An Overview: Transdermal Drug Delivery System (TDDS)

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ABSTRACT

Transdermal drugs have made an important contribution to pharmaceutical dosage forms, nevertheless have yet to fully accomplish its potential as an alternative to oral dosage form and hypodermic injections. A transdermal drug delivery system (TDDS) represents the most attractive method among these because of its low rejection rate, excellent ease of administration, and superb convenience and persistence among patients. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream.Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The main objective of this work is to be study on transdermal drug delivery system is to preparation and composition, evaluation, transdermal drugs and its types.

KEYWORDS: Transdermal Drugs, Patch, Composition, Types, Evaluation.

1.0 INTRODUCTION:

There are various routs of drug administration available for dosage form such as Oral, Parenteral, Optimal, Buckle, Inhaler, Suppository, Sublingual, Topical and Transdermal Patches. The most common routes of drug delivery are the oral and parenteral routes with the majority of small molecule drugs conventionally delivered orally. The oral route has the advantage of pre-determined doses, portability and patient self-administration. For these reasons, the oral route remains the most convenient means of delivering medications. However, most therapeutic peptides or proteins are not delivered by the oral route, due to rapid degradation in the stomach and size-limited transport across the epithelium. The primary mode of administering macromolecules is therefore via injection. Which is not without limitations, such as the invasive nature of injections eliciting pain and lower acceptance/compliance by patients, in addition to the

requirement for administration by a trained administrator. Rationally, the conventional routes of medication delivery have many inherent limitations which could potentially be overcome by advanced drug delivery methodologies such as transdermal drug delivery system (TDDS).

Transdermal Drug Delivery System (TDDS) is also well-known as a transdermal patch or skin patch which deliver a specific dose of medication in to the systemic circulation. It is a medicated adhesive patch. Morphological, biophysical and physicochemical properties of the skin are to be considered when therapeutic agents are delivered through the human skin for systemic effects.

Transdermal Drug Delivery System (TDDS) are defined as self-contained, discrete dosage forms which are also known as "patches"w hen patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation.

1.1 ADVANTAGES AND DISADVANTAGES OF TDDS:

Advantages of TDDS over other dosage form

- Self-administration and removal when required.
- Pain, inconvenience of injections can be overcome by this non- invasive and safe parenteral route of drug.
- Transdermal delivery avoids the stomach environment so that patient avoid first pass effect.
- Transdermal drug delivery provides steady plasma levels. When a patch is applied that lasts for 24 hours, or even 7 days, once steady state is reached the plasma levels remain constant because the rate of drug delivered from the patch is constant.
- Unlike the limited controlled release from oral and intravenous routes, TDDS provides steady infusion of drug over an extended period of time.
- Therapeutic failure or adverse effects frequently associated with intermittent dosing for the chronic diseases can be avoided.
- Transdermal drug delivery systems, especially simple patches, are easy to use and noninvasive and patients like non-invasive therapies.
- If a transdermal delivery system is used in place of a needle, then medical waste can also be decreased, again, decreasing healthcare costs.

Disadvantages:

Some of the challenges of transdermal drug delivery include:

- Only a narrow range of molecules can currently be delivered transdermally.

- Only small, relatively lipophilic molecules can pass through the lipid bilayer “mortar” of the stratum corneum using traditional patch technology.
- As drug treatments become more and more complex.
- High dose cannot be introduced by transdermal drug delivery system.
- Skin irritation and allergic reaction may be Cause by patches

Factors Influencing Transdermal Drug Delivery System or Transdermal Patches:

The effective transdermal drug delivery system can be formulated by considering three major factors as Drug, Skin, and the vehicles. Therefor mainly two factors i.e. biological factors and physicochemical factors.

Biological factors: Skin Condition, Skin age, Blood supply, regional skin site, Skin metabolism, Species difference, genetically skin problems, environmental factors.

Physicochemical factors: Skin hydration, Temperature and pH, Diffusion coefficient, Drug concentration, Partition coefficient, Molecular size and shape.

2.0 ANATOMY OF SKIN:

Skin is the most available and largest organ of the body with a surface area compromising 16% of the total body mass of an average person. The main function of the skin is to provide a protective barrier between the body and the external environment against microorganisms, the permeation of ultraviolet (UV) radiation, chemicals, allergens and the loss of water. Skin can be divided into three main regions (Figure 1):

The outermost layer, the Epidermis, which contains the stratum corneum,
Themiddle layer, the Dermis and the inner most layer, the hypodermis,
The inner layer, the Subcutis or Subcutanious, containadipose tissue, artery and veins

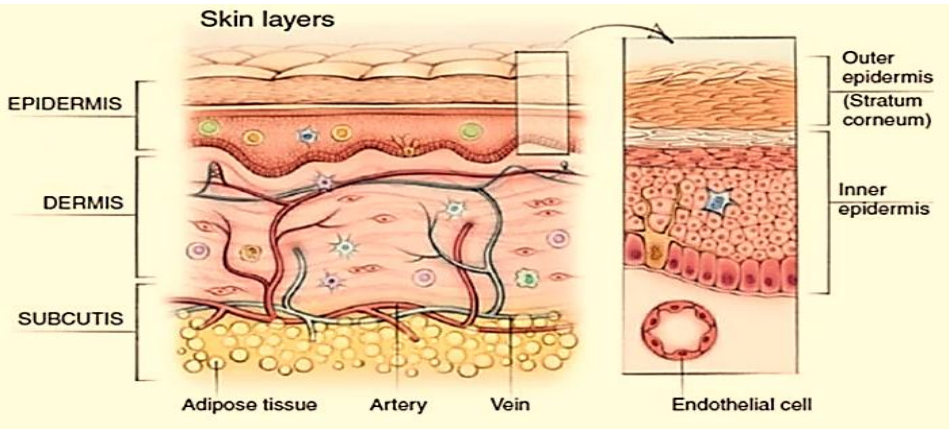

Figure 1: Skin layers

This multi-layered organ receives approximately one third of all blood circulating through the body. Epidermis results from an active epithelial basal cell population and is approximately 150 micrometres thick. It is the outermost layer of the skin and the process of differentiation results in migration of cells from the basal layer towards skin surface. Below this layer are the other layers of the epidermis - the stratum lucidum, stratum granulosum, and stratumspinosum and stratum germinativum. Together, these other layers constitute the viable epidermis. Dermis is foundation of firm connective tissue upon which epidermis is laid and is of mesoderm origin. 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. The innermost layer of skin is subcutis, it contain endothelial cell moreover comprises adipose tissue, artery and vein.

3.0 TRANSDERMAL DRUG AND THEIR TYPES:

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December. The highest selling transdermal patch in the United States was the nicotine patch which releases nicotine to help with cessation of tobacco smoking. The first commercially available vapour patch to reduce smoking was approved in Europe in 2007. In addition, various other patches are available in market including fentanyl, an analgesic for severe pain, nitroglycerin patches for angina, lidocaine patches, marketed as Lidoderm, relieve the peripheral pain of shingles (herpes zoster), Buprenorphine, marketed as BuTrans, as analgesia for moderate to severe chronic pain. It is also now commonly used off-label, for pain from acute injuries and chronic pain. Flector (DiclofenacEpolamine) patch is an NSAID topical patch for the treatment of acute pain due to minor strains, sprains, and contusions. It is also being used in the treatment of pain and inflammation for chronic conditions benefiting from NSAIDs including fibromyalgia and arthritis. Recent developments expanded their use to the delivery of hormonal contraceptives, antidepressants and even pain killers and stimulants for Attention Deficit Hyperactivity Disorder (ADHD) (Berner and John 1994). In 2005, the FDA announced that they are investigating reports of death and other serious adverse events related to narcotic overdose in patients using Duragesic, the fentanyl transdermal patch for pain control.

The pharmaceutical transdermal patches comprises Backing- Surrounds the drug, protects the patch from the outer environment; Adhesive- Adhere the components of the patch together, adhere the patch to the skin; Membrane - Control the release of the drug; Drug- Direct contact with the release liner, Liner - Protect the patch during storage, removed prior to use.

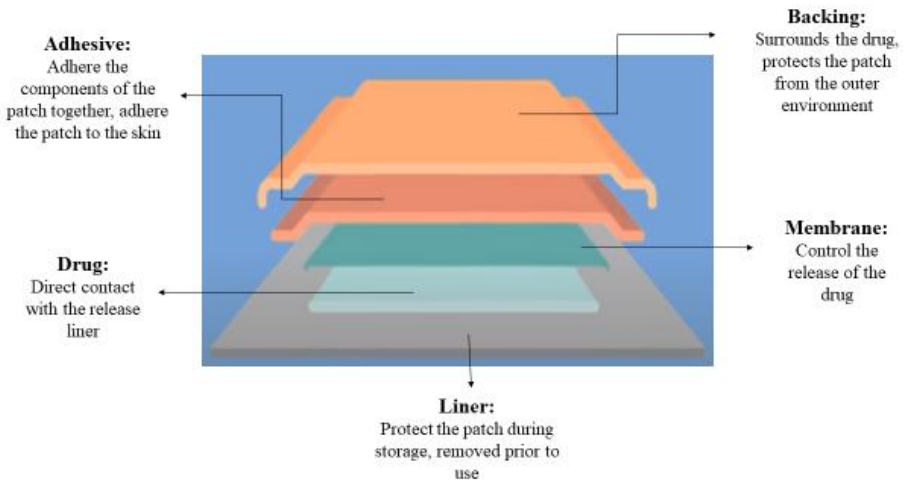

Figure 2: Component of Transdermal Drug Delivery System (TDDS)

3.1 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 this type of layer is responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

3.2 Multi -layer drug in adhesive:

This type is also similar to the single layer but it contains a immediate drug release layer which is different from other layer which 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 (Pellet *et al*., 2003).

3.3 Vapour patch:

In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves market, commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions

3.4 Reservoir system:

In this system the drug reservoir is embedded between the two layers; 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. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

3.5 Matrix system:

a) Drug-in-adhesive system:

In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

b) Matrix-dispersion system

In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. 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.

3.6 Microreservoir Controlled TDDS:

This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. The thermodynamically unstable dispersion is stabilized quickly by immediately cross linking the polymer in situ. A Transdermal system therapeutic system thus formed as a medicated disc Positioned at the center and surrounded by an adhesive rim.

4.0 PREPARATION AND COMPOSITION OF TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS):

TDDS comprises the Polymer matrix / Drug reservoir, Drug (Main constituent), Permeation enhancer, Pressure sensitive adhesives, Backing membrane, Release liner, other excipients.

4.1 Polymer matrix:

Polymer matrix, prepared by the spreading of a drug in a suitable polymer, controls the release of the drug from the transdermal drugs. Polymers used in TDDS should be stable, compatible and non-reactive with the drug and other components of the system, should provide effective release of the drug throughout the device. They should be easily fabricated to the desired product. Polymers and their degradation products must be non-toxic and non- antigenic to the host.

a. Natural polymers:

Currently for TDDS formulation mostly used natural polymers likeHydroxypropyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (sodium CMC), cellulose acetate, methyl cellulose, ethyl cellulose, gelatin, chitosan, sodium carboxymethylguar, sodium alginate, polymerized rosin etc.

b. Synthetic polymers:

Polyvinyl alcohol, polyethylene, polyethylene glycol, polyvinylpyrrolidone, eudragits, ethylene vinyl acetate copolymer, ethyl vinyl acetate, silicon rubber etc.

4.2 Drug: Drug is a main constituent for patches contain Active Pharmaceutical Ingredients, Pharmacologically active drugs. For successfully development of a transdermal drug delivery, the drug should full fill the following properties such as physicochemical properties and Biological properties.

a. Physicochemical properties:

The drug should have some degree of solubility in both oil and the substance should have melting point less than 200 °F. Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point (in degree absolute of the drug). In order to obtain the best candidates for TDD, an attempt should be made to keep the melting point as low as possible. Substances having a molecular weight of less than 1000 units are suitable. A saturated aqueous solution of the drug should have a pH value between 5 and 9. Drugs highly acidic or alkaline in solution are not suitable for TDD; because they get ionized rapidly at physiological pH and ionized materials generally penetrate the skin poorly.

b. Biological properties:

Drug should be very potent, i.e., it should be effective in few mgs per day (ideally less than 25 mg/day) the drug should have short biological half-life. The drug should be non-irritant and non-allergic to human skin. The drug should be stable when in contact with the skin. The drug should not stimulate an immune reaction to the skin. Tolerance to drug must not develop under near zero order release profile of transdermal delivery. The drug should not get irreversibly bound in the subcutaneous tissue. The drug should not get extensively metabolized in the skin.

4.3 Permeation enhancers:

a. Chemical permeation enhancers:

They disrupt the highly ordered intercellular lipid bilayers of the stratum corneum by inserting amphiphilic molecules or by extracting lipids, reversibly decreasing the barrier resistance and allowing better permeation of the co-administered drugs. An ideal enhancer should be inert, non-toxic, non-allergenic, non-irritating, work unidirectional and compatible with the excipients and drugs. Their potency appears to be drug, skin and concentration dependent.

b. Physical permeation enhancers:

Iontophoresis enhance and control drug penetration through the skin by applying low density electric current. Electroporation applies high voltage pulses across the skin for a fraction of second, creating new aqueous pathways in the stratum corneum for drug diffusion Erbium: yttrium-aluminium-garnet laser applies

single pulse of low energy to ab-late the stratum corneum layers. Ul-trasound or micro needle application breach the stra-tum corneum and create micro channels for the drug permeation

c. Other permeation enhancers:

Ethanolic liposomes, noisome, protransferosome gel and prodrug approach are reported to increase permeability by increasing the drug solubilisation and partitioning into the skin

4.4 Pressure sensitive adhesives (PSAs):

PSAs affix TDDS firmly to the skin on applying light pressure. They should be skin-compatible, non-irritant, easily removable without leaving a residue or inflicting pain. They ensure intimate contact between the drug releasing area of TDDS and the skin surface which is critical for the controlled release of drug. Commercially available PSAs include polyacrylate, polyisobutylene and silicones.

4.5 Backing membrane:

Backing materials must be flexible while possessing good tensile strength. Commonly used materials are polyolefin's, polyesters, and elastomers in clear, pigmented, or metallized form. Elastomeric materials such as low-density polyethylene conform more readily to skin movement and provide better adhesion than less compliant materials such as polyester. Backing materials should also have low water vapour transmission rates to promote increased skin hydration and, thus, greater skin permeability.

4.6 Release Liner:

Release liner is a protective liner for the TDDS patch that is removed prior to the application on the skin. Typically, it consists of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer of silicon.

4.7 Other excipients:

Various solvents such as water, ethanol, isopropylmy-ristate, isopropyl alcohol, and dichloromethane are used alone or in combination to prepare the drug reservoir. Propylene glycol, ethanol are used as co solvents along with the permeation en-hancer. Plasticizers like diethyl phthalate, dibutylpthalate, glycerol, triethyl citrate, polyethylene glycol 400, eudraflex and propylene glycol provide plasticity to the trans-dermal patch.

Some Transdermal Drugs Approved by the US FDA

Sr. No.	Drug	Indication	Approved Year	Product Name
1	Scopolamine	Motion sickness	1979	Transderm-Scop
2	Nitroglycerin	Angina pectoris	1981	Transderm-Nitro
3	Clonidine	Hypertension	1984	Catapres-TTS
4	Nicotine	Smoking cessation	1991	Nicoderm, Habitrol, ProStep
5	Lidocaine	Post-herpetic neuralgia pain	1999	Lidoderm

6	Methylphenidate	Attention deficit hyperactivity disorder	2006	Daytrana
7	Rivastigmine	Dementia	2007	Exelon

5.0 EVALUATION OF TDDS:

a. Evolution of TDDS

a. Peel adhesion properties

b. Tack properties

c. Quick- stick (peel tack)

d. Probe tack test

b. In-vitro drug release evalution

a. Keshary- Chien (K-C) cell

c. In-vivo evaluation

a. Animal models

b. Human volunteers

d. Other Evaluation Parameter

a. Thickness

b. Moisture content

c. Folding endurance

d. Tensile strength

6.0 CONCLUSION:

Transdermal Drug Delivery System represents one of the most rapidly advancing areas of novel drug delivery. Due to currentimprovements 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. Potential development in drug delivery systems include the use of improved adhesive, enhancer technologies and minimizing the problems; and systems that exploit thermal, electrical, ultrasonic, or other forms of energy to “drive” molecules through the stratum corneum or microneedles to bypass the occlusive nature of the stratum corneum in a controlled fashion.

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