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Review on Transdermal Drug Delivery System

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Review Article

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ABSTRACT

Skin is also used as a result of the positioning for drug administration for continuous transdermal drug infusion into the circulation. For the continual diffusion/penetration of the medication through the intact skin surface membrane-moderated systems, matrix dispersion kind systems, adhesive diffusion controlled systems and little reservoir systems square measure developed. Varied penetration enhancers unit used for the drug diffusion through skin. In matrix dispersion kind systems, the drug is distributed inside the solvent alongside the polymers and solvent allowed to evaporate forming a solid drug-polymer matrix. Matrix kind systems were developed inside the gift study. Inside the gift work, an attempt has been created to develop a matrix-type transdermal therapeutic system comprising of Budesonide with all completely different ratios substance mixtures exploitation solvent evaporation technique. The patches were subjected to varied physical evaluations alongside the in-vitro diffusion studies. On the premise of results obtained from the in-vitro study and physical analysis the patches containing hydrophilic substance poly vinyl pyrrolidone, polyehylene glycol as a result of the penetration attention (5%) were thought of as applicable for giant scale manufacturing with a backing layer and an appropriate adhesive membrane.

INTRODUCTION

Controlled drug delivery is one of the delivery system in which the drug is released for a prolonged period of time with predetermined rate for both locally and systemic effect. [1-3]. Controlled drug delivery accompanies with drug encapsulation techniques which delivers drug at regular intervals for a period from days to months. These are more advantageous and the same time have some disadvantages compared with traditional medication.

The classification of controlled drug delivery can be given as follows.

1. Rate-determined drug delivery systems
2. Dissolution controlled drug delivery systems
3. Encapsulated drug delivery systems
4. Diffusion controlled drug delivery systems
5. Matrix type

Among these class 1 contains new drug delivery systems as transdermal delivery, intra uterine delivery, ocular inserts, and sub dermal implants [4-6]. The transdermal drug delivery has

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advantage to deliver medicines through skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for prolong period of time.

Transdermal drug delivery

A transdermal patch is a medicated adhesive pad that is used on the skin for delivering the drug in a specified dose in a specified region through skin into the skin [7]. The main advantage of the transdermal drug delivery system over the other route of administrations like oral, intravenous, sublingual, intramuscular is its controlled release of the drug through skin usually by a porous membrane covering the medication or through body temperature which melts down the thin layers of medication embedded in the adhesive [8,9]. The only disadvantage is the drugs whose molecules are lower than the skin can only penetrate through the skin. The use of transdermal patches for has been restricted because of its penetration rate. A transdermal patch uses a special membrane to regulate the speed of the liquid drug contained within the reservoir among the patch.

Medication administered via skin patches embodies oscine, nicotine, estrogen, vasodilator, and topical anesthetic [10,11]. Non-medicated patch markets embody thermal and cold patches, nutrient patches, skin care patches (a class that consists of 2 major sub-categories therapeutic and cosmetic), aroma patches, and weight loss patches, and patches that measure daylight exposure. Transdermal drug delivery has many advantages over conventional drug delivery [12].

Advantages:

1. Using Transdermal drug delivery system, it is possible to achieve the following advantages:
1. Avoids the 'first pass effect' [13].
2. A stable and controlled blood level concentration of the drug.
3. Characteristics similar to intravenous infusion.
4. Can stop the further administration, if not necessary.
5. Long-term drug delivery ranging from a few hours to one week.
6. No interference with gastric and intestinal fluids, food, drinks and other oral medications.
7. Administration of drugs with a very short half-life, narrow therapeutic window, poor oral absorption
8. Improved patient compliance and reduced inter intra-patient variability.
9. Self-administration is possible.
10. Systems are non-invasive.
11. Minimizes side effects like vomiting and diarrhea [14].

Disadvantages:

1. The drug should have some desirable physico-chemical properties like lower molecular size, for penetrating through stratum corneum.
2. May cause skin irritation or dermatitis due to drug or excipient interaction.
3. The barrier function of skin varies from site to site on the same person, from person to person and with age
4. It requires high blood concentration [15].
3. It may be uneconomic [16].

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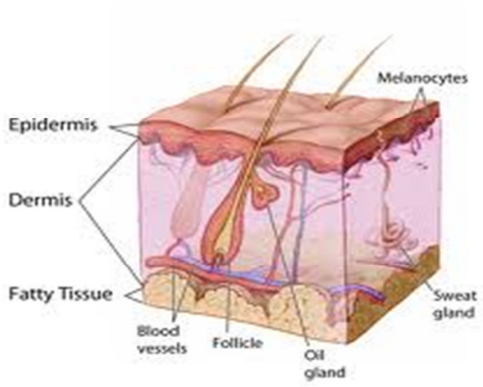

Figure 1: Structure of Skin (image courtesy: http://cosbiology.pbworks.com/f/1248965341/module%206%20-%2001.png)

MORPHOLOGY OF SKIN

Skin has three major tissue layers- the epidermis, the dermis and the hypodermis [17]. The epidermis along with its epithelium forms the surface layer of the body. It is a stratified squamous keratinized epithelium, and is present in majority of areas of the body. The cells divide constantly in the lowest cellular layers, the basal and prickle cell layers [18-20]. In this process, one daughter cell migrates to the surface, and the other divides again. As the cells migrate toward the surface they become cornified and form granules (stratum granulosum). The major barrier within the skin is the stratum corneum and the top layer of the epidermis. The stratum corneum consists of keratinized, flattened remnants of once actively dividing epidermal cells. Hygroscopic, but impermeable to water, it behaves as a tough, flexible membrane. The intercellular space is rich in lipids. The stratum corneum is about 10μ thick, but on the palms and soles it ranges up to 600μ in thickness [21].

CLASSIFICATION

Transdermal patches are categorized into five major types based on its composition and mechanism. A brief about the individual type is given below [22-25].

- **Single-layer Drug-in-Adhesive:** The Adhesive used in this type of patches not only holds all the layers together along with the entire system to the skin but also releases the drug. The adhesive is surrounded by layer of liner and backing.
- **Multi-layer Drug-in-Adhesive:** Multi-layer drug-in-adhesive is a collection of one or more single-layer drug-in-adhesive. These layers are separated by a membrane but not in all cases. One of the layers is for immediate drug release and rest of the layers are for controlled drug delivery. This patch is also covered with layer of thin liner and permanent backing.
- **Reservoir:** In contrast to the above types reservoir type of patch has a separate drug layer which contains the drug in liquid state in the form of solution or suspension separated by the adhesive layer. The drug reservoir is completely encapsulated in a shallow compartment embedded from a drug-impermeable metallic plastic laminate, with a vinyl acetate rate-controlling membrane on one surface. The patch is surrounded with backing layer. The reservoir patch follows Zero Order [26].
- **Matrix:** The matrix patch contains drug solution or suspension embedded in a semi-solid matrix which acts as drug layer. The adhesive layer in this type slightly overlays the drug layer and surround it. This type is also known as monolithic device [27].

- **Vapor Patch:** In Vapor patch the adhesive layer not only sticks all the layers and system to the skin but also releases the vapor from the patch. The activity of the patch ranges from 5-6 hours. This patch is used in the treatment of decongestion, sleep aid and smoking cessation [28].

However, transdermal drug delivery systems are most commonly classified into two groups:

A. Matrix patches: In the matrix system, the inert polymer semisolid matrix binds with the drug and forms drug layer which controls its release from the device [29].

B. Liquid reservoir patches: In the reservoir system, the polymer matrix is not responsible for drug release. Instead, a rate-controlling membrane present between the drug matrix and the adhesive layer acts as the rate-limiting barrier for drug release from the device [30-32].

COMPONENTS OF TRANSDERMAL PATCH

Both matrix patches and liquid reservoir patches comprise of various components. Some are similar in both classes, while others are type-specific. The common components include: [33-35]:

1. Backing Films: Backing films play a vital role in the transdermal patch and also while using the system. The role of the film is to protect the active layer and safeguard the stability of the system, and to affect skin permeation and tolerance, depending on occlusion or breathability. In order to avoid any type of incompatibility the release liner must be fully inert to the ingredients. It must also be flexible, comfortable and must have good affinity with the adhesive and excellent printability. The most common release liners are polypropylene, polyesters, PVC and nylon [36-39].

2. Release Liners: An anti-adherent coating will be covering the release liners. The role of the release liner is to protect the system when it is in the package, it will be removed just before the application of TDDS to the skin. Release liners play an important role in the stability, safety and affectivity of the patch. Care should be taken to choose the release liners. An incorrect release liner will not permit the easy release of the patch, and can interfere with the active(s) or other components, thereby reducing its shelf life. The most common films used as release liners are paper-based, plastic film-based and composite films. The two major classes of coating are silicones and fluoro-polymers [40-43].

3. Pressure Sensitive Adhesives: For both types of TDDS, pressure-sensitive adhesives (PSAs) play an important role, by serving as the matrix that carries the active like additives and permeation enhancers and the means for making the patch stick to the skin. There are three categories in PSAs: rubber-based, acrylic in the form of acrylic solutions, emulsion polymers or hot melts, and silicon PSAs. For each category there are several sub-categories that give the required flexibility to the patch [44-46].

4. Penetration Enhancers: These are the completely different chemical substances that belong to the same family by characteristics. They increase the permeation rate by several times of the active ingredient through the skin. This enhances the feasibility of a system, because most of the actives do not enter the skin in the required dosage through a relatively small area. Sometimes a combination of these ingredients is needed to create the correct enhancing effect [47-49].

5. Micro porous or Semi-Permeable Membranes: Porous membrane is a special type of membrane mostly used in all liquid transdermal patches and some of the matrix type patches. Its

role is to regulate the flow of the semi-solid content from the liquid reservoir, and to act as a rate-limiting membrane for the systems. The ability of the membrane depends on the design of the system, size of the active component and the need to have a rate-limiting factor in order to satisfy the release and absorption characteristics of the system. The permeation rate depends mostly on the chemical composition of the membrane [50-52].
There are two types of porous membranes as shown below
A. Ethylene Vinyl Acetate Membrane
B. Micro porous Polyethylene Membrane [53-55]

6. Pouching Materials: Most of the TDDS that are available in the market are packaged as unit doses in sealed pouches. The pouching material should be inert and should maintain the stability and integrity of the product. When there are two films with similar desired characteristics, the one with the lower cost, better function and printability will be chosen [56-58].
There are three main layers in the composite materials used for pouches they are a). Internal plastic heat sealable layer, b). The aluminium foil layer, c). The external printable layer. If the film is a lamination, an adhesive is used to keep the layers intact.
a. Heat Sealable Layer: This layer plays an important role in the functionality, stability and protection of the patch. Several plastic films or coatings can be used for its formation, including polyethylene [59-61].
b. Aluminium Foil Layer: This layer plays an important role in protecting the product from light and oxygen. In ideal conditions the foil needs to have a thickness of more than 1mil or 25 micrometers to be a real barrier. If any less than this thickness level is used, there will always be pinholes reducing the barrier properties [62-64].
c. External Layer: The external layer of a composite film is responsible to achieve a better finishing and printing quality. It acts synergistically with the aluminium foil. Paper or polyester film is used as an external layer, but the polyester film creates a better-looking pouch and better barrier [65-58].

FACTORS EFFECTING TRANSDERMAL PERMEABILITY

The factors effecting transdermal drug permeability are classified into following three factors [59-63].
A. Penetrants physicochemical properties
B. Drug delivery system and its physicochemical properties
C. Pathological and physiological conditions of the skin

A. Penetrants physicochemical properties

1. Partition coefficient: Drugs possessing which are water and lipid soluble are predominantly absorbed through skin. Transdermal permeability coefficient is directly dependent on partition coefficient. A lipid/water partition coefficient of 1 or greater is favorable for optimal transdermal permeability [64].
2. pH conditions: pH condition of skin and that of the patch affect the extent of dissociation of ion drug molecules and its permeability [65].
3. Penetrant concentration: Transdermal permeability through the skin follows the passive diffusion process. Hence the concentration gradient of penetrant molecules on the surface layers of the skin is required. [66-68].

B. Drug delivery system and its physicochemical properties

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1. Release characteristics: Generally, more the drug is released from the delivery system higher will be the rate of permeation. The mechanism of drug release depends on whether the drug molecules are dissolved or suspended in the delivery system, interfacial partition coefficient between the drug system and the skin.
2. Composition of drug delivery systems: The composition of drug delivery system has a crucial influence on percutaneous absorption of the drug molecule. It affects the rate of drug release and the permeability of stratum corneum by means of hydration, mixing with skin lipids and so on [69].
3. Enhancement of transdermal permeation: Addition of a sorption or permeation promoter in the drug delivery system will enhance the transdermal permeation of drugs [70-72].
(a) Organic solvents as permeation promotor: Some of the organic solvents used as permeation promoter are Dimethylsulfoxide, Ethanol, Ethylene glycol, Polyethylene glycol.
(b) Surface active agent as permeation promoter- Comparatively anionic surfactants are more effective permeation promoters. Some of them are (SLS) Sodium lauryl sulfate, Sodium dioctyl sulfosuccinate.

C. Pathological and physiological conditions of the skin

1. Reservoir effect of the horny layer: The horny layer and its deeper layer act as a depot or reservoir of the drug and modify permeation characteristics of some drugs [80].
2. Lipid film: The barrier function of the stratum corneum is maintained by the thin lipid film on skin surface formed by result of the product excretion of sebaceous gland and epidermal cell.
3. Skin hydration: Hydrated stratum corneum have eight folds more permeability than the normal skin.
4. Skin temperature: Skin permeation was raised by 10 folds with raise in temperature from 10º to 37º C of acetyl salicylic acid and glucosteroids was noticed with the environmental temperature [81-82].

Patient should be advised about the following instructions

1. The transdermal patch should be applied to a clean and dry skin relatively free of hair, sebaceous or any other oil, and external injuries with broken skin. Moist skin can accelerate the drug permeation. Oily skin will hamper the adhesion of the patch to the skin [83]. If any hair is present on the desired location, it should be cut but not shaved because the later can remove the upper horny layer which affects the rate and extent of drug permeation.
2. Use of skin moisturizer or any lotion should be avoided at the application area, because hydrating the skin can alter partition coefficient of drug [84-86].
3. The protecting backing should be removed with care without touching with fingertips. The transdermal patch should be pressed firmly against skin site with the heel of hand for about 10seconds [87-89].

APPROACHES FOR DEVELOPING TRANSDERMAL DRUG DELIVERY SYSTEM

There are four different approaches that have been utilized to obtain transdermal drug delivery systems [90]
1. **Membrane permeation controlled systems:** In this TDDS the drug reservoir is totally encapsulated in a shallow compartment mounted from a drug impermeable metallic plastic

laminate and rate controlling membrane made up of polymers which may be micro porous or non-porous for example ethylene vinyl acetate(EVA) copolymer , with a defined drug permeability property [91,92].

The major advantage of this transdermal system is the constant release of the drug. Ex. Nitroglycerin releasing transdermal system

2. Adhesive dispersion type systems: This TDDS is similar to membrane permeation controlled system but simpler than that. Drug is dispersed directly on to the adhesion polymer and this adhesive is spread on the thin impermeable metallic plastic laminate by solvent casting or hot melt which acts as drug reservoir. Ex. Isosorbide dinitrate transdermal therapeutic system [93-95].

3. Matrix diffusion controlled systems: In this drug is dispersed onto the hydrophilic or lipophilic polymer matrix. This medicated matrix is carefully transferred to a plastic medicated disc with a predefined surface area and thickness. This drug containing polymer disc is then transferred to a fabricated impermeable plastic backing. The adhesive polymer is then placed around this disc to form the adhesive rim [96-98].

4. Micro reservoir type or microsealed dissolution controlled system: This is a fusion model of both reservoir and matrix type of TDDS. First the drug solids are suspending in a aqueous solution of water soluble liquid polymer and this is again dispersed in a lipophilic polymer to form several discrete, unleashing microscopic spheres of drug reservoirs [99,100].

CONCLUSION

Transdermal drug delivery system is a novel drug administration route. For drugs which have incompatibilities or reaction with gastric contents or food or drinks like in case of oral administration can be administered as transdermal patch, which undergo biodegradation, drug that undergo first pass effect, drugs which has drug-drug interactions and also be administered as transdermal patches. It is more preferred due to its patient compliance, easy route of administration and desired therapeutic effect. This transdermal drug delivery is available with different techniques which make it easy for applying to different drug molecules based on their physic-chemical properties. Transdermal patches have various advantages and also disadvantages. It varies in its efficacy depending on various conditions. In general transdermal patch can be used for wide range of applications like contraceptives, smoking cessation, motion sickness, hormonal therapies, sleeping aids, pain medication, anti-hypertensive, treatment of overactive baldder and many more. The technology must evolve beyond and biotechnology should also be combined to invent many more innovative medications.

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