothe & soften skin. They form an occlusive film over the skin, preventing evaporation.

3) Adsorbents & protectives

Finally powdered, inert & insoluble solids capable of binding to their surface noxious & irritant substance They are also known as protective because they afford physical protection to their skin. Other protective form a continuous, adherent & flexible occlusive coating on the skin

Aloe Vera gel is mucilaginous preparation from the fleshy leaves of aloe vera plant with soothing & moisturizing property, widely included in cosmetics & care product Polyvinyl polymer on drying its solution forms an occlusive pellicle-like coating on abraded skin.

4) Drugs for acne vulgaris

Are the most common skin diseases in adolescent boys & girls. Under androgenic stimulation the sebaceous follicles of face & neck produce excess of sebum & get colonized by bacteria & yeast. Comedones are forms which may rupture into the dermis causing inflammation & pustulation.

5) Sunscreens

Substance that protects the skin from harmful effect of exposure to sunlight.

(a) Chemical sunscreens

They absorb & scatter UV rays that are responsible for sunburn & photo toxicity, but allow longer wave length to penetrate, so that tanning occurs

(b) Physical sunscreens

Heavy petroleum jelly, titanium dioxide, zinc oxide & calamine are opaque substances that stop and scatter not only UV but also visible light. They are also called sun shades & have to be applied as a thick lotion/ cream which may be cosmetically disagreeable

Topical Steroids

Glucocorticoids are used topically for a large variety of dermatological conditions. They benefit by virtue of their anti-inflammatory, immunosuppressive, vasoconstrictor & anti-proliferative (for scaling lesions) action. The intensity of action depends on the extent of absorption to the deeper layers, thus lipophilicity of the compound determines potency to a great extent.

Local adverse effects of topical steroids

- 1) Thinning of epidermis
- 2) Dermal changes- Atrophy
- 3) Telangiectasia, Striae
- 4) Easy bruising

5) Hypopigmentation delayed wound healing

6) Fungal & bacterial infection

General guidelines for the use of topical steroid

1. Penetration of the steroid at different sites differs markedly-high at axilla, groin, face, scalp, & scrotum, medium at limbs & trunk :- low at palm, sole, elbow & knee
2. Absorption into the skin also depends on the nature of lesion-high in atopic & exfoliative dermatitis, low in hyperkeratinized & plaque forming lesions. milder drugs should be use on acute lesion, stronger ones reserved for chronic lesion.
3. Lotion & creams (to some extend) are better for exudative lesion- they allow evaporation, have cooling, drying & antipruritic effect.
4. Absorption is greater infants & young children-milder agents should be used
5. Use of potent preparation should be short term or intermittent to prevent adverse effect & tachyphylaxis. sudden discontinuation should be avoided. upon improvmeant a less potent preparation may be substituted or the steroid may be alternated with an emollient till the lesion resolves.
6. More than two applications a day do not afford additional benefit. Generally twice daily application is satisfactory.

Transdermal Patches

The main components to a transdermal patch are liner- protects the patch during storage the linear is remove prior to use .Drug-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 reservoir & multilayer patches banking-protect the patch from the outer environment. the skin burns have occurred with metal containing Transdermal patches at the time of shock therapy from external as well as internal cardioverter defibrillators(ICD). (4)

Popular Uses

- 1) The highest selling transdermal patch in the united states is the nicotine patch, which release nicotine in controlled doses to help with cessation of tobacco smoking. the first commercially available vapour patch to reduce smoking was approve in Europe 2007
- 2) Two opioid medication use to provide round the clock relief for server pain are often prescribe in patch.

- 3) Estrogen patches are some time prescribed to treat menopausal osteoporosis
- 4) Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.
- 5)The anti-hypertensive drug clonidine is available in transdermal patch form under the brand name catapres-TTS.(4)

Mechanism of action transdermal patch

The transdermal patch & the flow of the active drug constituent from the patch to the patch to the circulatory system via skin occur through various method. Iontophoresis passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in

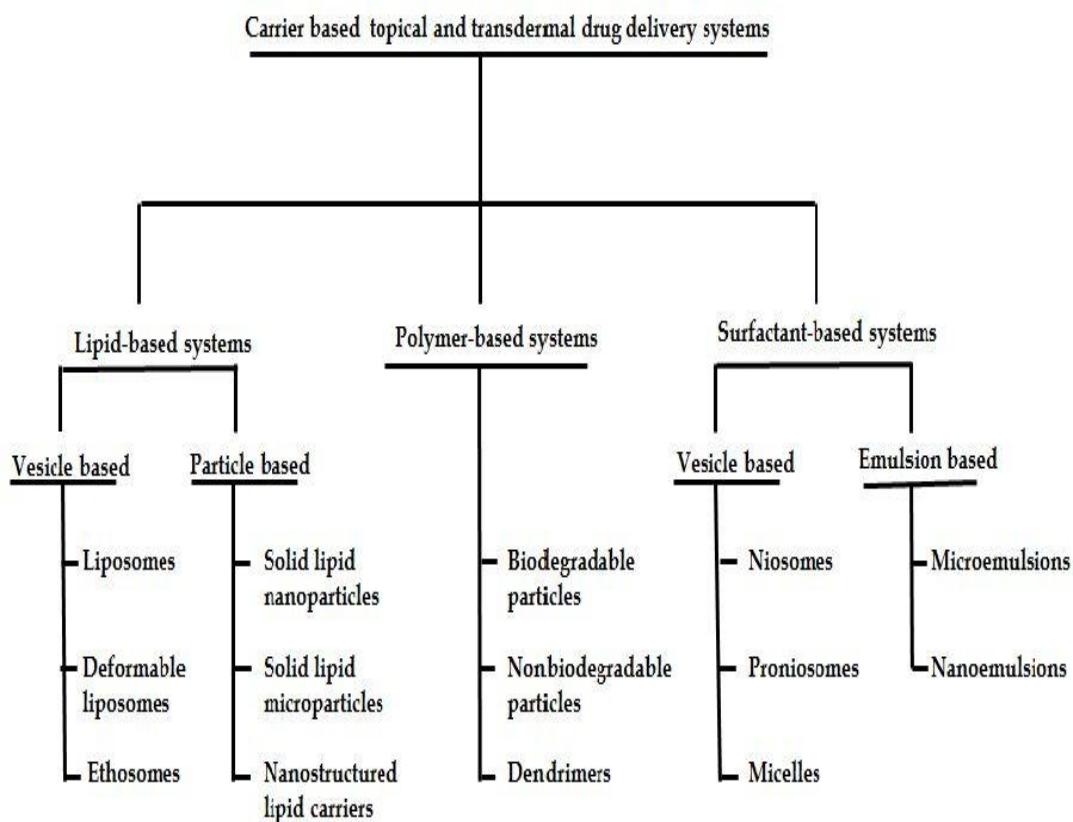


Fig.4: Carrier based topical and transdermal drug delivery systems

contact with facilitates drug delivery across the barrier. Mainly used of pilocarpine delivery to induced sweating as part of cystic fibrosis diagnostic test. iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia.

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. The electrical pulses can be administered painlessly using closely

spaced electrodes to constrain the electric field within the nerves-free stratum corneum. Transdermal patches with microscopic projections called micro needles were used to facilitate transdermal drug transport. They are used in development of cutaneous vaccines for tetanus and influenza. These methods are in their early stages of development & required further detail.(4)

Factors affecting transdermal bioavailability

1) Physiological factors:-

- * Stratum corneum layer of the skin.
- *Anatomic site of application on the body.
- * Skin condition & disease.
- * Age of the patient.
- * Skin metabolism.
- * Skin irritation & sensitization .
- * Race.

2) Formulation factor :-

- * Physical chemistry of transport .
- * Vehicles & membrane used .
- * Penetration enhancer used.
- * Method of application.
- * Device used. (4)

CONCLUSION:

TDSS is a newer approach in the area of dosage forms for many injected & orally delivered drugs having appropriate physiochemical & pharmacology properties. The TDSS ensure that a pharmacology active substance arrive at a relevant in vivo location with minimal side effects. Because of the several advantage the TDSS according to the duration of therapy, various drug are commercially available in the form of transdermal patches. (5)

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