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Review Article

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TRANSDERMAL SUSTAINED AND SAFE RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

Transdermal drug delivery system is most preferable route of drug administration. This route has high acceptability because of safe and effective delivery of drug. The human skin is a readily accessible surface for drug delivery. 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. Over the past decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The human skin surface is known to contain, on an average, 10- 70 hairs follicle and 200-250sweat duct on every square centimeters of the skin area. It is one of the most readily accessible organ of the human body. There is considerable interest in the skin as a site of drug application both for local and systemic effect. However, the skin, in particular the stratum corneum, poses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability. Skin penetration enhancement technique have been developed to improve bioavailability and enhance the range of drugs for which topical and transdermal delivery is a viable option. During the past decades, the number of drugs formulated in the patches has hardly enhance, and there has been little change in the composition of the patch system. Modification have been mostly limited to refinement of the material used. The present review article explores the overall study on transdermal drug delivery system which lead to novel drug delivery system.

KEYWORDS: Transdermal drug delivery, permeation enhancer, topical, epidermis.

INTRODUCTION

Transdermal drug delivery system are used to hold the rate of the drug concentration in which the reservoir contain the liquid drug which embedded in the polymeric membrane the drug are cross the skin to the systemic circulation. Transdermal drug delivery system are used for the better bioavailability and it is not go through the first pass metabolism system , it is liver bypass system. It is provide the metabolism of the drug through the contact with skin and show its action by the conventional dosage form as predetermined rate. Transdermal drug delivery system is varying from the other route of topical drug delivery systems. Transdermal drug delivery system involve the epidermal or and other tissues of the skin which are helps to increase the permeation of the drug to the systemic circulation. Transdermal drug delivery system have a critical situation on the adhesion of the patches.

It is patient compliance and it is decrease the oral route administration of drug and it is beneficial for the intravenous drug infusion by the by pass metabolism. It is avoid the hepatic first pass metabolism.

ANATOMY OF SKIN

Anatomy of skin is include

The epidermis: epidermis is firstly made by the two layer that is Malpighian layer and horny layer. Malpighian layer is also known as viable epidermis. It is divided into four parts that is.

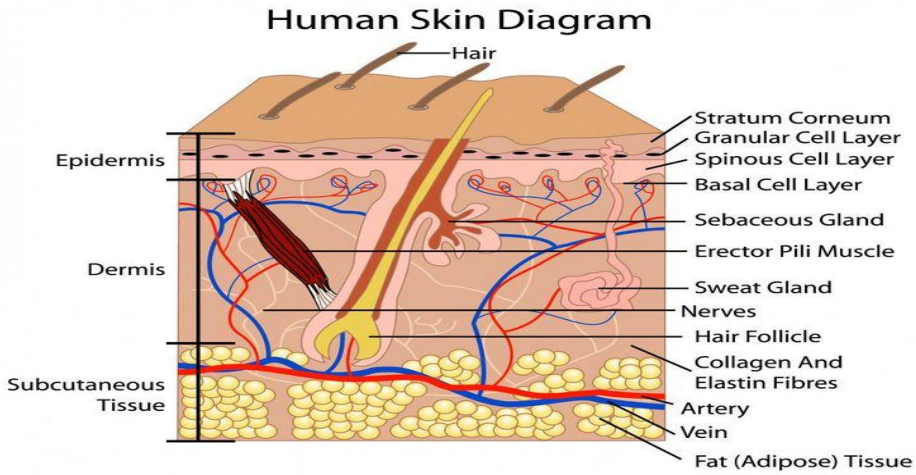

Fig 1: Diagram of the Skin.

- ***Stratus lucidium***
- ***Stratum granulosum***
- ***Stratum spinosum***
- ***Stratum basal***

These are the layers shown in fig.2:

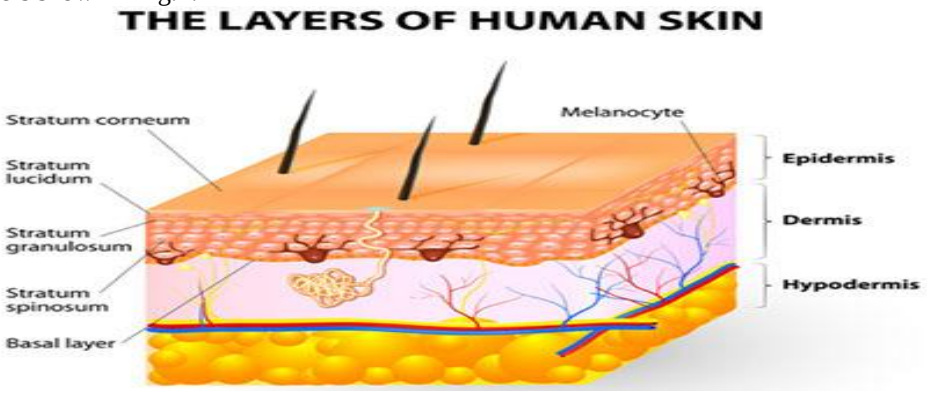

Fig 2: Layers of the skin.

Stratum corneum: It is the outer layer of the skin. it is the most important barrier of the skin to movement of the foreign particles into the outside to inside the skin. It is based on the components which are present in this layer 75-80% proteins, 5-15% lipids and 5-10% ondansetron on the dry skin nature.[5]

It is almost 10 micrometer thick. Stratum corneum have the protein that is keratin. Which is create a network and cohesion process of flexibility and recovery. It is a heterogeneous layer and it have both properties lipophilic and hydrophilic.

Viable epidermis

Viable epidermis is located on under the stratum corneum. Its thickness is 0.6mm present in eyelids and 0.8mm present in palms. It is have the different four layers of skin stratum lucidum, stratum granulosum, stratum spinosum, and stratum basal. It is alter the keratinization process which is form in the stratum corneum layer.[5]

Dermis: It is the 5mm thick which are formed by the connective tissues which have the blood vessels lymph vessels and nerves. T6he cutaneous layer are need to supply the blood and regulate the body temperature. It gives the nutrients and oxygen to the skin.

Hypodermis: Hypodermis is also known as the subcutaneous fat tissue. It is store the fatty substances. It is also helps to provide the nutrients or energy and it regulate the temperature of the body. These are the layers which is important for the topical drug delivery and these are also the barriers of the skin which are permeate to the drug which cross the direct to the systemic circulation.

Percutaneous absorption: It is the process in which the drug are passes through the different layers of the skin. it is penetrate through the stratum corneum. Percutaneous absorption is defined as the drug cross and penetrate the various layers and drug goes to systemic circulation and avoid the first pass metabolism.[5]

Percutaneous absorption involve the two mechanisms.

- Trans epidermal absorption.
- Trans follicular absorption.

TRANSEPIDERMAL ABSORPTION: Trans epidermal absorption involve the diffusion process, the drug are diffuses by the skin. This is process is start with the stratum corneum. Most of the substance goes under the stratum corneum absorption that is lipoid route. In this the hydrophilic, polar non-electrolytes, and ionic substances will cross the viable epidermis. While the hydrophobic drugs can cause the problem to cross the viable epidermis. Epidermal layer have very less interspaces to each other.

TRANS FOLLICULAR ABSORPTION: It mechanism by the shunt pathway. It is absorption by the sweat gland, hair follicle and the sebaceous gland for the transport the drug into the systemic circulation. This route are consider the higher permeability of drug and it shows better bioavailability for the polar substances. Which substances are rarely permeate to the stratum corneum those are follow this route of absorption.

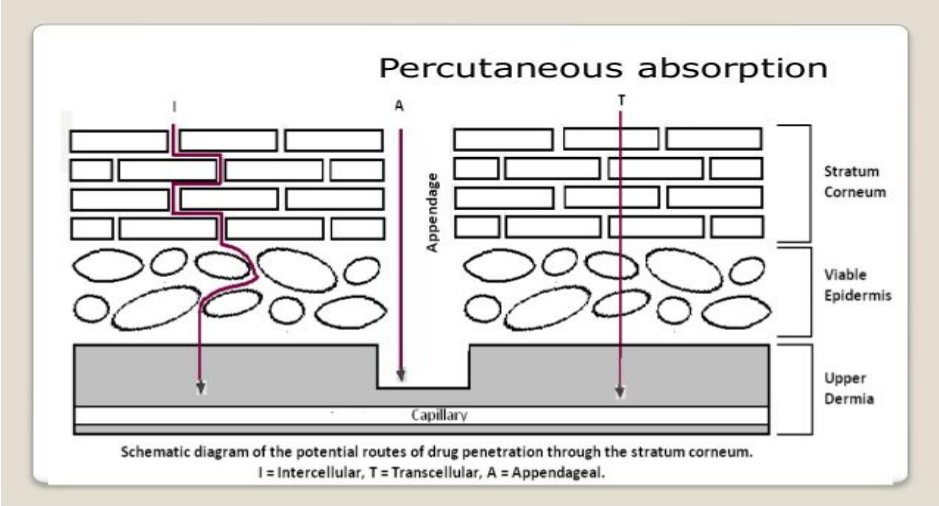

Fig 3: Percutaneous Absorption of The Drug.

Advantages of Transdermal drug delivery system

- ✓ It is avoid the hepatic first pass metabolism process.
- ✓ It is also avoid the gastro intestinal tract.
- ✓ It is get less side effect
- ✓ It is increase the bioavailability of the drug and shows maximum therapeutic effect.
- ✓ It can control plasma concentration of the drug.
- ✓ Avoiding the fluctuations of the drug.

Disadvantages of the Transdermal drug delivery system

- ✓ It can cause the sometimes irritation on the site of apply.
- ✓ Person to person the barrier function are different.
- ✓ It cannot deliver the ionic drug.
- ✓ It cannot afford the large molecular size of the drug.
- ✓ It is not for the delivery of drug for pulsatile function.

TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM

RESERVOIR SYSTEM: In this system the drug reservoir are embedded between the backing membrane and rate controlling membrane. This system patches made by the backed through the backing membrane. In this system the drug are present in the form of suspension, gel, solution which is dispersed in the polymeric membrane.

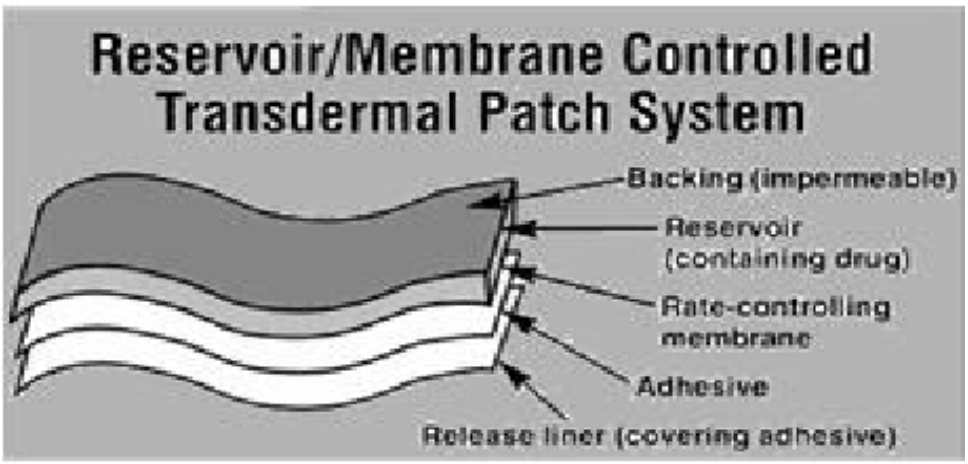

Fig 3: Reservoir System.

MATRIX SYSTEM: In this system the drug are loaded in the adhesive layer and the semisolid occlusive base plate or polymeric layer. In this the drug are suspended into the solution and suspension form.

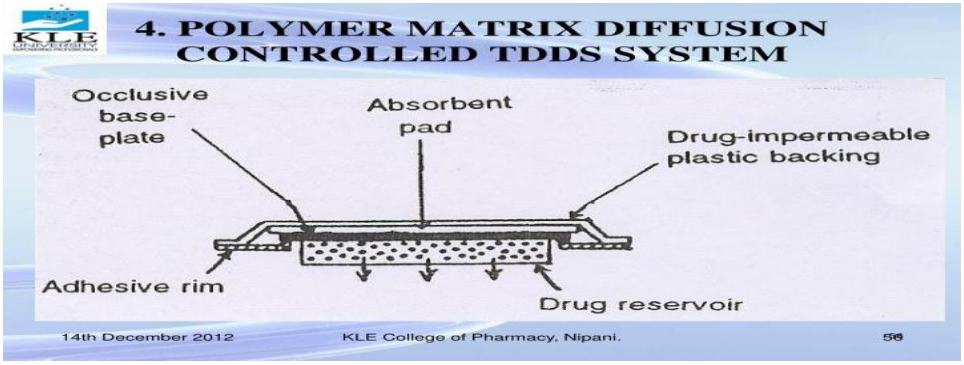

Fig 4: Matrix System.

MICRORESERVIOR SYSTEM: This system is the combination of the polymer matrix and reservoir system. In this system the drug firstly suspended in the water soluble polymer and then it dissolve in the lipophilic or lipid soluble polymer for formation of the microspheres or microcapsules of the drug reservoir. Than it is stable by the heat through the crosslinking reaction by addition the cross linkage agents.

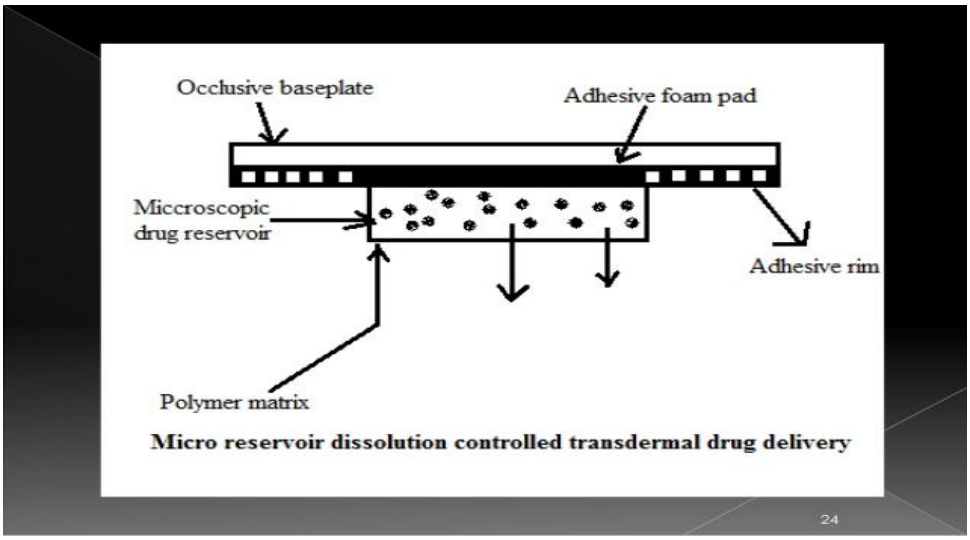

Fig 5: Micro Reservior System.

FACTOR AFFECTING TRANSDERMAL DRUG DELIVERY SYSTEM

1. **BIOLOGICAL FACTOR**

- **SKIN CONDITION**: Many of the agents are cross the skin barrier and penetrate through the skin like: acid, alkali. Because skin is the barrier of itself.
- **SKIN AGE:** In this the skin are vary from the age to age. Adult and young ones is more permeable than the old age.
- **BLOOD SUPPLY**: Peripheral circulation of drug change and it effect in the transdermal absorption.
- **SKIN METABOLISM**: Metabolism of the skin is like: steroids, hormones and chemical carcinogens and few drugs. Skin metabolism is to determine the therapeutic effect of the drug which is permeated through the skin.

2. PHYSICOCHEMICAL FACTOR

- **SKIN HYDRATION**: Skin hydration is the most important factor for the permeation of the drug for Transdermal drug delivery. For hydration of the skin the Transdermal delivery is added the humectants.
- **TEMPERATURE AND pH:** Temperature are also vary the skin permeation of the drug. Weak acid and weak basic drugs are dissociates according to the pH.
- **MOLECULAR SIZE AND SHAPE:** Drug absorption is inversely proportional of the molecular size and shape of the dosage form like suspension, gel, solutions are more preferred in the Transdermal drug delivery system.

2. **ENVIRONMENTAL FACTOR**

- **SUNLIGHT:** Most the drug are not given in the sunlight exposure because sunlight burn the skin cells and it can cause irritation or skin infection.

- **COLD SEASON:** Moisturizer are use in the cold season for prevent the breakage of the skin. And also the drinking of more water for hydration of the skin.
- **AIR POLLUTION:** Dust can block the pores of the skin. It can also increase the bacterial growth in the skin.

Formulation of transdermal drug delivery

- ❖ Drug reservoir/polymer matrix
- ❖ Drug
- ❖ Permeation enhancer
- ❖ Backing laminates
- ❖ Release liner
- ❖ Rate controlling membrane
- ❖ Other excipients

- **Drug reservoir/polymer matrix:** polymer are the main base of the transdermal drug delivery system. Which is help to hold the drug in the transdermal patches. The polymer are used in the patches which should be nontoxic, biocompatible and chemically inert with the drug and other excipients.
- **Drug:** The drug is the active constituent of the formulation. It is responsible for showing the therapeutic and pharmacological action. It is the medicament which is directly attached to the release liner.
- **Penetration enhancers:** Penetration enhancer are the compound which are enhance the permeability of the drug through altering the skin barriers. The compounds which is release the drug through the stratum corneum.
- **Backing laminates:** Backing laminates are the supportive part of the dosage form. It is responsible for providing the release of drug to the dosage form. They should always be impermeable to drug and to penetration enhancers.
- **Release liner:** during the storage release liner provide to protect the drug from the contamination and adulterant. It is the primary part of the storage condition.
- **Rate controlling membrane:** Rate controlling membrane is control the release of drug into transdermal devices. These are made by the polymer that is chitosan which are shows the higher promises so this is use for the rate controlled. Some of other rate controlling membrane are there that is synthetic, poly ethylene sheets, vinyl acetate, co-polymer, cellulose derivatives.
- **Other excipients:** other excipients like chloroform, methanol, acetone, isopropanol, and dichloromethane, these are used for the preparation of the formulation. Some plasticizers are added in the formulation of patches.

These are the components which are used in formulation of transdermal patches shown in fig.4:

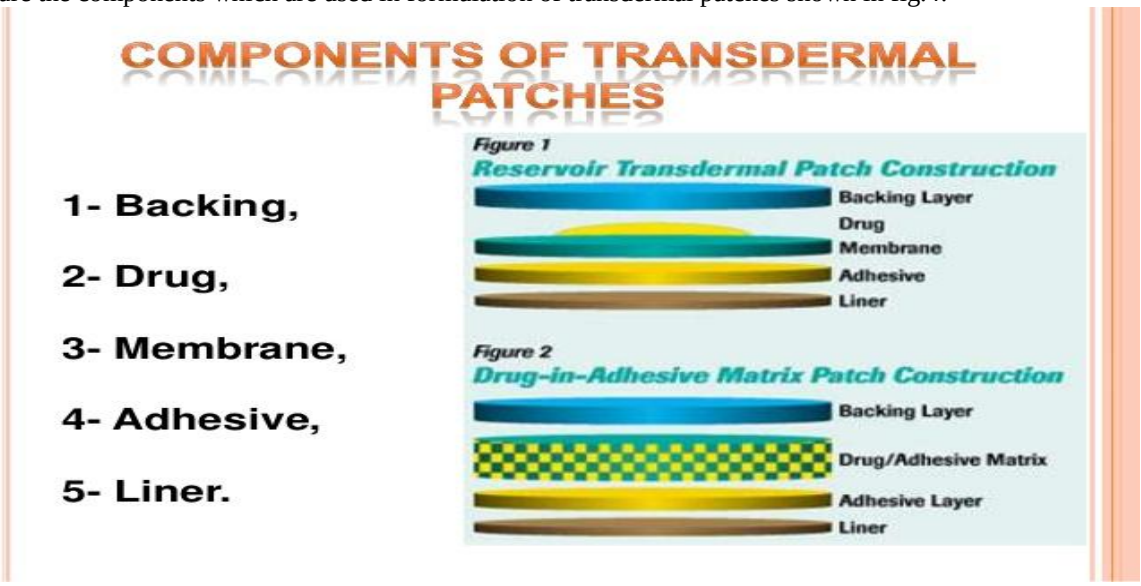

Fig 4: Components of Transdermal Patches.

EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM

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

➢ **PHYSICOCHEMICAL EVALUATION**

THICKNESS-Thickness is evaluated by the travelling microscope, screw gauge, and micrometer at a glance of different points of the film of transdermal patch.

UNIFORMITY OF WEIGHT-It is evaluated by choosing the 10 patches randomly which are calculate the average weight of all 10 patches. And individual

weight of the patches are not fluctuate expressing from the average weight.

DRUG CONTENT UNIFORMITY-Patches have specified area (3.14cm). which is dissolved in the 5ml of dichloromethane and makeup the vol. up to 10ml.with phosphate buffer dichloromethane will be evaporated by using the vacuum evaporator. Than blank sample will be prepared by same procedure only the patch will not added than filtered the solution and diluted it as suitable. Now the absorbance will be determine by the double beam U.V visible spectroscopy at wavelength 242nm.

MOISTURE CONTENT-The prepared film are weighed individually and put in the desiccator which containing calcium chloride at the 27^{o}C (room temperature) for a one day almost. Than the film are reweighed and the weight is going to be constant weight. The percentage weight are calculated by the following formula:

$$\%\text{moisture content} = \frac{\text{Initial weight} - \text{final weight}}{\text{Final weight}} \times 100$$

FOLDING ENDURANCE-Take a patch and fold it up to the breakage of film. In which the no. of time patch folded at the same place if it is give result without breaking value that is folding endurance of it.

- **INVITRO EVALUATION**

1. **PEEL ADHESSION PROPERTIES:** In this test, we remove the adhesion from the test substrate through applying pressure is referred to as peel adhesion. Molecular weight and adhesive polymer helps to determine the adhesion properties. A single tape is applied to the stainless steel plate or a backing membrane and then the tape is pulled from the substrate at a 180^{o} angle and force are required for tape removal and measure the peel adhesion.
2. **THUMB TACK TEST:** In this test the thumb are track to the adhesive polymer and the tack property is determined.
3. **PROBE TACK TEST:** It is determine by the force are required to pull a probe away from the adhesive at a fixed rate is recorded as tack
4. **QUICK STICK (PEEL) TACK:** It is by the force are required for the breakage of bond which are between the adhesive and substrate is measured by the pulling the tape away from the substrate. At the speed of 90 of 12 inch /min.

- **INVIVO EVALUATION:** In vivo study can be determine by the two models

1-animal model
2-human model

1. **ANIMAL MODEL:** The most common animals are required for the study is hairless mouse, hairless monkey, Guinee, pig, hairless rat, rhesus monkey. Rhesus monkey most referred for the in vivo study of the transdermal drug delivery evaluation in man.
2. **HUMAN MODEL:** It is the stage of the transdermal drug delivery of the drug from done by the human volunteer. In this study we determine then therapeutic effect of the drug or dosage form. In this study evaluate see the pharmacokinetic and pharmacodynamics parameter. Clinical trial involve the risk assessment, side effect, and efficacy of drug patient compliance. In this study involve all the phases of clinical trial: phase 1, phase 2, phase 3 and phase4.

Phase1: It is conduct the safety of volunteer.
Phase 2: It is determine the short term safety and mainly the effectiveness of patient.
Phase3: It is conduct the large number of patient population effectiveness of the drug.
Phase 4: This phase is include the marketing surveillance the patches are expose to the market.

RESULT

Transdermal patches are used mostly. Transdermal drug delivery also use for the better absorption of the drug. It shows the better patient compliance to compare other dosage forms oral, IV, IM, and other form. This delivery of drug are shows overcomes the challenges of drug delivery. It avoid the first pass metabolism. It increase the therapeutic effect and minimize the side effect. It is easy to administer and patient agree to administer the drug by the transdermal route.

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