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A Review of Recent Advancement of Transdermal Drug Delivery Systems

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ABSTRACT

It works pretty simply; a medication is placed within patch, which is then worn on skin for an extended period of time. This results in a sustained medication concentration in blood for a considerable amount of time. A polymer matrix, a drug, & permeation enhancers are three main components of TDDS. Polymers can be either natural or manufactured & include Zein & Shellac as well as Poly-butadiene, Polysiloxane, Polyvinyl Chloride & Polyvinyl Alcohol. Reservoir & matrix systems, single layer drug in adhesive, multi layer drug in adhesive are some of several configurations of TDDS. More than 35 products are currently approved for sale in US, & roughly 16-active components are approved for use as TDDSs globally, indicating rapid expansion of the market for TDDS goods. Transdermal drug delivery is covert component of therapy employed in general population, despite fact that developing nations like INDIA have second biggest population & are also most expensive. TDDS is a relatively new technology that has potential to significantly decrease use for needles while dispensing a range of medications.

Keywords: *Advancement of TDDS, Polyvinyl Chloride, Dispensing a range of medications.*

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Introduction:

Transdermal drug delivery system:

The ideal drug delivery method to regulate & sustain drug release through skin is transdermal. Control release drug systems, which contain the same medication & are generally quick release systems, restrict drug release and increase drug efficiency [1].

Many medications are now administered orally, but first pass metabolism raises dose & lessens benefits of medication. Transdermal medication delivery systems are therefore created to decrease number of doses while increasing the effectiveness & bio-availability of medicine [2].

Drugs administered by transdermal drug delivery systems are directly injected into

bloodstream, maintaining ongoing efficacy. The numerous issues with oral products, including reduced bio-availability, improved 1st pass hepatic metabolism, relatively short residence time, dose dumping, & inflexibility in dosing, are all eliminated by these systems because they deliver drugs systemically at a predictable rate & maintain rate for an extended period of time [3].

An excellent transdermal medication candidate must satisfy a number of physicochemical criteria, including being highly lipo-philic by nature, having a melting point over 150, having a molecular wt. above 500 Dalton, having log p values between 1 - 5, & not having any local toxicity or skin irritation [4].

When Ciba-Geigy originally launched Transdermal (now branded as Transdermal scope) for motion sickness in 1981, it was 1st time that medications were delivered via skin for systemic effect, & transdermal delivery [5].

Benefits include avoiding first pass GI & hepatic metabolism & offering reliable regulated absorption.

Minimizes Adverse Consequences.

Due to the removal of multiple doses, there will be a decrease in exposure to unwanted metabolites and an increase in patient compliance.

- Increase the effectiveness of treatment.
- Simple to apply & take off.
- Painless & non-invasive.
- Self-management.
- Effective for medications with limited therapeutic windows & short biological half-lives.
- Simple to stop dosage if an unpleasant reaction happens.
- Release with continuous sustainment [6, 7, 8, 9, 10, and 11].

Disadvantages of TDDS:

- The medication that needs high blood levels cannot be used and it may even irritate or sensitize skin.
- The adhesives could be difficult to wear and might not stick to all types of skin well.
- The product's high price is another big deterrent to its widespread acceptance.
- Physical activity & perspiration can cause patch to come off.
- Erythema, itching, & local oedema can all be brought on by medication, adhesive, or any other excipients used in patch formulation medicines with substantial therapeutic effects that are hydrophilic diffuse slowly because skin facilitates penetration of lipophilic medicines [12].

Limitations:

- It is unable to give medications that need high blood levels.
- Drugs and medication formulations may irritate & sensitize skin.
- The barrier function of skin varies with age, person-to-person, & site-to-site on same person.
- Not feasible if drug is heavily metabolized in skin & if molecular size is too large to allow for molecules to diffuse through the skin.
- Could result in an allergic reaction.
- Long-term compliance is challenging.
- It is not possible for medications with huge molecular sizes to develop.

- Pulsatile drug delivery is not possible with TDDS.
- If a medicine or formulation irritates skin, TDDS cannot occur [13, 14].

Transdermal Route and drug Delivery by Skin:

The largest organ:

The human body's largest organ, skin, accounts for roughly 16% of total body weight. A healthy adult man's skin measures 1.5 to 2 m2 and weighs b/w 6 & 10 kg. Cellular epidermis, underlying dermis, & subcutaneous layer are 3-main cell layers that make up skin. Fig.1. The dermis layer is formed by the rate ridges of epi-dermis that extend downward. The dermal-epidermal junction serves as both a partial barrier against exchange of cells & big molecules & a mechanical support for the epidermis. The subcutaneous layer, a fatty layer comprising panniculus adipose tissues, lies beneath dermis. Human skin comes in two varieties: glabrous skin, & skin without hair, and skin with hair. Thick epidermis and the presence of sensory organs in dermis are characteristics of glabrous skin. Both sebaceous glands and hair follicles are absent. The predominant areas of glabrous skin are palms and soles, & it has a continuously grooved surface with alternate ridges & sulci that create a distinctive individual pattern called dermatoglyphics. While the epidermis that produces hair possesses both hair follicles & sebaceous glands, sensory organs are absent [15].

Skin:

The skin, which has a surface area of about 2 square meters, is the biggest organ in the human body. and gets almost a third of blood that circulates through body. It acts as a permeability barrier to prevent different chemical & biological substances from being absorbed transdermally. It is one of body's most accessible organs & separates blood circulation network from outer environment with a thickness of only a few (2.97 0.28 mm). Acts as a defense against biological, chemical, and physical assaults. Acts as a thermostat to keep the body at the proper temperature. plays a part in blood pressure management. Prevents UV rays from penetrating skin. Skin may play a significant role in determining several elements of medication delivery, such as drug penetration and absorption across dermis. The anatomy & ultrastructure of skin have a significant impact on its diffusion resistance [16-18].

Anatomy & Physiology of Skin:

Three separate yet interdependent tissues make up human skin: "Epidermis" refers to stratified, vascular & cellular layer. Hypo-dermis, dermis of connective tissues beneath [19].

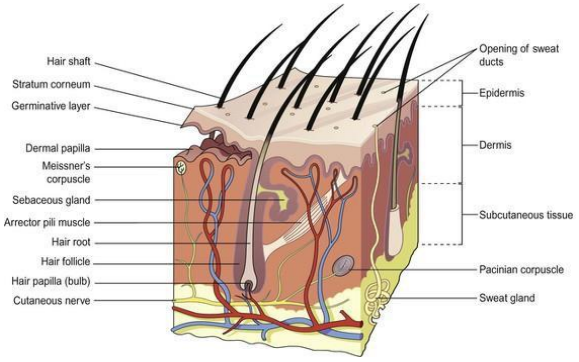

Fig 1: Anatomy of the Skin

Epidermis:

Depending on cell size and the number of cell layers, the multilayered epidermis can range in thickness from 0.8 mm on the palms and soles to 0.06 mm on the eyelids. The phrase "stratum corneum" refers to the skin's outermost layer. When fully hydrated, it expands to several times this thickness and is around 10mm thick when dry. It has between 10 and 25 layers of corneocytes, & dead, keratinized cells. Despite being somewhat

impermeable, it is flexible. The primary obstacle to drug penetration is the horny layer. The horny layer's architecture can be modeled as a wall-like structure. According to this theory, keratinized cells serve as protein "bricks" encased in lipid mortar [20].

Multiple bilayers of lipids are assembled. The lipid fraction contains enough amphiphilic material, such as polar free fatty acids & cholesterol, to keep a bilayer structure. Underneath stratum corneum, thickness of viable epi-dermis ranges from 0.06 mm on eyelids to 0.8 mm on palms. The stratum basal, stratum lucidum, stratum granulosum, & other strata can be found as one moves inward [21].

The epidermis is regularly renewed at basal layer by cell division known as mitosis, which makes up for loss of Horney cells from skin's surface. The basal layer's cells undergo morpho-logical & histo-chemical changes as they proli-ferate outward, undergoing keratinization to create stratum corneum's top layer [22-23].

Dermis:

The dermis is a 3 - 5millimetre thick layer made up of a connective tissue matrix that houses nerves, lymphatic vessels, & blood vessels. The control of body temperature relies heavily on cutaneous blood supply. While eliminating toxins & waste materials, it also gives skin nutrition & oxygen. Capillaries provide sink conditions for many molecules that penetrate skin barrier & extend to within 0.2millimetres of skin's surface. As a result, blood supply maintains a very low dermal concentration of a drug, & ensuing conc. gradient across epidermis is crucial for trans-dermal permeation [24].

Hypodermis:

The derma & epidermis are supported by layer of subcutaneous fat tissue. It functions as a place to store fat. This layer aids in temperature regulation, offers nutrient support, & protects mechanically. It should have sensory pressure organs & main blood vessels & nerves that supply skin. For transdermal drug administration, medication must pass through all three of these layers & enter bloodstream, whereas topical drug delivery just requires drug to pass through stratum corneum before the drug is retained in skin layers [25].

Skin Appendages:

The main skin appendages include hair & hair follicles, secretory ducts, sweat glands (sebaceous, eccrine & apocrine), & nails. A healthy human body has 200–250 sweat ducts and 40–70 hair follicles per cm2 on average. Appendages make up about 0.1% of total surface area of skin. Sweat from the eccrine glands ranges in pH from 4.0 - 6.8. Anti-bodies, proteins, & amino acids can be secreted by sweat glands. The palms & soles have 400 glands per cm2 on average. Sebaceous glands on skin of face, ears, nose, forehead, & anogenital region secrete sebum, an oily substance. The glands range in diameter from 200 - 2000 m. Glycerides, free fatty acids, cholesterol, cholesterol esters, and squalene are the sebum's primary components. Due to the presence of sebaceous glands, the outer surface of the SC has a pH of roughly 5, which is slightly acidic. The main function of sebaceous glands is to lubricate & act as a plasticizer on SC lipids [26-28].

Function of the Skin:

Protection: The human body's main physical defence against outside world is its skin. Against bacteria, poisons, dehydration, UV light, & mechanical harm, skin offers defence.

Sensation: To deep pressure, warmth, touch & pain.

Mobility: The capacity for fluid body movement.

Endocrine Activity: Vit-D synthesis, which is necessary for calcium absorption & healthy bone metabolism, is a bio-chemical process that begins in skin. Water, urea, and ammonia are released during exocrine action. Sebum, perspiration, and pheromones are among compounds that skin secretes. It also performs crucial immunologic tasks by releasing bioactive substances like cytokines.

Immunity: Protection from infections.

Control of Temperature:

Skin contributes to thermal control by storing or expending heat & aids in preservation of body's H2O & homeostasis [29, 30].

Basic Components of TDDS:

A. Polymer Matrix:

An essential & crucial part of transdermal drug delivery system is polymer. Rate-controlled medication delivery has been made possible by the use of many kinds of polymeric materials. The physicochemical characteristics of polymer & material utilised in creation of device determine how medication is released.A polymer must meet the following requirements in order to be employed in a transdermal system. Molecular weight, glass transition temperature, & chemical functionality of polymer must all permit specific drug's release and diffusion.

- The polymer should make it possible to incorporate a lot of medication.
- The medicine & polymer shouldn't interact chemically & physically.
- The polymer should be inexpensive & simple to produce into required product.
- The polymer must maintain its stability & not break down in presence of medicine & any other excipients used in formulation, in high humidity environments, & at body temperature.
- The degradation products of polymers must also be non-toxic.

No single substance can possess all of these qualities; some additives may be added to change some aspects, for instance, co-solvents such ethanol, propylene glycol, & PEG 400 may be added to boost drug solubility [31-33].

Table 1: Useful Polymers for Transdermal Devices

S.No.	Natural Polymer	Synthetic Elastomers	Synthetic Polymers
1.	Gelatin	Neoprene	Polyethylene
2.	Gum Arabic	Polysilozane	Polystyrene
3.	Methyl cellulose	Silicone rubber	Acetyl copolymer
4.	Arabino galactan	Chloroprene	Polyvinyl chloride
5.	Starch	Hydrin rubber	Polyester
6.	Shellac	Acrylonitrile	Polyamide
7.	Proteins	Butyl rubber	Polyvinyl acetate

The Polymer controls release of drug from device. Possible useful polymers for transdermal devices are:

(i). Natural Polymers:

E.g., cellulose derivatives, Zein, Gelatin,

(ii).Synthetic Elastomers

E.g., Polybutadieine, Hydrin rubber, etc (34).

(iii). Synthetic Polymers

E.g., Polyvinyl alcohol, Polyethylene, Polypropylene, Polyacrylate, Polyamide etc (35).

Various Methods for Preparation of TDDS:

Asymmetric TPX Membrane Method:

A heat-sealable polyester film (type 1009, 3 m) with a concave of 1cm diameter may be utilised as backing membrane in an example patch for this purpose. A TPX asymmetric membrane is deposited over concave membrane, which is then filled with drug sample & sealed with an adhesive.

Asymmetric TPX Membrane Preparation:

The dry/wet inversion technique is used to create them. To create a polymer solution, TPX is dissolved in cyclohexane, a solvent, and non-solvent additives. With the use of a garden knife, polymer solution is cast on a glass plate & stored at 40°C for 24 hours. Following a 30-second period of casting film evaporation at 50°C, glass plate is now to be submerged in a coagulation bath with a temperature of 25°C. The membrane may be removed after ten minutes of immersion & allowed to air dry for 12 hours at 50°C in a highly circulated kitchen appliance [36].

Circular Teflon Mould Method:

Solutions with different ratios of polymers are used in an organic solvent. Half of same organic solvent is used to dissolve calculated amount of medication. The second half of organic solvent is used to dissolve the enhancers in a number of concentrations before adding more. As a plasticizer, di-N-butyl-phthalate is added to medication chemical compound formulation. The entire mixture must be mixed for 12hrs before being placed into a Teflon mould with a circle shape. In order to regulate solvent vaporisation in a very streamline flow hood model with an air speed of 0.5m/s, moulds must be put on a level surface and coated with an inverted funnel. For 24hrs, solvent is allowed to evaporate. To counteract ageing effects, dried films must be kept for a further 24hrs at 250.5°C in a desiccator containing silica gel before examination. Within a week of their preparation, the type films must be reviewed [37].

Mercury Substrate Method:

This approach involves dissolving the medication & plasticizer in a polymer solution. The aforementioned solution should be agitated for 10 - 15 minutes to provide a uniform dispersion before being placed over a mercury surface that has been levelled and covered with an inverted funnel to prevent solvent evaporation.

By Using "IPM Membranes" Method:

This approach involves dissolving medication together with plasticizer in a polymer solution. The aforementioned solution must be agitated for ten to fifteen minutes to ensure a uniform dispersion before being poured into a mercury surface that has been levelled & lined with an inverted funnel to control solvent evaporation [38].

By Using "EVAC Membranes" Method:

I Chronicles carbopol reservoir gel, (PE), & ethylene vinyl acetate polymer (EVAC) membranes are frequently employed as rate control membranes in order to prepare the goal transdermal treatment system. When making a gel out of a medicine that isn't soluble in water, propylene glycol is used. Drug is dissolved in propylene glycol, carbopol resin is placed on top of solution, & 5-hitter sodium hydroxide resolution is used to neutralise the drug. The medication (in gel form) is applied to a backing sheet that covers targeted area. To create a leak-proof device, a rate dominating membrane is placed over the gel, & edges are then heated to seal them [39].

Aluminium Backed Adhesive Film Method:

If the loading dose is greater than 10mg, transdermal drug delivery systems may produce unstable matrices. Chloroform is chosen solvent since majority of medications & adhesives are soluble in it, making aluminum-backed sticky film approach an appropriate one for preparation of same. Chloroform is used to dissolve medicine, & adhesive material is then added & dissolved in drug solution. Aluminium foil is used to line a custom-made aluminium former, & ends are then sealed off with tightly-fitting cork blocks.

Preparation of TDDS by Using Proliposomes:

Proliposomes are created utilising film deposition technique & carrier technology. Lecithin and the preceding reference medication can be employed as an optimised quantitative relationship with a ratio of 0.1:2.0. A 100ml spherical bottom flask with a temperature of 60–70°C & a H2O bath set to 20–30°C is used to create proliposomes by adding 5mg of mannitol powder to it. In a suitable organic solvent mixture, drug & lecithin are dissolved. A 0.5ml aliquot of the organic solution is then added to spherical flat-bottom flask at 37°C. After the solution has dried completely, additional 0.5ml of the solution is to be added. Following final loading, flask containing proliposomes is attached to a lyophilizer. The drug-loaded mannitol powders (proliposomes) are then left in desiccator overnight before being sieved through a 100mesh screen. The gathered powder is put into a glass bottle & refrigerated until it is time for characterisation [40].

By Using Free Film Method:

Casting on the surface of the mercury creates a free film of cellulose acetate. Chloroform is to be used to prepare a two weight percent polymer solution. Plasticizers must be added at a 400th weight of polymer per weight concentration. A very glass Petri dish with a ring placed over the mercury surface received five millilitres of polymer solution. An inverted funnel is positioned above petri-dish to control solvent's rate of evaporation. Once solvent has completely evaporated, the mercury surface can be observed to detect film formation. The dried films are sorted out & stored in a desiccator b/w sheets of paper until needed. By continuously altering quantity of polymer solution, a free film of different thicknesses can be created [41-43].

Conclusion:

This page offers useful details on evaluation process for transdermal drug delivery systems, serving as a handy reference for researchers working on TDDS. The information above demonstrates that TDDS have significant potentials, since they can be used to create promising deliverable medications from both hydro-phobic & hydrophilic active substances. More knowledge of various biological interactions & polymer mechanisms is needed to optimise this drug delivery technology. The next generation of drug delivery systems, TDDS, has a realistic, practical use. Despite fact that transdermal drug delivery is not a new technique, it is now the most popular method of drug delivery since it allows medicine to be incorporated into skin without damaging skin membrane. In future, it promises to do away with necessity for needles when administering a range of pharmaceuticals.

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