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Review Article

Skin-Deep Insights: Exploring Transdermal Drug Delivery Systems in a Brief Review

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ABSTRACT

The transdermal drug delivery system is a technique that provides drug absorption via the skin. The system has many advantages over conventional administration routes such as intravenous or oral administration for systemic and local drug delivery with simple administration. It decreases loss from the fast-pass metabolism of the liver, delivered in a controlled manner. The skin barrier including the stratum corneum and epidermal layer, is necessary to develop transdermal drug formulations. So many chemical and physical enhancers have been developed, that they need high doses or high potency to exert efficiency, which induces irritation, causes damage, and reduces the skin barrier function. As a result, only medications whose molecules are small enough to penetrate the skin can be delivered in this method.

INTRODUCTION

What comes to mind when one hears the term transdermal drug delivery? Most likely, when one thinks of a nicotine patch, they picture a straightforward patch that is applied to the skin like an adhesive bandage.[1]

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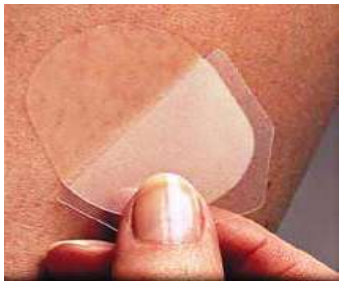

Fig.1 Transdermal Patch

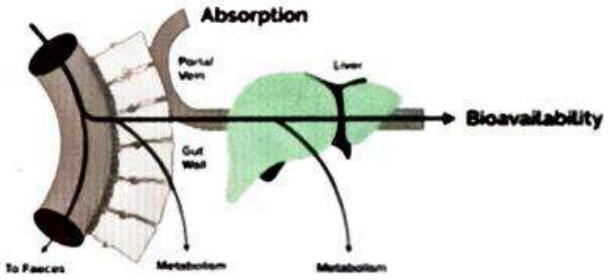

Fig.2 Absorption Mechanism

In addition to enabling continuous delivery of medications with brief biological half-lives, transdermal delivery also prevents pulsed entry into the systemic circulation, which frequently results in undesired side effects.[6]

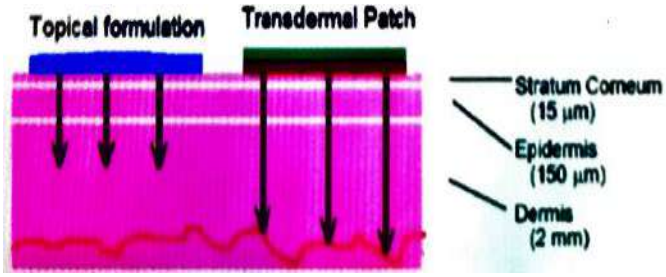

Fig.3 Permeation Mechanism Through Various Skin Layers

Effective drug delivery in addition to appropriate drug selection is necessary for the best possible treatment results. The surface of the human skin is easily accessible for medication administration. Creating regulated drug distribution has grown in importance during the last three decades becoming more significant in the pharmaceutical business. The reaction of the pharmacological is the intended therapeutic outcome and the unwanted side. A drug's effectiveness is based on the amount of the medication at the point of action, which is dependent on depending on the quantity and degree of absorption of the medication at its point of action Injections and tablets have been the conventional method of taking drugs; Popularity for new options is rising. Just one incredibly effective substitute delivery technique is the cross-talk. The skin on an adult average has a surface area of around 2 m/2, and it receives roughly 1/3 of the blood that circulates throughout the body Transdermal delivery of medication into the body layer of skin, it's important to comprehend the dermis. When drugs are administered in conventional dosage forms, there is typically a wide range of fluctuations in plasma drug concentrations, which can result in poor or unwanted toxicity. These elements combined with additional elements like inconsistent absorption and repeated dosage, resulted in the notion of a system of controlled drug delivery therapeutic framework. A dosage form with one or more releases more medications consistently in a planned manner for a set amount of time, either globally or to a predetermined A controlled drug delivery system is the intended organ. The main goals of medication delivery under control are to guarantee safety and enhance medication efficacy in addition to patient adherence. To do this, improved management of reduced dosage frequency and plasma drug levels. [1,4,6]

PROS and CONS: [1,7]

1. Simple to operate.
2. Prevent issues with drug absorption in the GIT.
3. prevents FP drug metabolism in the liver.
4. In the event of toxicity, quick termination is feasible.
5. It is possible to self-medicate. advantage: [1,6]
6. It is not feasible to take more than 10 mg per day.
7. Irritation locally is a serious issue.

8. Drugs that need high blood levels are inappropriate.
9. Long half-life drugs cannot be prepared in TDDS.

STRUCTURE OF SKIN: [16,24]

The largest organ in the body is the skin. It acts as a wall separating the body's interior from the outside environment. The skin's temperature fluctuates between 30 and 40 °C based on the external circumstances. There are three layers to it. The surface layer is referred to as the epidermis, the dermis is the middle layer, and the hypodermis is the deepest layer.

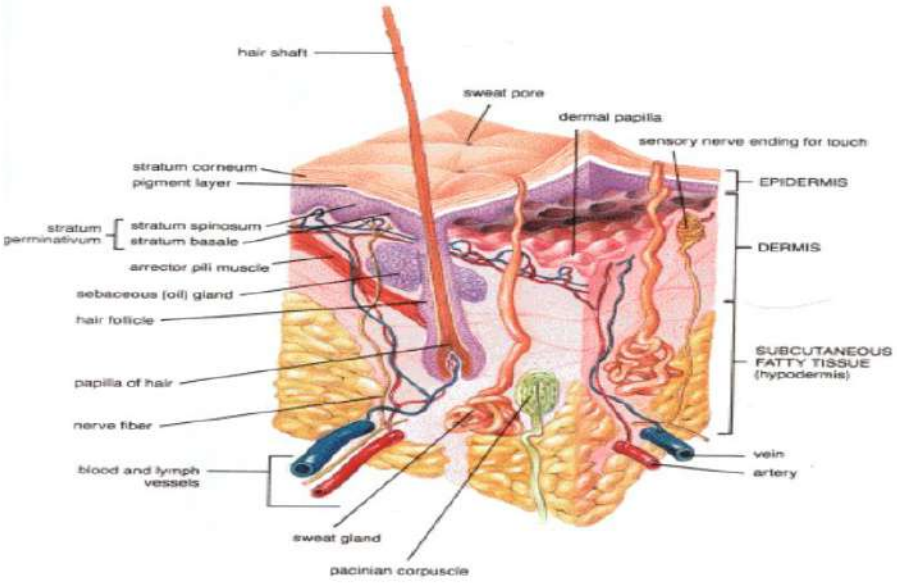

Fig.4 Structure of skin

Epidermis:

The topmost layer of skin, or epithelium, is called the epidermis. It functions as a physical barrier, keeping things and living things from entering the body and preventing the body from losing water. Its thickness varies based on the location of the body. The layer of skin is made up of squamous epithelium in layers. Thus, it is made up of layers of compressed cells. Keratinized skin, hair, and nails have an impermeable surface composed of keratin, a dead and hardened protein. Mucous membranes are wet and non-keratinized.

There are three primary cell types in the epidermis:

1. Keratinocytes [skin cells]
2. Melanocytes [pigment-producing cells]
3. Langerhans cells [immune cells]

Keratinocytes:

As they spread outward, the keratinocytes mature or differentiate and gather keratin. Eventually, they rub off or fall. They create four separate layers. Stratum corneum (Horny layer), and Stratum granulosum (granular layer). (Spiny cells layer), Stratum Basale (base layer).

Melanocytes:

Melanocytes are located in the epidermis basal layer. Different skin tones are caused by the pigment called melanin that these cells produce. Melanin is bundled into tiny packages (or melanosomes), which keratinocytes subsequently receive.

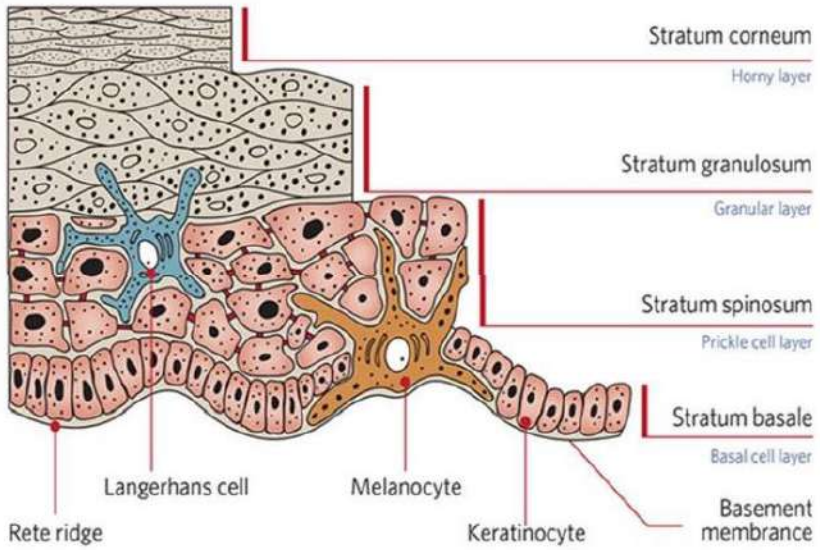

Fig:5 Different skin layer

Langerhans cells:

Immune cells called Langerhans cells are located in the epidermis and are in charge of assisting the body in identifying and eventually learning to tolerate new "allergens"—material that is foreign to the body. The allergen is broken down into smaller pieces by Langerhans cells, which then move from the epidermis into the dermis.

Dermis:

The skin's supportive layer or fibrous connective tissue is known as the dermis. Collagen fibers, which are primarily found in the dermis, are the main type of fibers. Collagen strands possess remarkable tensile strength and give the skin toughness and strength. Collagen A Little bundles in the papillary or upper dermis form thicker bundles located in the reticular or deeper dermis.

The following are examples of normal dermal cells: Mast cells are disturbed and release granules containing histamine and other chemicals.

Cells called vascular smooth muscle –

These enable blood vessels to dilate and contract, which is necessary to regulate body temperature.

Specialized muscle cells –

Myoepithelial cells, for instance, are present near sweat glands and contract to release perspiration.

Fibroblasts:

These are the cells that generate and accumulate collagen and additional dermal components as needed for growth or to mend injuries. A fibroblast at rest has very minimal cytoplasm in contrast to an active cell and seems to possess a "naked" nucleus.

Immune cells:

Immune cells come in a variety of forms. Histiocytes, or tissue macrophages, are responsible for removing and breaking down foreign or degraded material; this process is called phagocytosis.

Hypodermis:

Directly beneath the dermis, the hypodermis, also known as the subcutaneous layer or superficial fascia, connects the skin to the underlying fascia (fibrous tissue) of the bones and strength. One crucial approach to both local and systemic treatment is the topical administration of drug delivery via skin delivery is acknowledged as an efficacious treatment for localized inflammatory diseases. When applied to intact skin, transdermal drug delivery systems' discrete, self-contained dosage forms allow the drug to enter the systemic circulation at a controlled rate. Currently, Oral drug delivery is the most widely used method.

MECHANISM OF ABSORPTION THROUGH SKIN [17]

The mechanism involved is passive diffusion, which can be expressed by FICK's LAW of **DIFFUSION:**

dq/dt=DKA(C1-C2)/h

Dq/dt= rate of diffusion
D= diffusion coefficient
K= partition coefficient
The surface area of the membrane
H= thickness of the membrane

According to Fick's formula, the rate of diffusion is directly proportional to the partition coefficient. It means if the drug is more lipophilic then their rate of absorption and diffusion will be high. If the drug is hydrophilic then their rate of absorption will be slow. The rate of diffusion is directly proportional to the surface area of the membrane, which means that the larger the surface area of the membrane then the larger the diffusion will be maintained. The rate of diffusion is also directly proportional to the concentration gradient across the drug patches and bloodstream. The rate of diffusion is inversely proportional to the thickness if the thickness of the membrane is high or more than the rate of diffusion is less.

ROUTE OF DRUG ABSORPTION THROUGH SKIN

1. Trans-epidermal route
2. Trans-follicular route

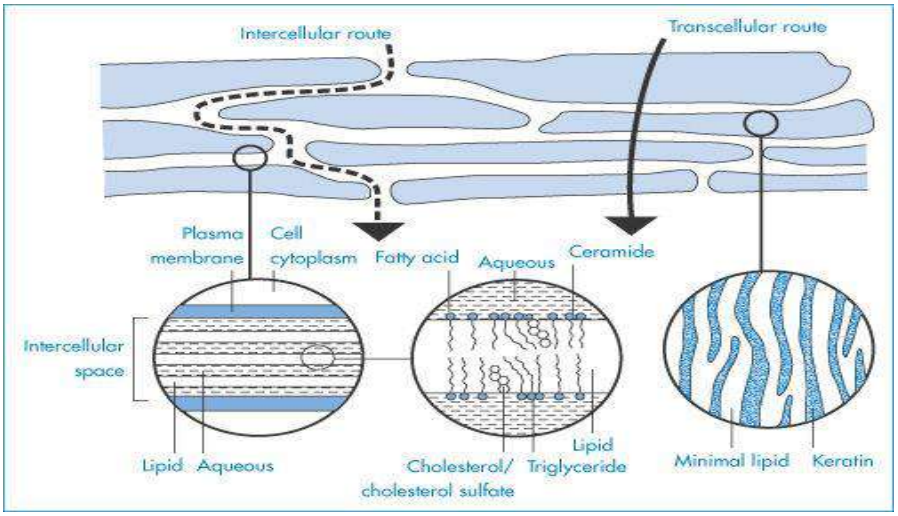

Fig:6 Absorption through skin

Trans-epidermal route:

- The stratum corneum is the main resistance for absorption through this route Permeation involves partitioning of the drug into the stratum corneum.
- Permeation through the skin depends upon the o/w distribution tendencies of the drug.
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- Lipophilic drugs concentrate in and diffuse with relative ease.
- Permeation through the dermis is through the interlocking channels of the ground substance.[14]

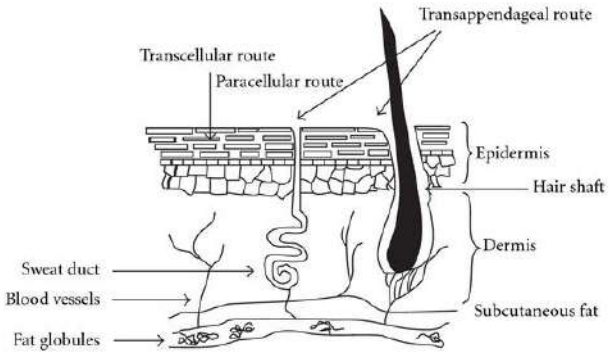

Fig:7 Trans-epidermal route

Trans-follicular route:

- The skin appendages (sebaceous and eccrine glands) are considered shunts for bypassing the stratum corneum.

- The follicular route is important for permeation because the opening of the follicular pore is relatively large and sebum aids in the diffusion of the penetrant.
- Partitioning into the sebum followed by the diffusion to the depth of the epidermis is the mechanism.
- Mainly water soluble are diffused faster through appendages than that of other layers.
- Sweat glands and hair follicles act as a stunt i.e. easy pathway for diffusion through rate-limiting stratum corneum.[14]

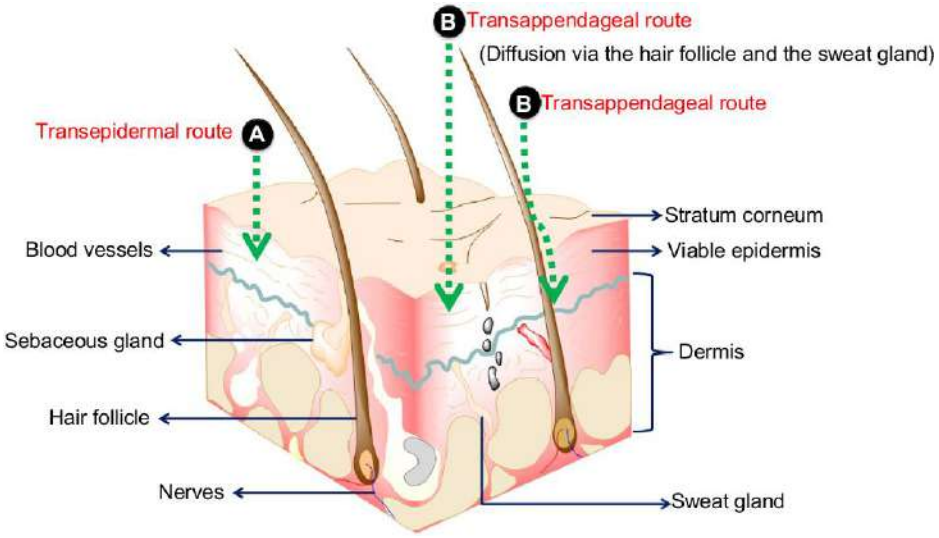

Fig:8 Trans-follicular route

FACTORS AFFECTING PERMEATION THROUGH SKIN

Physicochemical properties of the permeate molecule

1. **Solubility and partition co-efficient:**

The solubility of the drug is high when they are more lipophilic in nature and its partition coefficient is high. Then the rate of absorption will be high.

2. **pH condition:**

The pH condition of any drug should be equal to the systemic circulation and the site place where it is applied.

3. **Penetrant concentration:**

The penetrant concentration of any drug depends upon the drug concentration of any drug. If the concentration of the drug is high in the transdermal patches, then their rate of absorption will be high.

Physicochemical properties of the drug delivery system

1. **Release characteristic:**

The release characteristics of two types;

Reservoir system:

In this system when the polymer is destroyed the whole drug is removed and goes into the systemic circulation at one time.

Matrix system:

In this system, the single layer of polymers is destroyed, and a small or fixed quantity of drugs is released into the systemic circulation.

2. **Composition of drug delivery system:**

The composition of a drug delivery system can impact both drug release rate and systemic circulation permeability through hydration.

3. **Permeation enhancer used:**

Permeation enhancers are chemicals that are used along with the excipient to increase penetration of the drug into the skin.

Physiological and pathological condition of the skin:

1. **Skin age:**

Foetal and infant skin is more permeable than mature adult skin, allowing for faster percutaneous absorption of topical steroids. However, water permeation remains consistent between adults and children.

2. Lipid film:

Sebaceous glands and cell lipids, such as sebum and epidermal cells, produce a thin lipid film on the skin's surface. This film acts as a protective layer, preventing the removal of natural moisturizing factors and promoting skin health. Maintaining the barrier function of the systemic circulation.

3. Skin hydration:

Hydration of the systemic circulation can increase transdermal permeability. A study on the rate of salicylic acid penetration through skin with dry and hydrated corneum revealed that when tissues were hydrated, most water-soluble esters penetrated faster than others.

4. Skin temperature:

Raising skin temperature increases the rate of permeation. A rise in skin temperature may also increase vasodilation of blood vessels, which are in contact with the skin leading to an increase in percutaneous absorption.

5. Pathological injury to skin:

Injuries to the skin can disrupt the continuity of SC, increasing skin permeability.

6. **Species differences:**

Mammalian skin varies greatly in thickness, sweat gland count, and hair follicle density across species.

7. Cutaneous drug metabolism:

The drug enters the systemic circulation in both active and inactive forms, depending on the presence of metabolic enzymes in the skin layers. According to reports, over 95% of testosterone, the absorbed substance was metabolized as it passed through the skin.

TYPES OF TRANSDERMAL PATCHES [24,25]

Single-layer drug in adhesive:

It is distinguished by the presence of medicine directly within the skin-contacting glue. The adhesive doubles as the basis for the formulation in this transdermal system design, holding the medicine and all excipients in one backing film while also serving as a means of attaching the system to the skin.

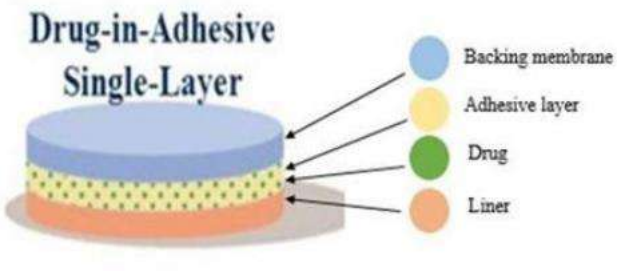

Fig:9 Single-layer Patch

Multi-Layer drug in adhesive:

The drug is incorporated directly into the adhesive, similar to the Single-layer Drug-in-Adhesive. The term "multi-layer" refers to the addition of a membrane or multiple drug-in-adhesive layers beneath a single backing film in between two distinct drug-in-adhesive layers.

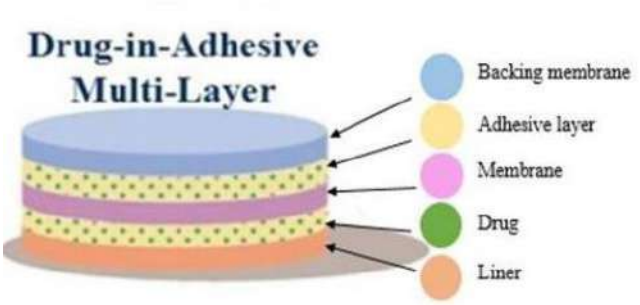

Fig:10 multi-layer patch

Drug reservoir in adhesive:

It has a liquid compartment containing a drug solution or suspension that is separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product can be included in either a continuous layer between the membrane and the release liner or a concentric design surrounding the membrane that is in charge of skin attachment.

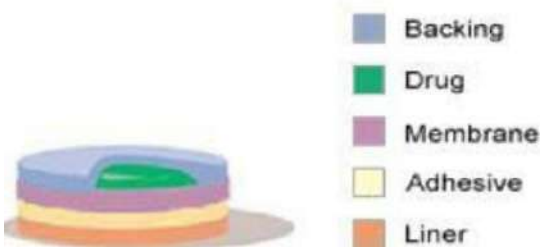

Fig:11 Reservoir patch

Drug matrix in adhesive:

It is distinguished by the presence of a semisolid matrix containing a drug solution or suspension in direct contact with the release liner.

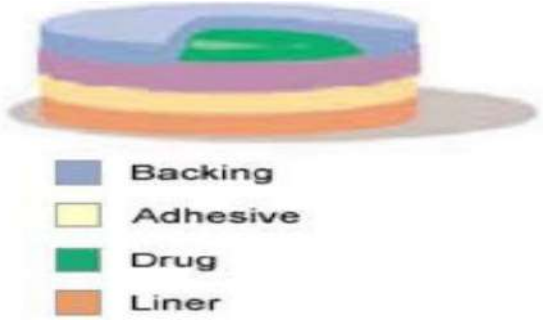

Fig:12 Matrix patch

Vapour patch:

The adhesive layer in this type of patch not only serves to adhere the various layers together but also to release vapor. The vapor patches are a new product on the market that releases essential oils for up to 6 hours. The market is only now seeing the introduction of vapor patches that can release essential oils for up to 6 hours. The vapor patches that Decongestion is mostly treated by releasing essential oils. Controller vapor patches, which improve sleep quality, are available. Alternatives are available. There are also vapor patches on the market that can help you reduce the number of cigarettes you smoke. Each month, a person smokes months are also for sale on the market.

COMPONENT OF TRANSDERMAL DEVICE INCLUDE [13,15]

Polymer Matrix:

The polymer controls the release of the drug from the device. Possible useful polymers for transdermal devices are

Nature polymer:

Ex-cellulose derivatives, zein, gelatine, shellac, waxes, proteins, gums, and their derivatives, natural rubber, starch, etc.

Synthetic elastomers:

Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene, and others are examples.

Synthetic polymer:

Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinyl pyrrolidine, epoxy etc.

Drug:

- The drug should have a molecular weight less than approximately 1000 Daltons.
- The drug should have an affinity for both lipophilic and hydrophilic phases.
- The drug should have a low melting point.
- Along with these properties, the drug should be potent have a short half-life, and be non-irritating.

Permeation Enhancers:

These are compounds that promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. Penetration enhancers are incorporated into a formulation to improve the diffusivity and solubility of the drug through the skin which would reversibly reduce the barrier resistance of the skin. These include water, fatty acid and alcohols zone and its derivatives, alcohol, and glycols, essential oils, terpenes and derivatives, sulfoxides like DMSO and their derivatives, urea, and surfactants.

Other Excipients:

Various solvents such as chloroform, methanol, acetone, isopropanol, and dichloromethane, are used to prepare drug reservoirs. In addition, plasticizers such as dibutyl-phthalate, polyethylene, glycol, and propylene glycol are added to provide plasticity to the transdermal patch.

FORMULATION APPROACHES OF TDDS [16,17,20]

The different formulation approaches for TDDS are discussed as follows;

Polymer membrane permeation controlled TDDS:

Sandwiched between a drug-impermeable backing laminate and a rate-controlling polymeric membrane is a drug reservoir. The drug is dispersed homogeneously in a solid polymeric matrix (e.g., polyisobutylene) in the drug reservoir compartment to form a paste-like suspension, using a leachable viscous liquid medium (e.g., silicon fluid). Rate The controlling membrane can be either microporous or nonporous polymeric, for example. The copolymer of ethylene and vinyl acetate.

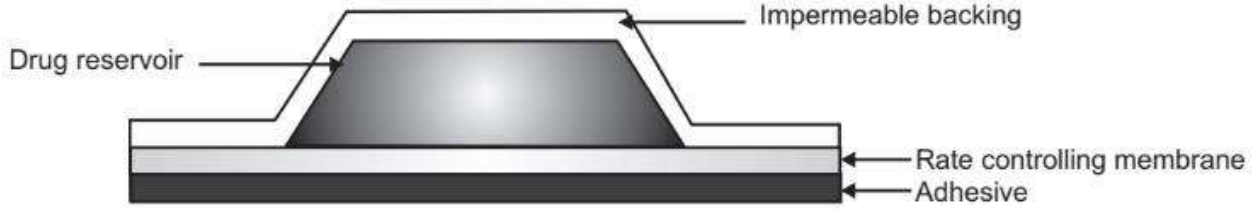

Fig:13 Membrane Permeation controlled system

Polymer matrix diffusion controlled TDDS:

The drug reservoir is created by dispersing drug particles homogeneously in a hydrophilic (or) lipophilic polymer matrix. The polymer matrix that results is then molded into discs with defined surface area and controlled thickness. After that, the medicated disc is molded onto an occlusive base plate in a compartment made up of a drug-impermeable backing.

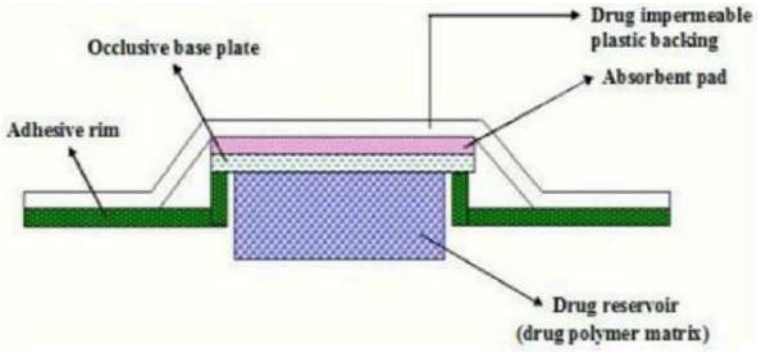

Fig:14 Matrix Diffusion controlled system

Adhesive Dispersion – Type System:

This is an abbreviated version of membrane Permeation-Controlled Systems. The drug and other selected excipients are directly incorporated into the adhesive solution in this system. Then they are the solvent is then evaporated by drying the film after it has been mixed and cast as thin films.

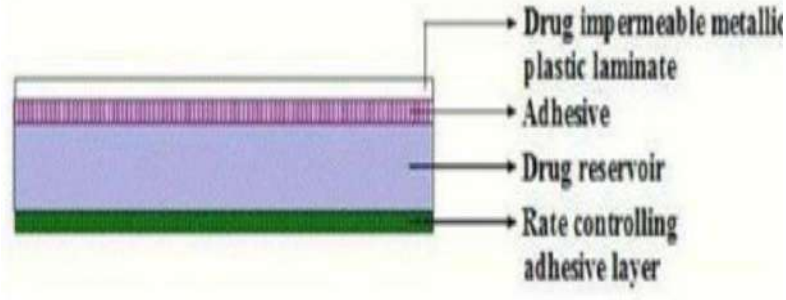

Fig:15 Adhesive Dispersion – Type Systems

Micro-reservoir dissolution controlled TDDS:

It is thought to be a hybrid system of reservoir and matrix dispersion drug delivery. The drug reservoir in this system is formed by first suspending the drug solids in an aqueous solution of a water-miscible drug solubilizer, such as polyethylene glycol, and then dispersing the drug suspension homogeneously with controlled aqueous soluble lipophilic high shear mechanical force is used to form thousands of un-leachable microscopic drug polymers reservoi

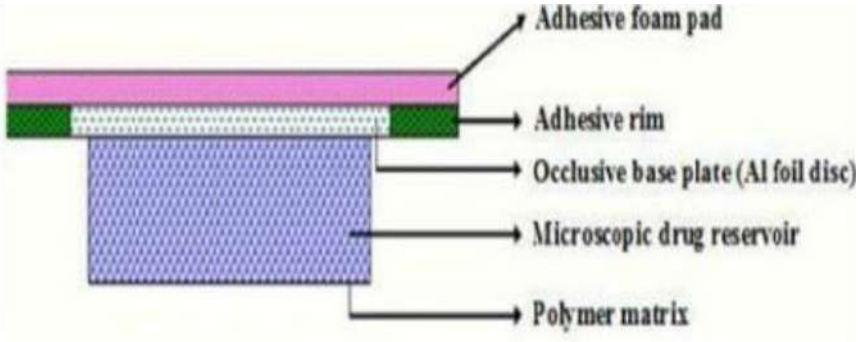

Fig:16 Micro reservoir type system

APPLICATIONS OF TDDS: [26,29]

1. Delivers drug at a controlled rate, either locally or to the systemic circulation.
2. Drug diffuses through the intercellular route.
3. Seif contained a single-use dosage form.
4. Applied to the intact skin.
5. Percutaneous penetration follows passive diffusion.

CONCLUSION:

Many factors must be considered for successful transdermal drug application. Keeping in mind that the skin's primary functions are protection and excretion, it appears that containment would be extremely difficult. to deliver drugs through the skin. However, in the case of our improved understanding of the structure of skin's function and how to change its properties, an increasing number of new drug products are being developed Transdermal delivery is being developed. The drug's properties, the drug's characteristics transdermal device, in-vivo model selection, and the condition of the patient's skin are critical for safety. and efficient drug administration. The transdermal medication day, delivery system could be among the best brand-new drug-delivery systems.

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