Review Article

Review About Transdermal Drug Delivery System

M Sakthivel[1]*, A Swetha[2], S Thangamaniarasan[2], S Velmathi[2], R Vengatesh[2]

1. Professor & Head of Department of Pharmaceutics, Dhanalakshmi Srinivasan College of Pharmacy, Perambalur, Tamilnadu, India.
2. Students, Department of Pharmaceutics, Dhanalakshmi Srinivasan College of Pharmacy, Perambalur, Tamilnadu, India.

***Corresponding author's E-mail**: msakthi00767@gmail.com

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ABSTRACT

Transdermal drug delivery systems (TDDS) are pharmaceutical formulations designed to deliver drugs through the skin for systemic effects including their advantages, disadvantages, and various technologies employed in their development. Factors such as molecular weight, lipophilicity, and stability influence the skin permeation of drugs. Various enhancement techniques like chemical enhancers, iontophoresis, sonophoresis, and microneedles are utilized to improve drug permeation through the skin. transdermal drug delivery systems offer a promising alternative to traditional routes of drug administration. They provide several advantages in terms of patient compliance, sustained release, and improved bioavailability. However, careful consideration of drug properties and formulation techniques is necessary to overcome the limitations associated with TDDS.

Keywords: Transdermal drug delivery system (TDDS), Factors affecting, Types of TDDS.

INTRODUCTION

Oral administration of drugs has been practiced for centuries and most recently, through tablets and capsules. Injectables came into being approximately 130 years ago, but have only become acceptable since the development of a better understanding of sterilization. Topical application has also been used for centuries, predominantly in the treatment of localized skin diseases. Oral delivery is by far the easiest and most convenient way of delivering drugs especially when repeated and routine administration is required. Therefore, to achieve as well as to maintain the drug concentration within therapeutically effective range needed for treatment. It is often necessary to take this type of drug delivery system several times a day. This results in significant fluctuations in plasma drug concentration levels leading to marked side effects in some cases.

The next era of health care will demand more accommodating delivery systems for sensitive drug classes. Patient compliant, noninvasive and sustained delivery will become the key feature desirable of any drug delivery system.

Modified release drug delivery system can be divided into four categories:[1]

a) Delayed release.

b) Sustained release.

i. Controlled release.

ii. Extended release.

c) Site specific targeting.

d) Receptor targeting.

a) Delayed release:

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric coated tablets where timed release is achieved by a barrier coating.

b) Sustained release:

The term "sustained release" describes a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/ or prolonged. The onset of its pharmacologic action is often delayed and the duration of its therapeutic effect is sustained.

i) Controlled release:

The term "controlled release" implies the release of drug ingredient(s) from controlled-release drug delivery system proceeds at a rate profile that is not only predictable kinetically, but also reproducible from one unit to another.

ii) Extended release:

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate and necessarily reduce the dosage frequency by two folds.

c) Site specific targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

d) Receptor targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site

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specific targeting systems satisfy the aspect of drug delivery and are also considered to be controlled drug delivery systems.

Controlled drug delivery systems:[2]

In the mid to late 1960s, the term "controlled drug delivery'' came into being to describe new concepts of dosage form design. These concepts usually involved controlling drug dissolution, but also had additional objectives. The primary objectives of a controlled -release systems have been to enhance safety and extend duration of action. Today, we also have controlled-release systems designed to produce more reliable absorption and improve bioavailability and efficiency of delivery.

Controlled drug delivery systems hold the major credibility because of its obvious advantages of,[3]

a) Increase in patient compliance.

b) Reduction in total dose administered, thereby,

- Minimize or eliminate local and systems side effects.
- Minimize drug accumulation with chronic use.
- Obtain less potentiation or reduction in drug activity with chronic use.

c) Improve efficiency in treatment.

- Cure or control condition more promptly.
- Reduces fluctuation in plasma drug concentration.
- Improve bioavailability of some drugs.
- Possibly reduced patient care time.

Some of the disadvantages of controlled drug delivery systems are as follows,

- Longer time to achieve therapeutic blood concentration.
- Dose dumping.
- Sustained concentration declines in overdose cases.
- Lack of dosage flexibility.
- Usually, greater expense.
- Enhanced first pass effect.

Various forms of controlled drug delivery systems are[3]

- Oral drug delivery systems.
- Mucosal drug delivery systems.
- Nasal drug delivery systems.
- Ocular drug delivery systems.
- Transdermal drug delivery systems.
- Parenteral drug delivery systems.
- Vaginal drug delivery systems.
- Systemic delivery of peptide based pharmaceuticals.

Innovations in the area of drug delivery are taking place at a much faster as compared to last two decades. A large contribution to these novel systems appeared as Modifications of the active drug or use of formulation excipients to modulate drug pharmacokinetics, safety, efficacy and metabolism. one such approach, transdermal drug delivery, makes use of human skin as a part of entry for systemic delivery of drug molecules.

SKIN – AN EFFECTIVE BARRIER FOR PERMEATION:

Skin is the largest organ of the body. The skin an average adult body is about 20square feet and it received about one third of total available blood. The skin completely covers the body and is continues with the membranes lining the body orifice. (fig:1)

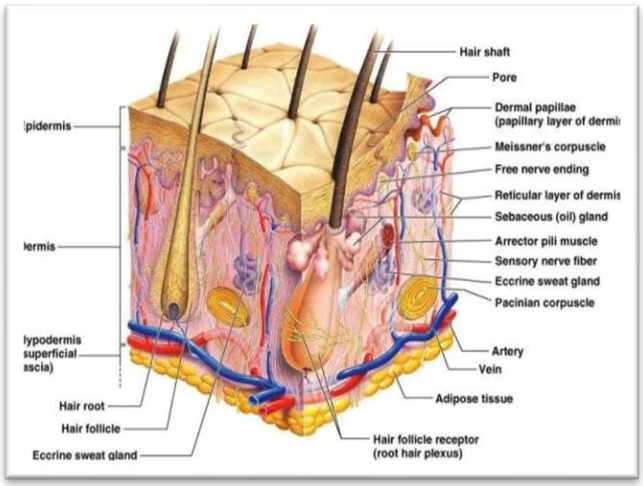

Figure 1: Structure of skin

The skin is multi- layered organ composed of three histological tissue:

- The outermost layer of skin, epidermis is which provides a waterproof barrier and creates our skin tone.
- Dermis beneath epidermis, contain tough connective tissue, hair follicles, and sweat glands.
- Deeper subcutaneous tissue (hypodermis) is mode of fat and connective tissue.[4]

Stratum corneum or horny layer is the outermost layer of epidermis, which restricts the inward and outward movement of chemical substance. These are compacted, flattened, dehydrated and keratinized cells which are physiologically inactive.

Stratum corneum has two distinct chemical region,

- The mass of intracellular (transcellular) protein.
- The intercellular lipoidal medium.

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The epidermis rest on the much thicker dermis. The dermis essentially consists of about 80% protein in a matrix of mucopolysaccharide ground.

Percutaneous absorption:[5]

Percutaneous absorption involves passive diffusion of substance through the skin. The mechanism of permeation can involve passage through the epidermis itself (transepidermal absorption) or diffusion through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands (transfollicular or shunt pathway absorption).

Transepidermal absorption:

Transepidermal or transcorneal penetration includes intracellular and intercellular penetration, hydrophilic drugs generally seen to permeate through intracellular pathway. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments.

Polar molecules appear to pass through this immobilized water. Non polar substance permeate through intercellular penetration.

Transfollicular (shunt pathway) absorption:

In transappendegeal permeation the drug molecule may transverse through the hair follicles, the sebaceous pathway of pilosebaceous apparatus or the aqueous pathway of the salty sweat gland.

Epidermis:

The main sources of resistance to penetration and permeation through the skin is the stratum corneum. It is composed of two parts like of the epidermis, and the thickness varies according to the number of cells and the cell layer of the dermis.

It is stratified squamous epithelium layer which is composed primarily of two types of cells dendritic and keratimocytes cells.

Dermis:

It provides physiological support for the epidermis. It is typically 3-5mm thick and is the major component of human skin. It is the home for most of the skin's structures including sweat glands and oil glands, hair follicles, nerve ending, and blood and lymph vessels. The main components of the dermis are collagen and elastin. It stores much of the body's water supply.

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.[6]

Subcutaneous tissue (connective tissue):

The subcutaneous tissue or hypodermis is not actually considered as a true part of the structured connective tissue, which comprises of loose textured, fibrous, white, connective tissue containing blood and lymph vessels, secretary pores of the sweat gland and the cutaneous nerves. It serves as a fat storage area.

Blood and lymph vessels:

Arterioles form a fine network with capillary branches supplying sweat glands, sebaceous gland, hair follicles, and the dermis. Lymph vessels form a network through the dermis.

Sensory nerve ending:

Sensory receptors sensitive to tough, temperature, pressure, and pain are widely distributed in the dermis. Stimuli activate different type of sensory receptors. Nerve impulses, generated in the sensory receptors in the dermis, then to the sensory area of the cerebrum where the sensations are perceived.

Sweat glands:

These are widely distributed throughout the skin. They are formed from epithelial cells. There are two types of sweat gland. The commonest type opens onto the skin surface through tiny pores, and the sweat produced here is clear, watery fluid important in regulating body temperature.

The skin has evolved into an extremely efficient barrier, which prevents both excessive water loss from the body and the ingress of xenobiotics.

The skin is a very effective barrier for the permeation of most xenobiotics. Only a very drug actually arrives at the site action.

There are main three pathways through which foreign particles diffused or penetrate in to skin:

- Transcelluar /intracellular permeation through stratum corneum
- Intracellular permeation through the stratum corneum
- Transappendageal permeation via the hair follicles, sweat and sebaceous gland.

TRANSDERMAL DRUG DELIVERY SYSTEMS:(7)

Transdermal delivery systems are specifically designed to obtain systemic blood levels and have been used in U.S since in 1950s. Transdermal permeation, or percutaneous absorption, can be defined as the passage of a substance such as a drug, from the outside of the skin through its various layers into the bloodstream.

Over the last 25 years, the transdermal patch has become a proven technology accepted as offering a variety of significant clinical benefits over other dosage form. Drug delivery to systemic circulation via the application to the skin appears to be a desirable alternative to oral delivery for several good reasons:

- Improved patient compliance.

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- Greater flexibility of dosage in that dosing can be easily terminated by removal of the TDDS.
- A controlled delivery of drugs through the skin can provide less fluctuation in the circulating drug levels.

TRANSDERMAL DRUG DELIVERY SYSTEMS

Transdermal drug delivery systems are defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drugs(s), through the skin, at a controlled rate to the systemic circulation. Transdermal drug delivery is a viable administration route for potent, low molecular weight therapeutic agents which cannot withstand the hostile environment of gastrointestinal tract and /or subject to considerable first- pass metabolism by the liver.

Transdermal drug delivery system in which rate of drug absorption increases ultimately bioavailability of drug is increases.

A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with predetermined rate of release to reach into the bloodstream.

Today the most common transdermal present in the market mainly based on semipermeable membranes which were called as patches.

A transdermal patch containing high dose of drug inside which is retained on the skin for prolonged period of time, which get enters into blood flow via diffusion process.

Drug can penetrate through skin via three pathways-

A) Through hair follicles.

B) Through sebaceous glands.

C) Through sweat duct.

Transdermal adsorption occurs through a slow process of diffusion by the gradient between the high concentration in the delivery system and the zero concentration prevailing in the skin. Thus, the delivery system must be kept in continuous contact with the skin for a considerable time (hours to days).[8] (fig:2)

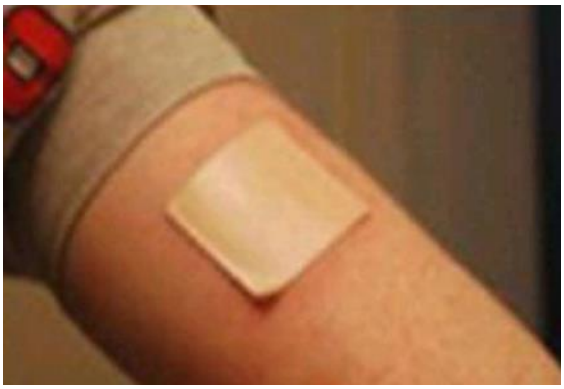

Figure 2: Transdermal patches

The worldwide transdermal market approaches 2 billion, yet is based on only ten drugs- scopolamine (hyoscine), nitroglycerine, clonidine, estradiol(with and without norethisterone or levonorgestrel), testosterone, fentanyl and nicotine, with a lidocaine patch soon to be marketed.

Advantages:

- Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
- Improved bioavailability.
- More uniform plasma levels and maintain plasma concentration of potent drugs.
- Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.
- Reduce dosing frequency.
- First pass metabolism of drug gets avoided.
- Self –medication is possible.
- They provide extended therapy with single application.
- Ability to deliver drug more selectively to a specific site.

Disadvantages:

- Not suitable for high drug doses.
- Adhesion may vary with patch type and environment conditions.
- Skin irritation and hypersensitivity reactions may occur.
- Long time adhere is difficult.
- Transdermal drug delivery system does not suitable for delivery of ionic drug.
- Drug that require high blood levels cannot cannot be administered.
- The patches can be uncomfortable to wear.
- Poor diffusion of large molecules.
- This system may not be economical for some patient.

Principle of transdermal permeation:[9]

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration ,skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separate its surface from underlying capillary network . The various steps involved in transport of drug from patch to systemic circulation as follows,

1. Diffusion of drug from drug reservoir to the rate controlling membrane.

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2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary.
5. Effect on target organ.

MECHANISM OF TRANSDERMAL DRUG PENETRATION OF PATCH:[10]

- Release of base material of patch
- Diffusion into stratum corneum
- Diffusion into epidermis
- Diffusion into dermis
- Migration of capillaries
- Migration into lesion

Pathway of transdermal permeation[11]

The permeation of drugs through the skin includes the diffusion through intact epidermis and through the intact epidermis and through the skin appendages, i.e., hair follicles and sweat glands, which form shunt pathways through the intact epidermis.

However, these skin appendages occupy only 0.1%of the total human skin surface and the contribution of this pathway is usually considered to be small (with only a few exceptions having been noted). As stated above, drug permeation through the skin is usually limited by the stratum. (fig 3)

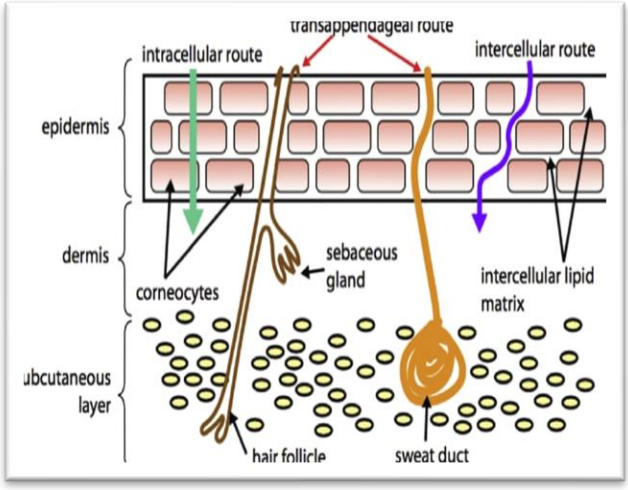

Figure 3: Structure of skin penetration

Two pathways through the intact barrier may be identified the intercellular lipid route between the corneocytes and the transcellular route crossing through the corneocytes and the intervening lipids that is, in both cases the permeant must diffuse at some point through the intercellular lipid matrix, which is now recognized as the major determinate of percutaneous transport rate.

Kinetics of transdermal permeation:[12]

The knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic system. Transdermal permeation of a drug involves the following steps:

1. Sorption by stratum corneum.
2. Penetration of dug through epidermis.
3. Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physicochemical properties. The rate of permeation across the skin is given by

$$Dq/dt = Ps(Cd-Cr) \text{--------} 1$$

Where the Cd and Cr are the concentration of the skin penetrant in the donor compartment i.e. on the surface of stratum corneum and in the receptor compartment i.e. body respectively. Ps is the overall permeability coefficient of the skin tissue to the penetrant. this permeability is given by the relationship

$$Ps = DssKs/hs \text{----------} 2$$

Where Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum, Dss is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and hg is the overall thickness of skin tissue. As Ks, Dss and hs are constant under given conditions the permeability coefficient Ps for a skin penetrant can e considered to be constant.

From equation (1) it is clear that a constant rate of drug permeation can be obtained only when Cd>>Cr i.e. the drug concentration at the surface of stratum corneum Cd is consistently and substantially greater than drug concentration in the body Cr.

The equation becomes

$$dQ/dt = PsCd \text{----------} 3$$

the rate of skin permeation is constant provided is constant provided the magnitude of Cd remains fairly constant through the course of skin permeation. For keeping Cd constant the drug should be diffusion from the device at a rate Rr>>Ra , the drug concentration on the skin surface Cd is maintained at a level equal to or greater than the equilibrium solibility of the drug in the stratum corneum Cs .i.e. Cd>>Cs.

Therefore, a maximum rate of skin permeation is obtained and is given by the equation;

$$(Dq/dt)m = PsCs \text{----------} 4$$

From the above equation it can be seen that the maximum rate of skin permeation depends upon the skin permeability coefficient PS and is equilibrium solubility in

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the stratum corneum Cs. Thus skin permeation appears to be stratum corneum Limited.

FACTORS AFFECTING TRANSDERMAL DRUG DELIVERY SYSTEM CAN BE DIVIDED INTO THREE CLASSES

1. Biological factors
2. Physiochemical factors
3. Formulation factor

1. Biological Factors:

PH of the skin:

The PH of the skin is usually acidic i.e., 4-6. The PH is responsible for regulating permeability of drug. According to PH – Penetration hypothesis, only the unionized form of drug can permeate through lipid barrier.

Skin hydration:

Hydration is most important factor increasing the permeation of skin. So Use of humectant is done in transdermal delivery.

Site of application:

The site on which the transdermal patches are applied will affect the permeation.

The thickness of the skin, nature of stratum corneum vary site to site which affects permeation.

Skin age:

It is assumed that skin of young and elderly are more permeable than middle aged persons. In premature infants, stratum corneum is absent and children are more susceptible to toxic effects of drugs through the skin.

Pathological conditions of the skin:

Injuries that disrupt the continuity of the stratum corneum increases permeability due to Lipid film.

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

2. Partition Coefficient:

The optimal partition coefficient (k) is required for good action. (b/w 1 and 4). Drug 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 with high molecular weight have low permeation (less than 400 daltons)**.**

Smaller particle size has more permeability than the larger particles.

Drug concentration:

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

Stability and half life:

Drug should be stable when it comes in contact with the skin. It should have low melting point. Half-life of drug should be less than 10 hours.

3. Formulation Factors:

Release characteristics:

Solubility of drug in dosage form determines the release time.

PH of the vehicle:

The acidic or alkaline pH may cause irritation to skin and may affect drug release, degree of hydration of polymers, therefore these surface PH of patches was determined to optimized both the drug and adhesion.

Permeation enhancers:

Physical permeation enhancers.

Chemical permeation enhancers.

TYPES OF TRANSDERMAL PATCHES:

1) Single layer of drug in adhesive patches:(13)

In these systems, the drug is remains in contact with the adhesive layer which is attached to the skin. In the layer of adhesive helps to releasing the drug and also serve to adhere to various layers together along with the skin, but also serves of the formulation foundation, containing the drug and all the excipients under a single backing film. The rate of diffusion of drug from these types of system is dependent on the diffusion across the skin. The intrinsic rate of drug diffusion from this type drug delivery system is defined by

$$dQ/Dt=Cr/(1/Pm+1/Pa)$$

Where,

Cr is the drug concentration in the reservoir compartment.

Pa and Pm are the permeability coefficients of the adhesive layer and the rate controlling membrane.

$$Pm = Km/r\ Dm\ /hm$$

$$Pa = Ka/m.Da/ha$$

Where,

Km/r and Ka/m are the partition coefficients for the interfacial partitioning drug from the reservoir to the membrane and from the membrane to adhesive.

Dm and Da are the diffusion coefficients in the rate controlling membrane and adhesive layer.

hm and ha are the thickness of the rate controlling membrane and adhesive layer.(fig :4)

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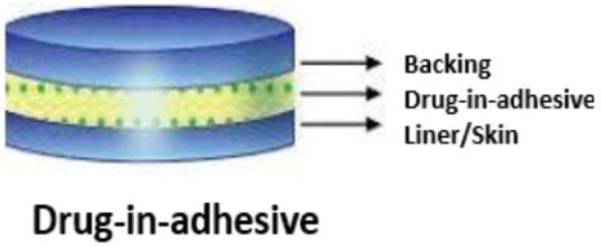

Figure 4: Single layer of drug adhesive

2) Multi- layer Drug- in -Adhesive:

The multi- layer Drug-in-adhesive is similar to the single-layer drug-in-adhesive in that the drug is incorporation directly into the adhesive. However, the multi-layer encompasses either the addiction of a membrane between two distinct drug- in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film.

The rate of drug diffusion in this system is defined by:

$$Dq/dt=Ka/r.Da/ha(cr)$$

Where,

Ka/r is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer. (fig:5)

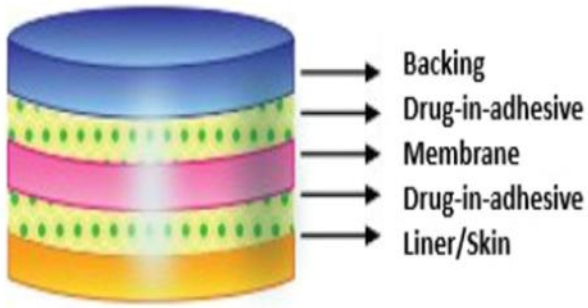

Figure 5: Multi layer drug adhesive

3) Reservoir type patches:[14]

The reservoir transdermal system has a separate drug layer unlike the single layer drug in adhesive and multilayer drug in adhesive system. In this system it includes compartment for liquid that contains a solution or suspension of drugs separated from the liner by a membrane adhesive. This patch system is also backed by the backing layer. In the reservoir system the rate of release is zero order. (fig:6)

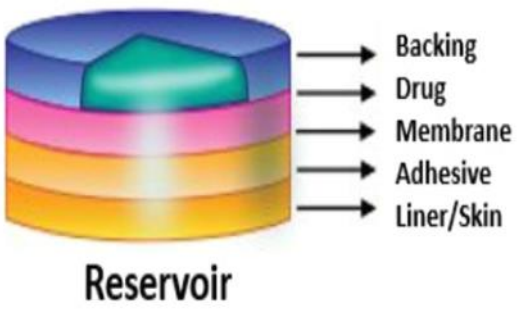

Figure 6: Reservoir type patches

4) Matrix type patches:

The matrix system consists a medicament layer of a semisolid matrix that contains a drug as a solution or suspension, that is direct contact with the liner layer. In this device the adhesive layer surrounds the drug layer partially overlaying it. (fig:7)

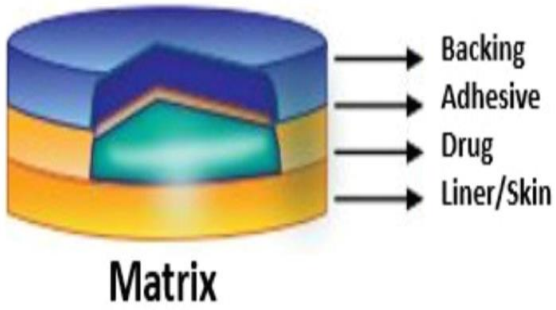

Figure 7: Matrix type patches

5) Vapour patches:

In this type of patch system, the adhesive layer not only serves to adhere the various layers together but also releases vapour. This patches are new to the market, and commonly used for releasing of essentials oils for up to 6hrs.These patches release essential oils and are used in cases of decongestion mainly. Many types of vapour patches are available in the market which are used to improve the quantity of sleep and reduces the cigarette smoking condition.

CONCLUSION

Transdermal drug delivery is a painless, convenient and potentially effective way to delivery regular doses of many medication. Wide range of drug can be delivered improved drug uptake minimal complications and side effect low cost and easy to use. Transdermal delivery of drug product which is currently approved as oral dosage form allows for the avoidance of first pass metabolism. Transdermal medication delivery system may not change the physiology of skin. Future development of TDDS will likely focus on the increased control of therapeutic regimens and the continuing expansion of drugs available for use.

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