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Review Article

MEDICATED TRANSDERMAL THERAPEUTIC SYSTEMS: AN UPDATED OVERVIEW

Mithilesh Sahu[1*], Mithun Bhowmick[1], Rajesh Kushwaha[2] and Jagdish Rathi[1]

[1]NRI Institute of Pharmaceutical Sciences, Bhopal, Madhya Pradesh, India.

[2]Alkem laboratories ltd, Mumbai, Maharashtra, India.

ABSTRACT

The Discovery of Transdermal Drug Delivery System (TDDS) is a breakthrough in the field of controlled drug delivery systems. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a time released dose of medication systemically for treating illnesses. The ability of TDDS to deliver drugs for systemic effect through intact skin while bypassing first pass metabolism has accelerated transdermal drug delivery research in the field of pharmaceutics. The skin as a route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic systems in the form of patches. An essential prerequisite for the development of TDDS is that the drug must be capable of passing through skin at a sufficiently high rate to achieve therapeutic plasma concentrations. Over a decade of such extensive research activities, many transdermal patches have been developed and successfully commercialized.

Keywords: Transdermal Drug Delivery System, bypassing first pass Metabolism.

INTRODUCTION

Throughout the past two decades, the Transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms. 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, painless and offer multi-day dosing. It is generally accepted that they offer improved patient compliance. Although Transdermal drug delivery patches have a relatively short regulatory history compared to other, more traditional dosage forms, the technology has a proven record of FDA approval. Since the first Transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness, the FDA has approved, throughout the past 22 years, more then 35 Transdermal patch products, spanning 13 molecules. The Transdermal route is ideally suitable for drugs that need to be administered for diseases those are chronic in nature and required a steady state drug concentration throughout the treatment. The present study is an attempt to develop a Transdermal system capable of delivering the selected anti-diabetic drug in the desired therapeutic concentration for prolong period.[1,2]

ANATOMY AND PHYSIOLOGY OF SKIN[2,13,14,17]

The skin can be considered to have four distinct layers of tissue. 1. Non- viable epidermis (stratum corneum) 2. Viable epidermis 3. Viable dermis 4. Subcutaneous connective tissue Located within these layers are skin circulatory system (arterial plexus) ans appendages (hair follicles, sebaceous and sweat glands).

1. Non Viable Epidermis: Stratum corneum or horny layer is the outer most layer of epidermis, which is actual physical barrier to most substances that come in contact with the skin. The stratum corneum is 10 to 20 cell layers thick over most of the body, generally made up of flattened dead keratinocytes. Cells are sloughed from the

surface continually and replaced by new ones that have formed and matured below the viable epidermis. Stratum corneum consists of lipids (5-15%) including phospholipids, glycosphingolipids, cholesterol and neutral lipids, proteins (75-85%) mainly keratin. In the outer layers of the stratum corneum, the moisture barrier has a slightly acidic pH (4.5 to 6.5).

2. Viable Epidermis: This layer of skin resides between stratum corneum and dermis. It has a thickness ranging from 50 to 100 µm. Cells are held together by together by tonofibrils. The water content is about 90%.

3. Dermis: Just beneath the viable epidermis is the dermis. It is a structural fabric and very few cells are to be found histological in normal tissue. The dermis ranges from 2000 to 3000 µm thick, consists of a matrix of loose connective tissue composed of fibrous proteins (collagen, elastin and reticulum) embedded in an amorphous ground substance.

4. Subcutaneous Connective Tissue: The subcutaneous tissue or hypodermis is not actually considered a true part of the structure of the skin. It is composed of loose textured, white, fibrous connective tissues in which fat and elastic fibers are intermingled. It contains blood and lymph vessels, the base of hair follicles, often the secretory portion of the sweat glands and cutaneous nerves.

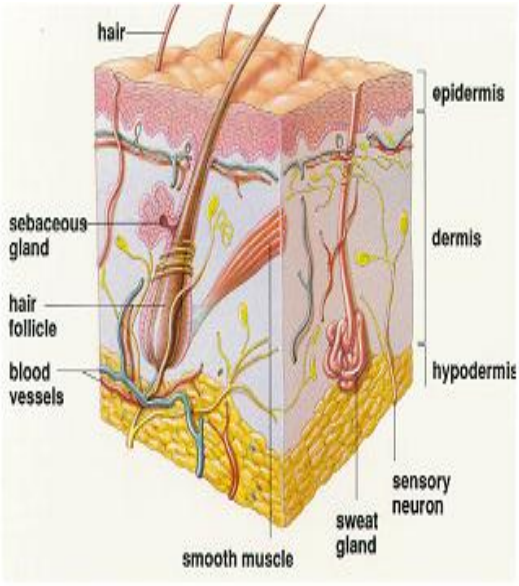

Fig. 1: Anatomy of Skin

PATHWAYS OF TRANSDERMAL PERMEATION [4]

Permeation can occur by diffusion via: a. Transcellular permeation, through the stratum corneum b. Intercellular permeation, through the stratum corneum c. Transappendageal permeation via the hair follicles, sebaceous and sweat glands. The first two mechanisms require further diffusion through the rest of the epidermis and ermis. The third mechanism allows diffusional leakage into the epidermis and direct ermeation into dermis. For drugs penetrating directly across the intact stratum corneum, ntry may be Transcellular or intracellular. The relative importance of these alternatives epends on many factors, which include the time scale of permeation (steady state Vs. ransient diffusion), the physiochemical properties of penetrant (pKa, molecular size, stability nd binding affinity, and its solubility and partition coefficient), integrity and thickness of stratum corneum, density of sweat glands and follicles, skin hydration, metabolism and vehicle effects.[17]

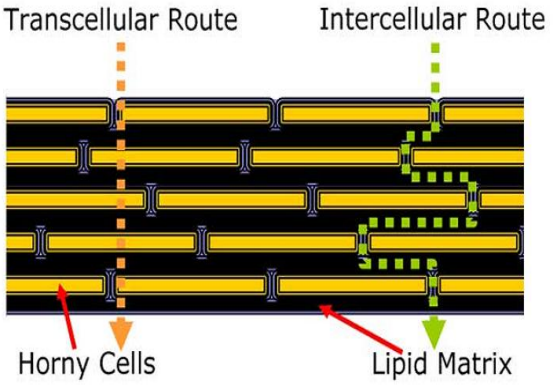

Fig. 2: Transport of drugs through stratum corneum

FACTORS AFFECTING TRANSDERMAL PERMEABILITY [17]

The factors controlling transdermal permeability can be broadly placed in the following cases:

I. Physico-chemical properties of the penetrant molecules

1. Partition coefficient: Drugs having both lipid and water solubilities are favorably absorbed through skin. Transdermal permeability coefficient shows a linear dependency on partition coefficient. A lipid /water

partition coefficient of one or greater is generally required.

2. pH conditions: The pH value of high or low can be destructive to the skin. With moderate pH values the flux of ionisable drugs can be affected by changes in pH that alter the ratio of charged to uncharged species and their transdermal permeability.

3. Penetrant concentration: Increasing concentration of dissolved drug causes a proportional increase in flux. At higher concentration excess solid drug function as reservoir and help to maintain a constant drug concentration for a prolonged period of time.

II. Physico-chemical properties of drug delivery systems

1. Release Characteristics: Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depend on the following factors:
a) Whether the drug molecules are dissolved or suspended in the delivery system.
b) The interfacial partition coefficient of the drug from the delivery system to skin.
c) pH of the vehicle.

2. Enhancement of transdermal permeation: Majority of drugs will not penetrate the skin at rates sufficiently high for therapeutic efficacy. The permeation can be improved by the addition of permeation enhancer into the system.

III. Physiological and pathological condition of skin:

1. Reservoir effect of horny layer: The horny layer especially is deeper layer can sometimes act as a depot & modify the transdermal permeation of drugs. This effect is due to irreversible binding of a part of the applied drug with the skin.

2. Lipid film: The lipid film on the skin surface acts as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of stratum corneum.

3. Skin hydration: Hydration of stratum corneum can enhance permeability. Skin hydration can be achieved simply by covering or occluding the skin with plastic sheeting, leading to accumulation of sweat. Increased hydration appears to open up the dense closely packed cells of the skin and increases its porosity.

4. Skin temperature: Raising the skin temperature results in an increase in the rate of skin permeation; this may be due to availability of thermal energy required for diffusivity.

5. Regional variation: Differences in nature and thickness of the barrier layer of skin causes variation in permeability.

6. Pathological injuries to the skin: Injuries that disrupt the continuity of the SC increases permeability due to increased vasodilation caused by removal of the barrier layer.

7. Cutaneous self metabolism: Catabolic enzymes present in the epidermis may render the drug inactive by metabolism and the topical bioavailability of the drug is greatly reduced.

TRANSDERMAL DRUG DELIVERY SYSTEMS[3-9]

1.1.1 DEFINITION Transdermal therapeutic systems are defined as 'self-contained' discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation'.

ADVANTAGES

The advantages of Transdermal delivery over other delivery modalities are as follows:

1. Avoidance of 'first-pass' metabolism of drugs.
2. Peak plasma levels of drugs are reduced, leading to decreased side effects.
3. Reduction of fluctuations in plasma level of drugs.
4. Utilization of drug candidates with short half-life and low therapeutic index.
5. Easy termination of drug delivery in case of toxicity.
6. Reduction of dosing frequency and enhancement of patient compliance. For Transdermal drug delivery system to be effective, the drug must obviously be able to penetrate the skin barrier and reach the target site.

DISADVANTAGES

1. Drug Requiring higher blood level can not be administered.
2. Transdermal Patches may not add to all types of Skin.
3. Unsuitable for drugs that irritate or sensitize the skin. 4. Useful for only low doses of drugs.

LIMITATIONS

For a drug candidate to be incorporated into a Transdermal delivery system are:

1. Higher molecular weight candidates (>500 Da) fail to penetrate the stratum corneum.
2. Drugs with very low or high partition coefficient fail to reach systemic circulation. Such candidates can not be delivered across the skin without effectively making suitable modifications in the conventional Transdermal delivery systems.

BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEMS [3,5,15]

The components of Transdermal devices include:

1) Polymer matrix or matrices
2) The drug
3) Permeation enhancers
4) Other excipients

1) **Polymer Matrix**

The polymer controls the release of drug from the device. The polymer used should be stable, non-reactive with the drug, inexpensive, should allow the drug to diffuse properly and release through it. Some of the useful polymers are as follows:

Natural Polymers: Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

Synthetic Elastomers: Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylionitrile, Butyl rubber, Styrene-butadiene rubber, Neoprene etc.

Synthetic Polymers: Polyvinyl alcohol, Polyvinyl Chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethymethacrylate, Epoxy etc.

2) Drug

For successfully developing a Transdermal drug delivery system, the drug should be osen with great care. The following are some of the desirable properties of a drug for ansdermal delivery.

- The drug should have molecular weight less then 1000 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases.
- The drug should have a low melting point.
- The half-life of drug should be short.
- The drug should be potent with a daily dose of the order of a few mg/day.
- The drug must not induce a cutaneous or allergic response.
- Drugs, which degrade in the GI tract or inactivated by hepatic first-pass effect, are suitable candidates for Transdermal delivery.
- Tolerance to the drug must not develop under the near zero-order release profile of Transdermal delivery.
- Drugs which have to be administered for a long period of time or which cause adverse effects to non-target tissues can also, be formulated for Transdermal delivery.

3) Permeation Enhancers These are compounds, which promote skin permeability by altering skin as a barrier to the flux of a desired penetrant. The various permeation enhancers are:

Solvents: These compounds increase penetration possible by swelling the polar pathway and/or fluidizing lipids. **Examples:** Methanol, Ethanol, dimethylsulfoxide, Dimethyl formamide, Pyrollidones, Propylene glycol, Glycerol, Isopropyl palmitate etc.

Surfactants: These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length

a) Anionic Surfactant: Sodium laurate sulphate, Dioctyl sulphosuccinate, Decodecylmethyl Sulphosuxide etc.

b) Nonionic Surfactant: Pluronic F127, Pluronic F68 etc.

c) Bile salts: Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

Binary Systems: These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways. **Examples:** Propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid.

Miscellaneous Chemicals: Urea, N, N-Dimethyl-m-toluamide, Calcium thioglycolate, Anticholinergic agents.

Other Excipients

a) Adhesives: The fastening of all Transdermal devices to the skin is done by using a pressure sensitive adhesive, which can be positioned on the face of the device or to the back of the device and extending peripherally. These adhesives should fulfill the following criteria:

- Should not irritate or sensitize the skin and adhere to the skin. Should be easily removed.
- Should be physically and chemically compatible with the drug, excipients and enhancers of the device.
- Should not affect the permeation of the drug. Some of the widely used pressure sensitive adhesives are Polyisobutylenes, Acrylics and Silicones.

b) Backing Membrane They are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is an impermeable substance that protects the product during use on skin e.g., Metallic plastic laminate, Plastic backing with absorbent pad and occlusive base plate (aluminum foil), Adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminum foil disc) etc.[8].

APPROACHES USED IN THE DEVELOPMENT OF TRANSDERMAL DRUG DELIVERY SYSTEMS[3-5,15-16]

Four different approaches have been utilized to obtain Transdermal drug delivery systems.

1) Membrane Permeation – Controlled Systems In this type of system, the drug reservoir is totally encapsulated in a shallow compartment moulded from a drug-impermeable metallic laminate and a rate controlling membrane which may be micro porous or non-porous.

The drug molecules are permitted to release only through the rate-controlling membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an unreachable, viscous liquid medium such as silicone fluid to from a paste like suspension. A thin layer of drug compatible, adhesive polymer like silicone or polyacrylate adhesive may be applied to the external surface of rate controlling membrane to achieve an intimate contact of the Transdermal system and skin surface. The rate of drug release from this type of system can be varying the polymer composition, permeability coefficient and thickness of the rate limiting membrane and adhesive. The major **advantage** of membrane permeation controlled Transdermal system is the constant release of drug. However, a rare risk also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or a rapid release of the entire drug content.

Examples:

a. Nitroglycerin-releasing Transdermal system (Transdermal-Nitro/ciba, USA) for once a day medication in angina pectoris.
b. Scopolamine-releasing Transdermal system (Transdermal-Scop/Ciba, USA) for 72 hrs prophylaxis of motion sickness.
c. Clonidine-releasing Transdermal system (Catapres/Boehriger Ingelheim, USE) for 7- day therapy of hypertension. d. Estradiol-releasing Transdermal system (Estraderm/Ciba, USA) for treatment of menopausal syndrome for 3-4 days.

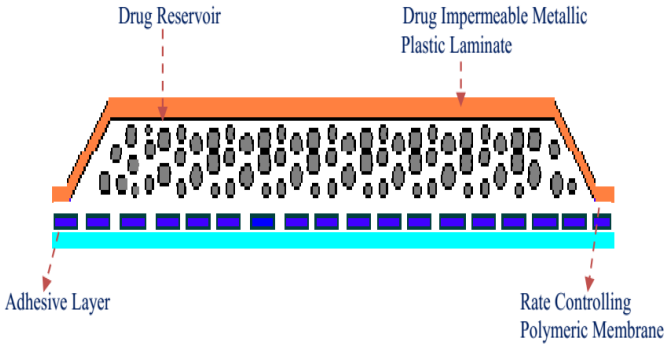

Fig. 3: Cross-Section of Membrane Moderated Systems

2) Adhesive Dispersion-Type Systems This system is a simplified form of the membrane permeation-controlled system. Here the drug

reservior is formulated by directly dispersing the drug in an adhesive polymer e.g., Poly (isobutylene) or Poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the top of the drug reservoir layer, thin layers of non-medicated, rate controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion-controlled delivery system.

Example:

Isosorbide dinitrate-releasing Transdermal therapeutic system (Frandoltape/Yamanouchi, Japan) ones-a-day medication of angina pectoris.

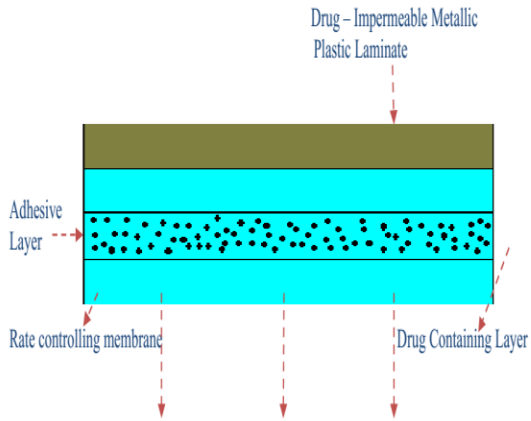

Fig. 4: Cross-Section of Adhesive Controlled TDDS

3) **Matrix Diffusion-Controlled Systems** In this approach, the drug reservoir is prepared by homogenously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness. The drug reservoir can be formed by dissolving drug and polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vacuum. The drug reservoir containing polymer disc is then pasted onto an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing. The adhesive polymer is then spread along the circumference to from a strip of adhesive rim around the medicated disc.

The **advantage** of this type of system is the absence of dose dumping since polymer can not rupture.

Example:

Nitroglycerin-releasing Transdermal therapeutic system (Nitro-dur and Nitro-Dur II/Key Pharmaceuticals, USA).

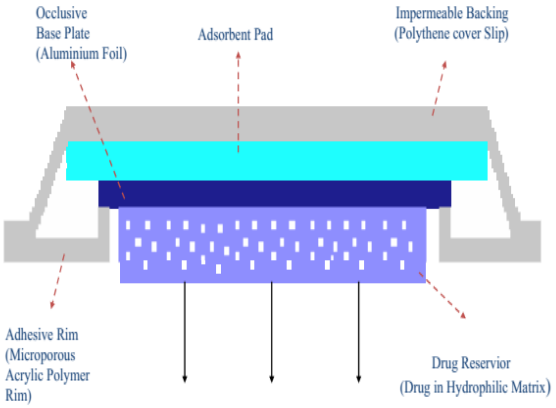

Fig. 5: Cross Section of Matrix Dispersion TDDS

4) Micro reservoir Type or Micro sealed Dissolution Controlled Systems This system is a combination of the reservoir and matrix diffusion type drug delivery systems. The drug reservoir is formed by first suspending the drug solids in an aqueous solution of water-soluble liquid polymer viz. silicone Elastomers by high-energy dispersion technique to form several discrete, unleachable microscopic spheres of drug reservoirs.

The quick stabilization of this thermodynamically unstable dispersion is accomplished by immediately cross-linking the polymer chains in *situ*, which produces a medicated polymer disc with a constant surface area and fixed thickness. Positioning the medicated disc at the center and surrounding it with an adhesive produce a Transdermal therapeutic system.

Example:

Nitroglycerin releasing Transdermal therapeutic system (Nitro disc, Searle, USA) for once a day therapy of angina pectoris.

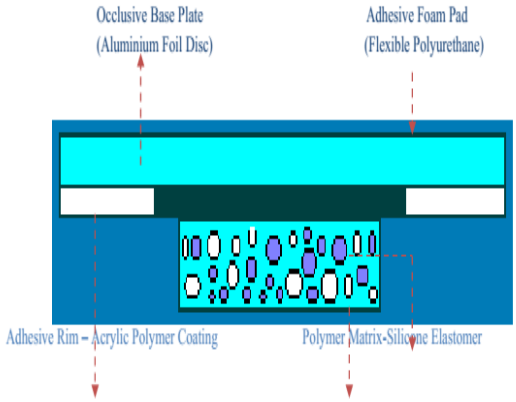

Fig. 6: Cross Section of Micro reservoir TDDS

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