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A REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs through the skin. Transdermal drug delivery system can improve the therapeutic efficacy and safety of the drugs because drug delivered through the skin at a predetermined and controlled rate. Skin is the important site of drug application for both the local and systemic effects. Skin of an average adult body covers a surface of approximately 2 m2 and receives about one-third of the blood circulating through the body. Skin is an effective medium from which absorption of the drug takes place and enters the circulatory system. Transdermal patch is a medicated adhesive patch that is placed on the skin to deliver the drug through the skin in order to achieve systemic absorption of drug at a predetermined rate over a prolonged period of time. This review article covers a brief outline of the transdermal drug delivery system, advantages over conventional drug delivery system, Layers of the skin, various components of transdermal patch, penetration enhancers, and evaluation of transdermal system and applications of Transdermal patch.

KEYWORDS

Penetration enhancers, Transdermal patches and Adhesive patch.

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INTRODUCTON

Transdermal drug delivery system is defined as the topically administered medications in the form of patches which when applied to the skin deliver the drug, through the skin at a predetermined and controlled rate. In transdermal drug delivery system (TDDS), transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver drug through the skin and to the systemic circulation at a predetermined rate over a prolonged period of time[1]. A drug is applied in a relatively high dose inside of a patch, which is worn on the skin for an

extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration in the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch.

ANATOMY AND PHYSIOLOGY OF SKIN

Human skin comprises of three but mutually dependent tissues:

· The stratified, vascular, cellular called as "epidermis"
· Underlying dermis of connective tissues
· Hypodermis

Epidermis

The multilayered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids.

Stratum corneum

This is the outermost layer of skin also called as horny layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called corneocytes. It is flexible but relatively impermeable.

It is the principal barrier for penetration of drug. The architecture of horny layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein "bricks" embedded in lipid "mortar." The lipids are arranged in multiple bilayers. There is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bilayer form shown in Table No.1.

Viable Epidermis

This is situated beneath the stratum corundum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. In the basal layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead Horney cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum cornium[2].

Dermis

Dermis is 3 to 5 mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeate very low and the resulting concentration difference across the epidermis provides essential concentration gradient for transdermal permeation. The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as afat storage area. This layer helps to regulate temperature, provides nutritional support and mechanically protection. It carries principal blood vessels and nerves to skin and maycontain sensory pressure organs. For transdermal drug delivery, drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum.

FACTORS AFFECTING TRANSDERMAL BIOAVAILABILITY (Physicochemical factors)

Skin hydration

In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectant is done in transdermal delivery.

Temperature and pH

The permeation of drug increase ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important 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[3].

Drug Concentration

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

Partition Coefficient

The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

Molecular Size and Shape

Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

BIOLOGICAL FACTORS

Skin Condition

Chloroform, methanol damage the skin cells and promotes penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.

Skin age

The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDS.

Blood flow

Changes in peripheral circulation can affect trans dermal absorption.

Regional Skin Sites

Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.

Skin metabolism

Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.

Species Differences

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

Basic Components of TDDS

A. Polymer matrix/ Drug reservoir
B. Drug
C. Permeation enhancers
D. Pressure sensitive adhesive (PSA)
E. Backing laminates
F. Rate controlling membrane
G. Release liner
H. Other excipients like plasticizers

Solvents

Various solvents are used to solve ordisperse the polymer and adhesive or drug used in preparation of transdermal system. Among those chloroform, methanol, acetone, isopropanol and dichloro methane are used frequently.

TYPES OF TRANSDERMAL PATCHES

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 shown in table no.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[4].

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.

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.

MATRIX SYSTEM

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.

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.

Microreservoir System

In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. 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. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer insitu by using cross linking agents.

EVALUATION OF TRANSDERMAL PATCHES

Evaluation studies of Transdermal patches are more important because of their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types;

- Physicochemical evaluation.
- In vitro evaluation.
- In vivo evaluation.

Technologies for Developing Transdermal Drug Delivery Systems

The technologies further can be classified in four basic approaches:

- Polymer membrane partition-controlled TDDS
- Polymer matrix diffusion-controlled TDDS
- Drug reservoir gradient-controlled TDDS
- Micro reservoir dissolution-controlled TDDS.

EXAMPLES OF TRANSDERMAL DRUG DELIVERY SYSTEMS FOR ANTIHYPERTENSIVE DRUGS

Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs Hypertension, a cardiovascular diseases account for a large proportion of all deaths and disability worldwide. Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals and approximately 7.1 million deaths per year may be attributable to hypertension Clonidine was the first antihypertensive drug developed in the transdermal form in figure no.1.

The major problem associated with the dermal delivery system is the excellent barrier property of the skin (Fig.1).This resides in the outermost layer, the stratum corneum. The intercellular channels contain a complex milieu of lipids that are structured into ordered bilayer arrays. It is the combination of the nature of these and the tortuous route that is responsible. A molecule that is hydrophilic in nature will be held back by the lipophilic acyl chains of the lipids and conversely, a lipophilic permeant will not penetrate well through the hydrophilic head-group regions of the lipids. Transdermal delivery system of an antihypertensive

drug, clonidine, has already been marketed. Other antihypertensive drugs that have been explored for their transdermal delivery potential are propranolol, metoprolol, mepindoldol, captopril, verapamil, diltiazem, nifedipine and others [5].

Some of the Most Important Antihypertensive Drugs

- Clonidine
- Timolo lmaleate
- Indapamide
- Verapamil hydrochloride
- Nifedipine
- Lisinopril dihydrate

METHODS FOR ENHANCING TRANS DERMAL DRUG DELIVERY

Skin penetration can be enhanced by following methods

Drug and Vehicle Interactions

- Ion pairs and complex coacervates
- Eutectic systems

Stratum Corneum Modification

- Hydration
- Chemical penetration enhancers

Stratum Corneum Bypassed or Removed

- Microneedle based devices
- Needle-less injection
- Radio frequency
- Suction ablation
- Skin abrasion

Electrically Assisted Methods

- Electroporation
- Iontophoresis
- Ultrasound (Phonophoresis, Sonophoresis)
- Magnetophoresis
- Laser radiation and photomechanical
- Waves
- Thermophoresis

Vehicles and particles

- Micro or Nanocapsules
- Nanoemulsions/submicron ,emulsions/miniemulsions
- Solid lipid nanoparticles
- Multiple emulsions
- Microemulsions
- Liposome
- Transfersomes
- Ethosome
- Aquasomes

MERITS AND DEMERITS

Merits of TDDS

- Improved bioavailability and longer duration of action resulting in a reduction in dosing frequency
- Steady permeation of drug across the skin, allowing consistent serum drug level; often a goal of therapy
- Reduced side effects and in addition, if toxicity develops from a drug administered transdermally, the effects could be moderated by removing the patch
- Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug degradation effects ·
- Topical patches are a painless, noninvasive way to deliver substances directly into body· This is an effective route to deliver drugs that are broken down by the stomach acids, not well-absorbed from the gut, or extensively degraded by the liver· Transdermal patches are alternative to oral route for people who cannot, or prefer not to take medications or supplements orally. It is of great advantage in patients who are nauseated or unconscious. Topical patches are cost-effective, convenient; especially notable parameter in some patches is that it requires only once weekly application.

Demerits and Limitations of TDDS

- Many drugs especially those with hydrophilic structures permeating the skin too slowly, may not achieve therapeutic level
- The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema
- The barrier function of the skin changes from one site to another on the same person, from person to person and also with age

- TDDS cannot deliver ionic drugs.
- TDDS cannot achieve high drug levels in blood/plasma
- TDDS cannot be developed for drugs of large molecular size
- TDDS cannot deliver drugs in a pulsatile fashion
- TDDS cannot be developed if drug or formulation causes irritation to skin.

Applications of Transdermal Patches

- Transdermal patch of nicotine, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
- Nitroglycerine patches are also sometimes prescribed for the treatment of Angina.
- Clonidine, the antihypertensive drug and ketoprofen, the non-steroidal anti-inflamatory drug are also available in the form of transdermal patches.
- Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.
- Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).

Table No.1: Regional Variations in Water Permeability of *Stratum Corneum*

S.No	Skin Region	Thickness (mm)	Permeation Rate ($mg/cm^2/hr$)	Diffusitivity (cm/sec x 1010)
1	Abdomen	15.00	0.34	6
2	Volar forearm	16	0.31	5
3	Back	10	0.29	3
4	Forehead	13	0.85	12
5	Forehead	5	1.70	7
6	Back of hand	49	0.56	32
7	Palm	400	1.14	535
8	Plantar	600	3.90	930

Table No.2: Significant Properties of TDDS

S.No	Properties	Comments
1	Shelf life	Up to 2 years
2	Patch size	< 40 cm2
3	Dose frequency	Once a daily to once a week
4	Aesthetic appeal	Clear, tan or white color
5	Packaging	Easy removal of release liner and minimum number of steps required to apply
6	Skin reaction	Non irritating and non-sensitizing
7	Release	Consistent pharmacokinetic and pharmaco dynamic profiles
8	Dose	Should be low
9	Half-life (h)	10 or less
10	Molecular weight	< 400
Skin reaction		Non irritating and non-sensitizer
Oral bioavailability		**Low**
Therapeutic index		**Low**

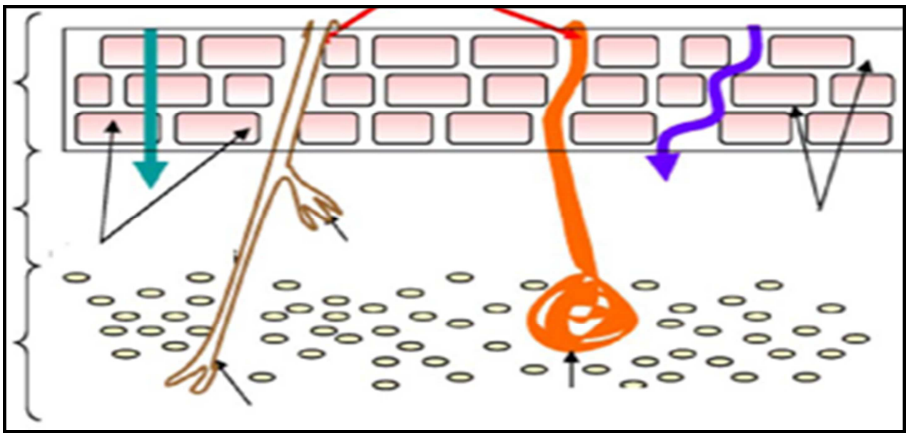

Figure No.1: Permeation through Skin

CONCLUSION

The use of transdermal drug delivery devices has experienced a remarkable increase in recent years. This interest in transdermal products can be attributed to many advantages offered by this unique route of administration. Although, the transdermal patches have become a proven technology that offers variety of significant clinical benefits over other dosage forms, the systems still offer many challenges in evaluation and testing area of transdermal patches. Transdermal Drug Delivery System a realistic practical application as the next generation of drug delivery system.

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CONFLICT OF INTEREST

None declared.

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