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A Review on Transdermal Drug Delivery System

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ABSTRACT

Transdermal drug delivery as a replacement for the oral route allows gastrointestinal absorption to be avoided, with its related pit drops of deactivation connected with enzymatic and pH. Transdermal delivery has many benefits over standard drug administration methods, thus avoiding first-pass hepatic metabolism and enhancing patient compliance. Its primary benefits include controlled drug release with minimal side effects, enhanced bioavailability, first-pass metabolism bypass, and much more. There are variables such as both physiochemical and biological that influences the transdermal drug's bioavailability. The number of drugs formulated in the patches has hardly increased over the past decade; there has been little change in the patch system's composition. Changes were mostly restricted to refining the materials used. This review paper discusses the general research on the Transdermal Drug Delivery System (TDDS) leading to the development of a new drug delivery system (NDDS).

Introduction

Transdermal patch which delivers specific amount of the drug through the skin into the bloodstream when applied directly to the intact body. Currently, the oral route of administration is most widely used to administer the drugs to humans for a few days, but in this route the drawback such as drug degradation can occur first pass metabolism. Active blood moiety including bioavailability may be reduced. To rectify the difficulties in the oral drug delivery process. The new drug delivery systems were developed. The TDDS is one of the novel drug delivery systems here in the form of transdermal patch, the drug will be administered through the bodyTransdermal drug delivery system (TDDS) is characterized as self contained, discrete dosage forms at a controlled level for systemic circulation when applied to intact skin [1].

Skin anatomy and physiology [2-4]

There are three distinct but mutually dependent tissues in the human skin.

A) The stratified, vascular, cellular epidermis

B) Underlying dermis of connective tissues and

C) Hypodermis.

Epidermis

The multilayered epidermis varies in thickness, depending on the size of the cell and the number of epidermis cell layers, ranging from 0.8 mm on the palms to 0.06 mm on to the eyelids. Table 1 includes epidermis density, water permeability and water diffusivity.

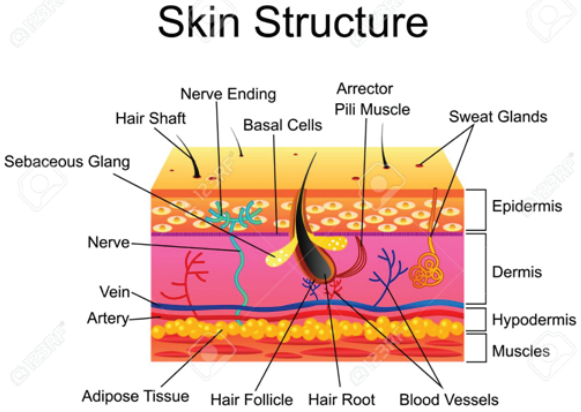

Figure 1: Skin Structure

a) Stratum corneum

This is also called the furthermost layer of the skin as a horny layer. Once dry it is about 10 mm thick, but when completely hydrated it swells to several times this thickness. It has 10 to 25 layers of dead, keratinized cells known as corneocytes. It is flexible, but it is relatively impervious. The stratum corneum is the main drug penetration barrier. Horny layer architecture can be designed as a wall like structure. Keratinized cells behave as protein "bricks" embedded in "mortar" lipid in this model. Lipids are arranged in several bilayers. Amphiphilic content, such as polar free fatty acids and cholesterol, is necessary in the lipid fraction to maintain a bilayer shape.

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b) Viable epidermis

This is situated beneath the stratum corneum and varies in thickness from 0.06mm on the eyelids to 0.8mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. In the basale layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

Dermis

Dermis is 3 to 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. 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. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeant very low and the resulting concentration difference across the epidermis provides the essential concentration gradient for transdermal permeation.

Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanic al protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs.

Structure of the Skin Barrier [5]

The skin is the largest human organ and consists of three functional layers: epidermis, dermis, and subcutaneous tissue. It has a wide variety of functions. One major task of the skin is to protect the organism from water loss and mechanical, chemical, microbial, and physical influences. The protective properties are provided by the outermost layer of the skin, the epidermis. Although its thickness measure on average only 0.1 mm (from 0.02mm on the face up to 5 mm on the soles of the feet) it is specially structured to fulfill this challenging task. Out of the five layers of the epidermis, it is mainly the upper most layer. Which forms the permeability barrier. The stratum corneum consists of horny skin cells which are connected via desmosomes (protein-rich appendages of the cell membrane). The corneocyte are embedded in a lipid matrix. Thus the structure of the stratum corneum can be roughly described by a "brick and mortar" model.

Routes of Penetration

Illustrates the possible pathway for a penetrant to cross the skin barrier. Accordingly, a molecule may use two diffusional routs to penetrate normal intact human skin: the appendageal route and the trans epidermal route. The appendageal route comprises transport via the sweet glands and the hair follicles with their associated sebaceous glands. The routes circumvent penetration through the stratum corneum and are therefore known as shunt routes. Although these routes offer high permeability, they are considered to be of minor importance because of their relatively small area, approximately 0.1 % of the total skin area. The appendageal route seems to be most important for ions and large polar molecules which hardly permeation the stratum corneum. Across the intact horny layer, through the hair follicles with the associated sebaceous glands, or via the sweat glands.

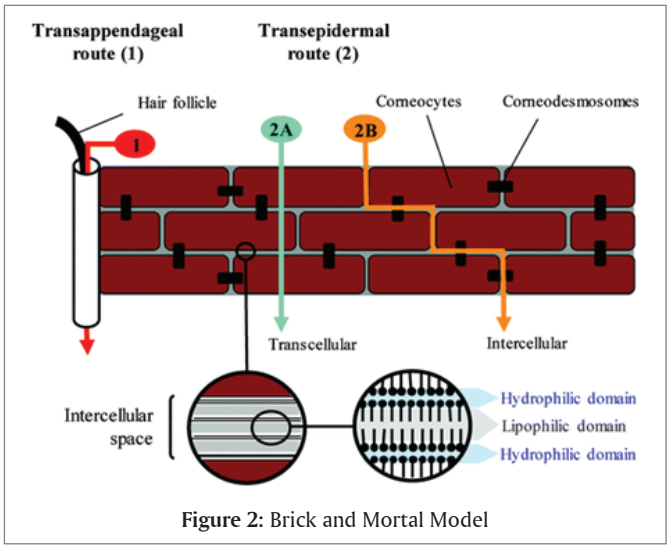

Figure 2: Brick and Mortal Model

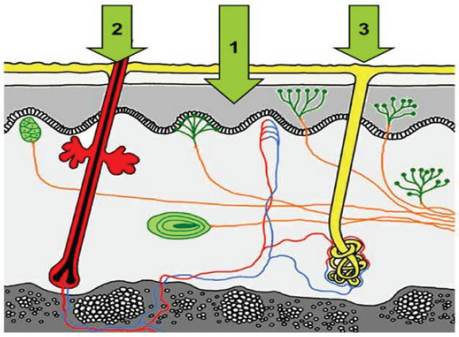

Figure 3: Possible pathways for a re-entrant to cross the skin barrier

Types of Transdermal Drug Delivery System [6]

Single-layer Drug-in-Adhesive

The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film. The rate of release of drug from this type of system is dependent on the diffusion across the skin.

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 incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film.

Drug Reservoir-in-Adhesive [7]

The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.

Drug Matrix-in-Adhesive

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.

Basic Principal of Transdermal permeation [1,2]

Transdermal permeation is based on passive diffusion1. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimetre of tissue separates its surface from the underlying capillary network. The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process.

Ideal Requirements of Transdermal Patches

- The shelf life of the patches up to 2 years.
- The patch should be in small size (i.e. < 40cm2)
- Should provide convenient dose frequency (i.e. once a day or once a week)
- Cosmetically acceptable (i.e. clear, white colour)

Advantages of transdermal drug delivery [1,7-9]

Transdermal drug delivery enables the avoidance of gastrointestinal absorption with its associated pitfalls of enzymatic and pH associated deactivation.

Avoidance of first pass metabolism

- The lack of peaks in plasma concentration can reduce the risk of side effects, thus drugs that require relatively consistent plasma levels are very good candidate for transdermal drug delivery.
- As a substitute for oral route.
- The patch also permit constant dosing rather than the peaks and valley in medication level associated with orally administered medication.
- Rapid notifications of medication in the event of emergency as well as the capacity to terminate drug effects rapidly via patch removal.
- Avoidance of gastro intestinal incompatibility.
- Convenience especially notable in patches that require only once weekly application, such a simple dosing regimen can aid in patient adherence to drug therapy.
- Minimizing undesirable side effects.
- Provide utilization of drug with short biological half-life, narrow therapeutic window.
- Avoiding in drug fluctuation drug levels.
- Inter and intra patient variation.
- Termination of therapy is easy at any point of time.
- Provide suitability for self-administration.
- They are non-invasive, avoiding the inconvenience of parental therapy.
- The activity of drugs having a short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
- It is of great advantages in patients who are nauseated or unconscious.
- Transdermal patches are better way to deliver substances that are broken down by the stomach aids, not well absorbed from the gut, or extensively degraded by the liver.

Disadvantages of Transdermal Drug Delivery [1,9,10]

- Transdermal drug delivery system cannot deliver ionic drugs.
- It cannot achieve high drug levels in blood.
- It cannot develop for drugs of large molecular size.
- It cannot deliver drugs in a pulsatile fashion.
- It cannot develop if drug or formulation causes irritation to skin.
- Possibility of local irritation at site of application.
- May cause allergic reaction.
- Sufficient aqueous and lipid solubility, a log P (octanol/ water) between 1 and 3 is required for permeate to transverse stratum corneum and underlying aqueous layer.
- Long-time adherence is difficult.

Properties that Influence Transdermal Delivery [10]

- Release of the medicament from the vehicle.
- Penetration through the skin barrier.
- Activation of the pharmacological response.

Conditions in which the Transdermal patches are not used

- The transdermal patch is not suitable when, treatment of acute pain.
- Where rapid dose irritation is required.
- Where the required dose is equal to or less than 30 mg/24 hours.
- Limitations
- The ionic drugs are not suitable in TDDS formulation.
- TDDS can't achieve high levels in blood plasma.
- TDDS can't able to formulate with drugs having high molecular size.
- Pulsatile Delivery System is not possible.
- Drugs having direct dermatological effects are can't able to formulate as transdermal patch. The above limitation may be rectified by using novel approaches like ionophoresis, electroporation &ultrasound etc.

Methods of Preparation of TDDS [11]

1. Asymmetric TPX Membrane Method
2. Circular Teflon Mould Method
3. Mercury Substrate Method
4. By using "IPM Membranes" Method
5. By using "EVAC Membranes" Method
6. Preparation of TDDS by using Proliposomes
7. By using Free Film Method

1. Asymmetric TPX Membrane Method- (Bernerand John 1994)

By this method prototype patch can be prepared by using heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter as the backing membrane. Drug dispersed on concave membrane, covered by a TPX {poly (4-methyl-1- pentene)} asymmetric membrane, and sealed by an adhesive. Asymmetric TPX membrane preparation: These are prepared by using the dry/wet inversion process. Here TPX is dissolved in a mixture of solvent (cyclohexane) and non solvent additives at 60°c to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate. Then casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs].

2. Circular Teflon Mould Method-(Baker and Heller1989)

Polymeric solution in various ratios is used as an organic solvent. Then that solution is divided in two half. In one half calculated amount of drug is dissolved & in another half enhancers in different concentration are dissolved, and then two halves mixed together. Plasticizer (e.g., Di-N butyl phthalate) is added into the drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular Teflon mould. The moulds are to be placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. The dried films are to be stored for another 24 h at25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects.

3. Mercury Substrate Method

In the polymeric solution drug & plasticizer get dissolved. It is kept for 10-15min stirring to produce homogenous dispersion then it is poured into leveled mercury surface, covered with inverted funnel to control solvent evaporation.

4. By using "IPM Membranes" Method

In the mixture of water & polymer (propylene glycol containing Carbomer 940 polymer) drug get dispersed and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanol amine. The drug solubility in aqueous solution is very poor then solution gel is obtained by using Buffer pH 7.4. The formed gel will be incorporated in the IPM membrane.

5. By using "EVAC Membranes" Method

For the preparation of target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is insoluble in water then use propylene glycol for gel preparation. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

6. Preparation of TDDS by using Proliposomes

By carrier method using film deposition technique proliposomes are prepared. Drug and lecithin ratio should be 0.1:2.0 taken as an optimized one from previous references. For the preparation of proliosome in 100 ml round bottom flask take 5 mg of mannitol powder, then it is kept at 60-70°c temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20- 30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

7. By using Free Film Method

Cellulose acetate free film can prepared by casting on mercury surface. 2% w/w polymer solution is prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

Evaluation of Transdermal Patches [11]

- The transdermal patches can be characterized in terms of following parameters Physicochemical evaluation
- *In vitro* evaluation
- *In vivo* evaluation

Physicochemical Evaluation

Transdermal patches can be physicochemically evaluated in terms of these parameters:

Thickness: The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight: Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight

Drug content determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Content uniformity test: 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Moisture content: The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

% Moisture content=Initial weight – Final weight X100

Moisture Uptake: Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.

35 % moisture uptake = Final weight – Initial weight X 100.

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

% constriction = I1 – I2 X 100

I2 = Final length of each strip

I1 = Initial length of each strip.

Folding Endurance: Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted.

Conclusion

Patient who cannot swallow or remember to take their medications transdermal drug delivery system is beneficial. Clinicians and other allied health professionals should understand the appropriate administration techniques for transdermal systems to ensure optimal patient outcomes and to ensure the safety of all who encounter patients who use transdermal drug delivery system. Future developments of transdermal drug delivery system will likely focus on the increased control of therapeutic regimens and the continuing expansion of drugs available for use. Transdermal dosage forms may provide clinicians an opportunity to offer their patients to optimize their care.

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Conflict of Interest

None

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