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Review Article

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A Review on Advance Technologies for Developing Transdermal Drug Delivery Systems

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ABSTRACT

Over the past decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry.Today about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged.Transdermal drug delivery represents one of the most rapidly advancing areas of novel drug delivery. Transdermal drug delivery system was introduced to overcome the difficulties of drug delivery through oral route. A transdermal patch is medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream.

With the advent of new era of pharmaceutical dosage forms, transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems.

The present article reviews the polymers suitable to be formulated as transdermal system, advantages, and disadvantages of formulation design.

Key-words: Transdermal drug delivery system, Transdermal patches, Design of transdermal patches

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1.1 Transdermal drug delivery:

Transdermal drug delivery systems have been recently developed to achieve the objective of systemic medication through topical application. The transdermal route of drug delivery is becoming popular because large number of drug can be delivered to treat various diseases. [1, 2]

Both topical and transdermal products are intended for external application. However, topical dermatological products are intended for local action whereas transdermal drug delivery system is used for systemic drug delivery.[3]

Several rate controlled transdermal drug delivery systems have been commercially developed because it has many advantages over conventional drug delivery. The advantages are discussed below.[3- 6.]

Advantages:

1. They facilitate more predictable drug absorption due to avoidance of GI tract variables such as pH, motility transit time, food, and enzyme activity.
2. Suitable for patients who are unconscious or suffering fromvomiting and diarrhea**.**
3. They avoid the *first-pass* metabolism in the gastrointestinal tract and avoid drug deactivation by liver enzymes.
4. The activity of drugs having short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
5. They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
6. Avoiding the inconvenience of parenteral therapy.
7. Drug therapy may be terminated rapidly by removal of the drug delivery system from the surface of the skin.
8. Drug levels can be maintained in systemic circulation, within therapeutic window.
9. Improved patient compliance and acceptability of drug therapy.

Disadvantages:

1. The limitations of transdermal drug delivery are mainly associated with barrier function of skin, so it is limited to potent drug molecules.
2. Skin irritation or contact dermatitis due to drug, excipients and enhancers is another limitation.
3. The use of transdermal delivery may be uneconomic.

1.2 THE SKIN: ANATOMY AND PHYSIOLOGY: [7- 10.]

Microscopically, the skin is a multilayered organ, composed of many histological layers (**Figure no.1**).

The skin or cutaneous membrane covers the external surface of the body. It is the largest organ of the body in surface area and weight. Skin consists of two main parts, the superficial, thinner portion, which is composed, of epithelial tissue is the **epidermis** and dipper thicker layer **Dermis.**

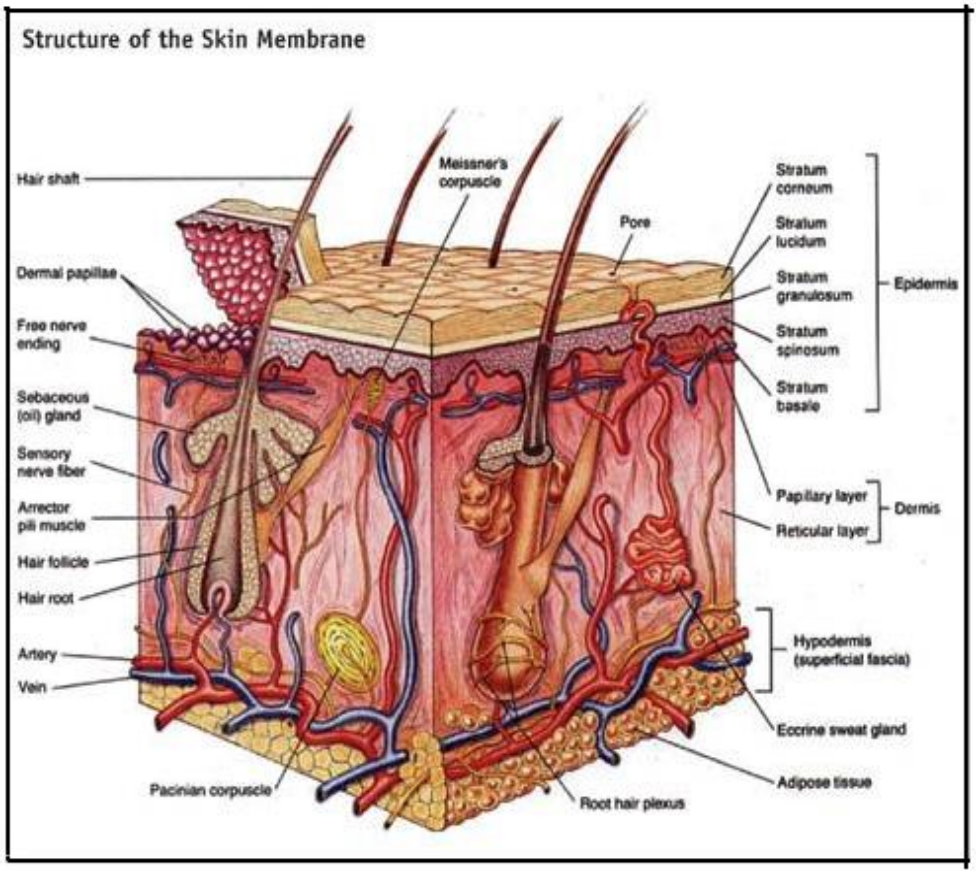

Figure no. 1: Structure of skin.[11]

A. Epidermis

It is composed of kertinised of stratified squamous epithelium. There are several layers of cells in the epidermis, which is extending from the dippiest germinative layer to surface stratum corneum. Stratum corneum cells are formed and continuously replenished by the slow upward migration of the cells produced by the basal cell layer.

Keratinocytes, comprise 90% epithelial cells. There are several distinct layers of keratocyte in various stages of development. Stratum corneum is underlined with three layers, stratum spinosem (prickly layer), stratum granulosum (granular layer) and stratum lucidum (clear layer). [10]

B. Dermis:

The dermis is vascular and supports the epidermis structurally and nutritionally. The second dipper part of the skin, the dermis is composed of mainly connective tissue containing collagen and elastic fibers. It varies in thickness from just over 1mm on the inner forearm to 4mm on the back.

The structures in dermis are

- Blood vessels.
- Lymph vessels.
- Sensory nerve ending.
- Sweat gland and their ducts.

- Hair roots, hair follicles and hair.
- Sebaceous glands.

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. For transdermal drug delivery, drug has to penetrate through all these three layers and reach into systemic circulation. In case of topical drug delivery penetration through stratum corneum is essential and then retention of drug in skin layers is desired.

1.3FUNDAMENTALS OF SKIN PERMEATION: -

The phenomenon of percutaneous absorption can be visualized as a of series of steps in sequence, sorption of a molecule onto the surface layer of stratum cornium, diffusion through it and various layers of epidermis. Finally at the papillary layer of dermis, the molecule is taken up in to microcirculation for subsequent systemic distribution. The viable tissue layers and capillaries are relatively permeable and peripheral circulation is sufficiently rapid. [12]

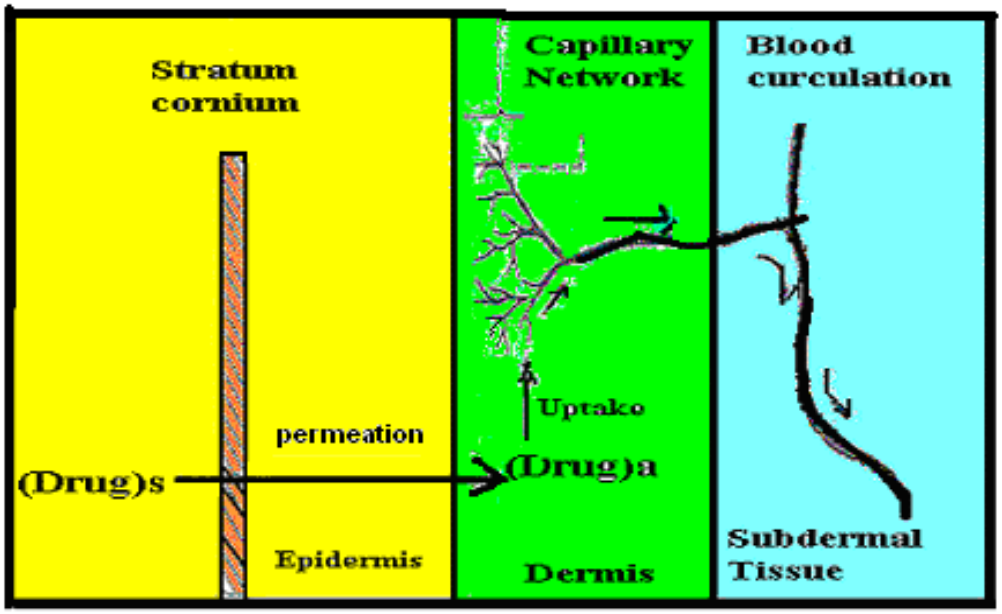

Figure no. 2: A multilayer skin model showing sequence of Transdermal permeation of drug for systemic delivery

The rate of transdermal permeation of drug at steady state (Rp)ss is mathematically related to both, actual drug delivery (R_d)a from a transdermal drug delivery system to skin surface and maximum achievable rate of skin absorption.(R_a)$_m$[10,12].

$$\frac{1}{(Rp)ss} = \frac{1}{(Rd)a} + \frac{1}{(Ra)m}$$

1.4 PERMEATION PATHWAYS:[13, 14, 15]

A molecule may use two diffusional routes to penetrate through skin, the appendagealroute and the epidermal route.

A. Appendageal route:

Figure no.33 depicts various routs of permeation through the skin. Route 1 is through sweat gland and route 3 is through hair follicle.

Skin Appendages have fractional area available for absorption is small (about 0.1%) and this route usually does not contribute appreciably to stead- state flux of a drug. However, the route may be important for ions and large polar molecule that cross intact stratum cornium with difficulty. [13.]

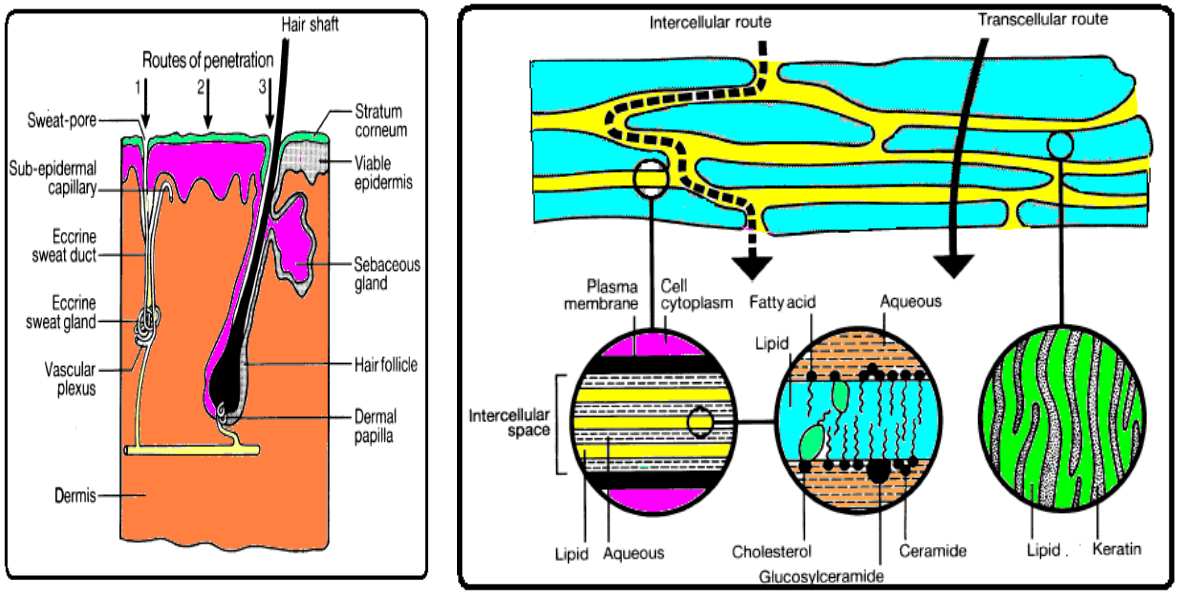

Figure no. 3: Routes for drug permeation and epidermal routes for drug permeation

B. Epidermal route: (Shown as figure no.3).

The stratum cornium is muilticelluar membrane and electron microscopic evidence implies that the intercellular regions are filled with a lipid-rich amorphous material. Although the intercellular volume is small, it is still sufficiently large to provide a significant route in theory provided that the diffusion coefficient for this pathway is large enough.

For drugs which mainly cross the intact horny layer, two potential micro routes of entry exists, the **transcellular** (or intracellular) and **intercellular** pathways (Figure3). The principal pathway taken by a permeant is decided mainly by the partition coefficient (log K). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permeates (octanol/water log K > 2) traverse the stratum corneum via the intercellular route. Most permeates permeate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route and major barrier to the permeation of most drugs.[14, 15.]

1.5 FACTORS THAT INFLUENCE TRANSDERMAL DELIVERY:[13, 14]

1. Biological parameters
2. Physicochemical parameters

1. Biological parameters:

a) Skin Condition: -

The skin is a tough barrier to penetration, but only if it is intact. Vesicants such as acid, alkalis injure barrier cells and there by promote penetration. In disease characterized by defective stratum cornium, percutenious absorption increases.

b) Blood flow: -

Theoretically, changes in peripheral circulation, or blood flow through the dermis, could affect percutenious absorption. Thus an increased blood flow could reduce time for whicha penetrant remain in the dermis and also raise the concentration gradient across the skin.

c) Regional skin sites: -

Variation in cutaneous permeability around the body depends on the thickness and the nature of stratum corneum and the density of skin appendages. However rate of absorption at identical skin sites in different healthy volunteers varies.

d) Skin metabolism: -

It has been recently reviewed the role which the skin plays in metabolism of drugs and steroidal hormones. The topical bioavailability should account for not only skin permeation but also cutaneous drug metabolism. [16.]

e) Species differences: -

Mammalian skin differs widely in characteristics such as horny layer thickness, sweat gland and hair follicle densities, and pelt condition, the capillary blood supply and the sweating ability from species to species, so affect the permeation.

2. Physicochemical parameters: -

a) Hydration of skin: -

When water saturates the skin; tissue swells, softens and wrinkles and its permeability increases markedly.

In fact, hydration of stratumcorneum is one of important factor in increasing the penetration rate of most substances that permeate the skin.

b) Temperature: -

The penetration rate of material through the human skin can change tenfold for large temperature variation, as the diffusion coefficient decreases as the temperature falls. Occlusive vehicles increase skin temperature by few degrees, but any consequent increased permeability is small compared to effect of hydration.

c) Diffusion coefficient: -

The diffusional speed of molecule depends mainly on state of matter in the medium. In gases and air, diffusion coefficients are large because the void space available to the molecules is large as compared to their size.

d) Drug concentration: -

The drug permeation usually follows the ficks law. The flux of solute is proportional to the concentration gradient across the entire barrier phase.

e) Partition Coefficient: -

Partition coefficient is important in establishing the flux of the drug through the stratumcorneum. The balanced partition coefficient is required for drug permeation.

f) Molecular size: -

Absorption is apparently inversely related to molecular weight. Small molecule penetrates faster than large once.

1.6GENERAL CLINICAL CONSIDERATIONS IN THE USE OF TDDSs[13, 17]

The patient should be advised of the following general guidelines. The patient should be advised for the importance of using the recommended site and rotating locations within the site. Rotating locations is important to allow the skin to regain its normal permeability and to prevent skin irritation.

TDDSs should be applied to clean, dry skin relatively free of hair and not oily, inflamed, irritated, broken, or callused. Wet or moist skin can accelerate drug permeation beyond predetermined rate. Oily skin can impair the adhesion of patch. If hair is present at the site, it should be carefully cut, not wet shaved, nor should a depilatory agent be used, since later can remove stratum corneum and affect the rate and extent of drug permeation.

Use of skin lotion should be avoided at the application site, because lotions affect the hydration of skin and can alter partition coefficient of drug.

The release liner should be removed with care. The TDDS should be pressed firmly against skin site with the heel of hand for about 10 seconds.

A TDDS should be placed at a site that will not subject it to being rubbed off by clothing or movement. TDDS should be left on when showering, bathing, or swimming.

A TDDS should be worn for full period stated in the product's instructions followed by removal and replacement with fresh system.

The patient or caregiver should cleanse the hands after applying a TDDS. Patient should not rub eye or touch the mouth during handling of the system.

If the patient exhibits sensitivity or intolerance to a TDDS or if undue skin irritation results, the patient should seek revaluation.

Upon removal, a used TDDS should be folded in its half with the adhesive layer together so that it cannot be reused. The used patch discarded in a manner safe to children and pets.

*Figure no.**4: Use of transdermal patch.***

It is important to use a different application site everyday to avoid skin irritation. Suggested rotation is: [30]

Day 1 -Upper right arm.
Day 2 -Upper right chest.
Day 3 -Upper left chest.
Day 4 - Upper left arm –then repeat from Day 1.

1.7 TRANSDERMAL PATCHES

1.7.1 Transdermal patches: [19]

Transdermal systems deliver medication directly through skin and into the bloodstream, offering an alternative to traditional delivery methods.

1.7.2 Working of transdermal patches: [20]

A skin patch uses special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass though skin and into bloodstream.

Traditionally, when patch is applied on skin the occlusion traps thee natural transepidermal moisture of the skin, which increases water content of horny layer and causes swelling of the membrane, thus compromising its barrier function[21]

1.7.3 Design of transdermal patches:

These are generally are composed of three key elements: a protective seal from the external surface and protect from damage, adhesive backing a component that holds the entire patch on skin‘s surface with little or no irritation and release liner that protects the adhesive layer during storage and removed just prior to application.

Transdermal patches designed in four basic types. Shown in **Figure no. 5.**

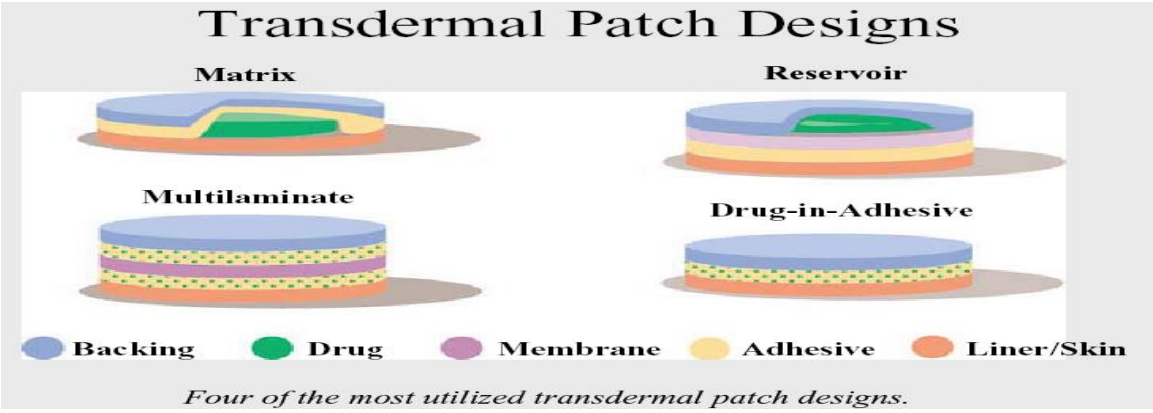

Figure no. 5: Four of most utilized transdermal patches designs.17.

1.8 TECHNOLOGIES FOR DEVELOPING TRANSDERMAL DRUG DELIVERY SYSTEMS:[10, 12, 18]

The technologies can be classified in four basic approaches.

A. Polymer membrane partition-controlled TDD systems:

In this type of systems, the drug reservoir is sandwiched between a drug-impermeable backing laminate and a rate controlling polymeric membrane. Figure no. 6.showscross-sectional view of polymer membrane permeation-controlled TDD system.

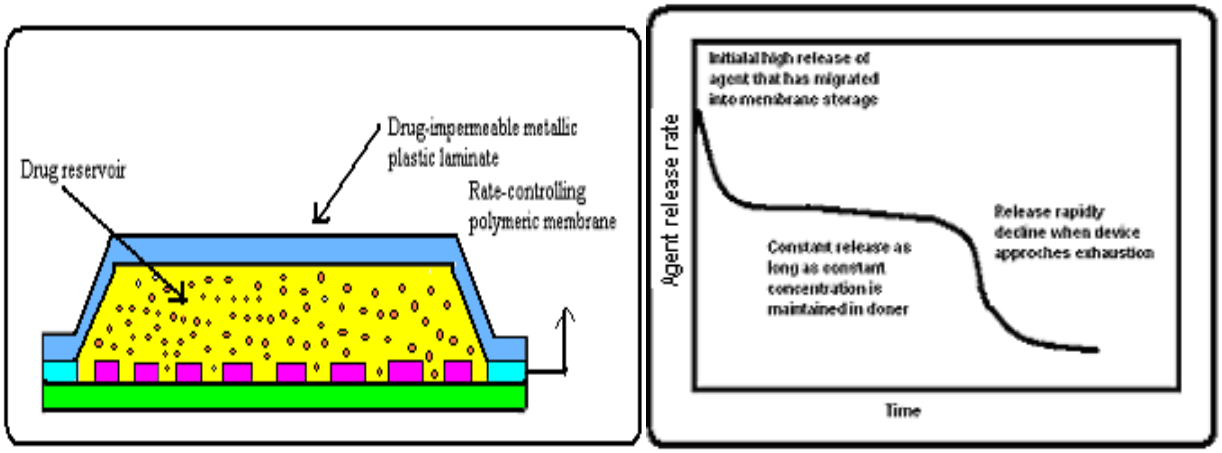

Figure no. 6: Cross-sectional views of polymer membrane permeation-controlled TDD systems and release rate obtained.

The drug molecules are released through the rate controlling membrane. In the drug reservoir component, drug is suspended in viscous fluid that forms paste like suspension.

The rate of drug release from this type of TDDS depends on polymer composition, permeability coefficient and thickness of rate controlling membrane. The rate controlling membrane can be either a microporous or a nonporous polymeric membrane. e.g. ethylene-vinyl acetate copolymer, with specific drug permeability e.g. Some US FDA approved systems are Transderm-Nitro for angina pectoris, Transderm- Scop as an antiemetic.

B. Polymer matrix diffusion-controlled TDD systems:

Polymer matrix diffusion-controlled TDD systems formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix, and then the medicated polymer is molded into medicated disks with defined surface area and thickness. This drug reservoir containing polymer disk is then mounted on occlusive base plate in a compartment fabricated from a drug-impermeable plastic backing.

Instead of coating adhesive polymer directly on the surface of medicated disk, it is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disk-.
e.g. Nitro-Dur system and NTS system for angina pectoris. (**Figure no. 7**.)

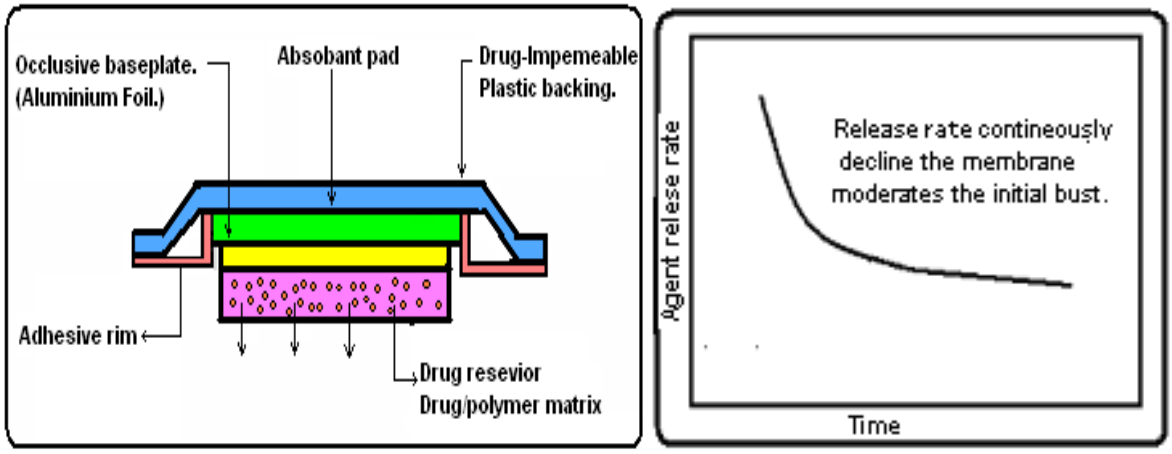

Figure no. 7: Cross-sectional view of polymer matrix diffusion-controlled TDD

Systems and release rate obtained.

Alternately, the polymer matrix drug dispersion-type TDD system can be fabricated by directly dispersing drug in a pressure-sensitive adhesive polymer, e.g. polyacrylate, and then coating the drug-dispersed adhesive polymer by solvent casting or hot melt onto a flat sheet of drug-impermeable backing laminate to form a single layer of drug reservoir this yields a thinner patch.

As compare to reservoir-membrane system, matrix systems have advantages of low cost, ease of fabrication and less risk of dose dumping which is mainly resulted from the damage of membrane. [18]

C. Drug reservoir gradient-controlled TDD systems:

Polymer matrix drug dispersion-type TDD systems can be modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multilaminate adhesive layers. The drug release from this type of drug reservoir gradient-controlled TDD systems can be expressed by

$$\frac{dQ}{dt} = \frac{KF_{a/r}\, D_a}{h_a(t)\, L_d(h_a)}$$

In this system the thickness of diffusional path through which drug molecules diffuse increases with time, i.e. h_a (t). The drug loading level in the multilaminate adhesive layer is also designed to increase proportionally i.e. L_d (h_a) so as to compensate time dependent increase n diffusional path as a result of drug depletion due to release. Thus, theoretically this should yield a more constant drug release profile.e.g. Nitroglycerine TDS for angina pectoris.

This type of system is depicted in **Figure no. 8**.

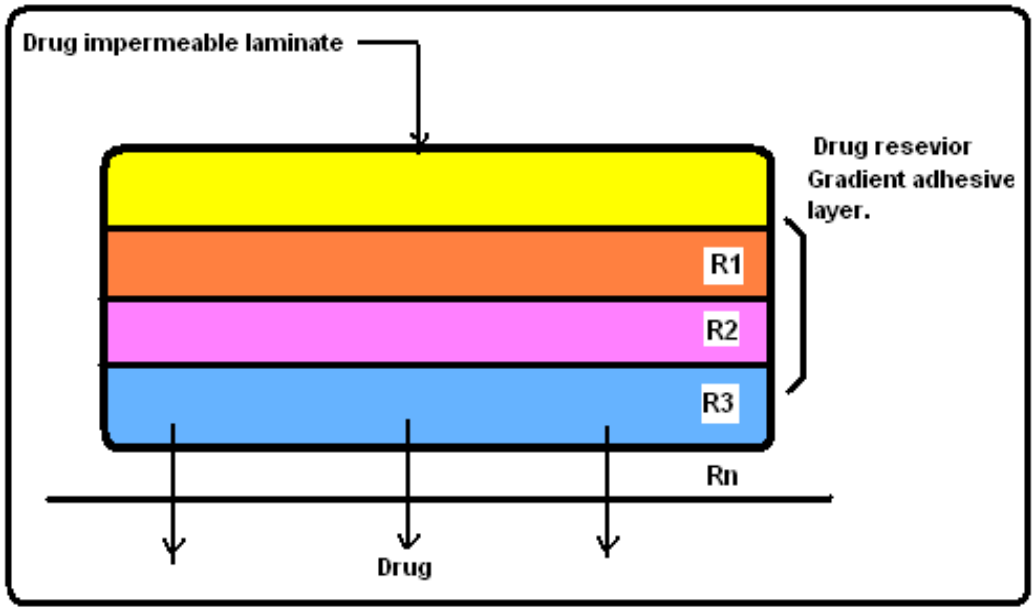

Figure no. 8:Cross-sectional view of a drug reservoir gradient-controlled TDD System.

D. Microreservoir dissolution-controlled TDD systems:

This type of delivery systems has some essential features i.e. hybrid of reservoir- and matrix dispersion-type In this approach drug reservoir is formed by first suspending the drug solids in an aqueous solution of water-miscible drug solubilizer. e.g. propylene glycol, then the drug suspension is homogeneously dispersed with lipophilic polymer, by high shear mechanical force, to form thousands of unleachable microscopic drug reservoirs.e.g. Nitrodisk system for angina pectoris. Figure no. 9.

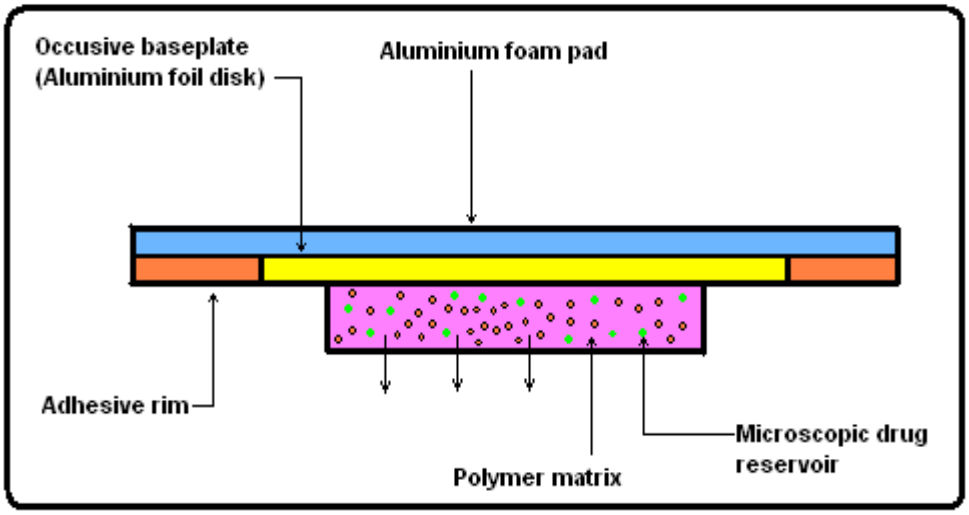

Figure no. 9:Cross-sectional view of a drug microreservoir dissolution-controlled TDD system.

1.9 COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM [6, 17, 22 - 25].

The main components to a transdermal patch are:

1. Release liner:

Release liner protects the patch during storage. The liner is removed prior to use.

2. Drug reservoir:

It consists of drug particles dissolved or dispersed in the matrix. The drug reservoir is sandwiched between a drug-impermeable backing laminate and a rate controlling polymeric membrane.

3. Adhesive:

Adhesive serves to adhere the components of the patch together along with adhering the patch to the skin.

Patches generally consist of a porous membrane, a drug, an adhesive and a release-liner. The pressure-sensitive adhesives are based on natural or synthetic rubbers, polyacrylates or silicone. Many manufacturers prefer silicone adhesives because they are kind to the skin. They are also chemically stable, biologically inert, and transparent, retain adhesive properties in the presence of moisture, and have high permeability. The release liner, or peel-away strip, consists of paper, polystyrene, polyethylene, polyester or other polymeric films with a light coating of compounds such as silicones.

*Figure no.**10:Manufacturing of patches26***
(Photo courtesy Alza)

Natural rubber and polyisobutylene were the earliest polymers used for formulating medical pressure sensitive adhesive (PSAs) due to their high peel strength, elongation, and ease of acceptance by skin tissue. However these are now largely replaced with modern, synthetic polymers as described below. [22 – 25.]

A. Acrylic based adhesives, are widely used. These are used in varied applications due to their good adhesive qualities and low levels of allergenicity.

B. Silicone based adhesives are used in devices needing an inert and biocompatible adhesive.

C. Polyvinyl ether based adhesive are employed in moisture permeable skin patches.

4. Membrane:

Membrane controls the release of the drug from the reservoir and multi-layer patches. It may or may not be rate-controlling membrane. It should be flexible enough not to split or crack on bending or stretching. Some of rate-controlling membranes are polyethylene sheets, ethylene vinyl acetate co-polymer, and cellulose acetate.

5. Backing membrane:[17, 19.]

Backing Membrane should be flexible and should provide a good bond to reservoir. It should be impermeable to the drug. Polymers like LDPE, LLDPE, MDPE and polyurethane are used in backing membrane. Membrane can be mono layer or multilayered. [17]

6. Other exicipents:

A) Penetration enhancers:[10, 21, 22, 27, 28.]

These are compounds, which promotes skin permeability by altering the skin as a barrier to the flux of a drug. Desirable properties of penetration enhancers are as follows.

- Pharmacologically inert.
- Nontoxic, nonirritating and nonallergic.
- Rapid onset of action, predictable and suitable duration of action for the drug used.
- Following removal of the enhancer, the stratum corneum should immediately and fully remover its normal barrier property.
- The barrier function of the skin should decrease in one direction only and flux of endogenous materials should not occur.
- Chemically and physically compatible with the delivery system.
- Readily incorporated in to the delivery system.
- Inexpensive and cosmetically acceptable.

Examples:

Dimethyl sulfoxide (DMSO), N, N-Dimethylformade (DMF),Pyrrilidones, Tetrahydrofurfuryl alcohol (THFA).

B) Solvents:

Alcohols and ethanol, in particular have been proposed as effective permeation enhancer.[10]

Examples:

Acetamide and derivatives, acetone, Dimethyl acetamide, Diethyl acetamide, Ethanol.

C) Surfactant:

These compounds are proposed to enhance substances polar transport, specific all hydrophilic drug. The ability of surfactant to alter the penetration is a function of polar head group and hydrocarbon chain length. Commonly used surfactants are.

- **Anionic surfactants:**

Dioctlysulthosuccinate, sodium lauryl sulfate, decodecylmethyl

sulphoxaide.

- **Nonionic surfactants:**

Pluronic F-127, pluronic F-66.

- **Bile salts**:

Sodium taurocholate, sodium deoxycholate, sodium tauoglycocholate.

1.10 MARKETED TRANSDERMAL PRODUCTS:

Tableno: 1.US Sales of Select Prescription Transdermal Products.29.

Drug	Examples of Brand Names	Annual Sales (US$) MAT 9/00	AnnualSales (US$) MAT 9/01	Annual Sales (US$) MAT 9/02
Fentanyl	Duragesic	1.15b	1.29b	1.59b
Estradiol	Climara, Vivelle-Dot, CombiPatch	260m	253m	279m
Clonidine	Catapres TTS	133m	147m	168m
Nitroglycerin	Nitro-Dur, Deponit	209m	182m	159m
Nicotine	Nicoderm CQ, Nicotrol	88m	72m	73m
Testosterone	Testoderm TTS	43m	44m	50m
Ethinylestradiol and Norelgestromin	Ortho Evra			19m
Scopolamine	Transderm-Scop	12m	14m	17m
Lidocaine	Lidoderm		27m	60m
Oxybutynin	Awaiting FDA approval			
Methylphenidate	Awaiting FDA approval			

Conclusion

Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. This article provides valuable information regarding the formulation and evaluation aspects of transdermal drug delivery systems. TDDS is a realistic practical application as the next generation of drug delivery system.

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