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A REVIEW ON PREPARATION METHODS AND EVALUATION OF TRANSDERMAL PATCHES

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ABSTRACT

Transdermal drug delivery was presented to overcome the difficulties of drug delivery especially oral route. Drug delivery through the skin a drug to achievea systemic of drug is known as transdermal patches. Transdermal patches are widely used as cosmetic, topical, transdermal drug delivery system. 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. Topical administration of therapeutic agent's 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 steadyplasma level of drug. The basic components of transdermal patch consists of polymer matrix\drug reservoir, active ingredient (Drug), permeation enhancer, pressure sensitive adhesive, backing laminates, release liner, other excipients like plasticizer and solvent. There are many methods of preparation of transdermal patches like circular Teflon mould method, assymetric tpx membrane method,mercury substrate methods, IPM membrane methods, EVAC membrane method, free film method. Cellulose derivative, zein, gelatin, polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene this are the polymersused in the preparation of transdermal patches. Also there are many evaluation parameter of transdermal patches like thickness, uniformity of weight, drug content determination, moisture content, moisture uptake, flatness, microscopic studies, adhesive studies, peel adhesion, tack properties, quick steel

(peel tack method) test . This review article provides anoverview of transdermal drug delivery system, its advantages over conventional dosage forms, drug delivery routes across human skin, permeation enhancer, and various preparation methods.

Keywords: TDDS, topical drug delivery, systemic blood circulation,

INTRODUCTION

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood strea[1]. Transdermal drug delivery system has been in existence for a long time. In the past commonly applied systems were topically applied creams and ointments for dermatologically disorders. The occurrence of systemic side effects with some of these formulations is indicative of absorption through the skin. A number of drugs have been applied to the skin for the systemic treatment.

Various types of patches along with various methods of applications have been discovered to deliver the drug from the transdermal patch.[2] Because of its great advantage, it has become one of the highly researched fields among the various drug delivery system. Here a general view over the transdermal patch has been discussed along with its advantages, disadvantages methods of applying, care taken while applying, types and applications of transdermal patch and recent advances and marketed products.[3][4]

ADVANTAGES :

1. Hepatic first pass metabolism, salivary metabolism and intestinal metabolism are avoided.

2. The ease of usage makes it possible for patients to self-administer these systems.

3. In case of an emergency, removing the patch at any point of time during therapy can instantly stop drug input.

4. Since the composition of skin structurally and biologically is the same in almost all the humans, there is minimal inter and intra patient variation.

5. Drugs showing gastrointestinal irritation and absorption can be suitably administered through the skin.

6. Continuous, non-invasive infusion can be achieved for drugs with short biological half lives, which would otherwise require frequent dosing.[5]

DISADVANTAGES

1. There is possibility of skin irritation due to the one or many of theformulation components.
2. Binding of drug to skin may result in dose dumping.
3. It can be used only for chronic conditions where drug therapy is desired for along period of time including hypertension, angina and diabetes.

4. Lag time is variable and can vary from several hours to days for differentdrug candidates.
5. Cutaneous metabolism will affect therapeutic performance of the system.
6. Transdermal therapy is feasible for certain potent drugs only.
7. Transdermal therapy is not feasible for ionic drugs.
8. It cannot deliver drug in pulsatile fashion.[4]

1. TRANSDERMAL PATCH

A transdermal patch or skin patch is a medicated adhesive patch that isplaced on the skin to deliver a specific dose of medication through the skin and into the blood stream[1]. Often, this promotes healing to an injured area of the body. The first commercially available prescription patch was approved by the U.S. December 1979 containing scopolamine for motion sickness . The highest selling transdermal patch in the United States was the nicotine patch which releases nicotine to help with cessation of tobaccosmoking. The first commercially available vapour patch to reduce smoking was approved in Europe in 2007.[7]

2. COMPONENTS OF TRANSDERMAL PATCHES

The basic components of transdermal patch consists :

1. polymer matrix / Drug reservoir
2. active ingredient (drug)
3. permeation enhancers
4. pressure sensitive adhesive (PSA)
5. backing laminates
6. release liner
7. other excipients like plasticizers and solvents[8]

2.1. Polymer matrix :

Polymers are the backbone of a transdermal drug delivery system. Systems for transdermal delivery are fabricated as multilayered polymeric laminates inwhich a drug reservoir or a drug–polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane. Polymer selection and design must be considered when striving to meet the diverse criteria for the fabrication of effective transdermal delivery systems.

The polymers utilized for TDDS can be classified:

i. natural polymers includes cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc .

ii. synthetic elastomers includes polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile,

acrylonitrile, neoprene, butylrubber etc,

iii. synthetic polymers includes polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea,polyvinylpyrrolidone, polymethylmethacrylate etc.

2.2. Drug :

The most important criteria for TDDS are that the drug should possess the right physicochemical and pharmacokinetic properties. Transdermal patches offer much to drugs which undergo extensive firstpass metabolism, drugs with narrow therapeutic window, or drugs withshort half-life which causes non-compliance due to frequent dosing. For example, drugs like rivastigmine for Alzheimer's and Parkinson dementia, rotigotine for Parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS.[9]

Table 1: Drug characterstics[10]

Sr.NO.	Parameter	Properties
1	Dose	Should be Low in weight (less than 20mg/day)
2	Half- life	10/less (hrs).
3	Molecular weight	<400dalton
4	Skin permeability coefficient	>0.5*10-3cm/h
5	Skin Reaction	Non irritating, Non sensitizing
6	Oral bioavailability	Non irritating, Non sensitizing

2.3. Permeation enhancers :

The chemical compounds that enhance the permeability of stratum corneum so as to attain therapeutic levels of the drug candidate.[10] To increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug permeation enhancers interact with structural components of stratum corneum i.e., proteins or lipids.[11]

Ideal Properties of Permeation Enhancers**:**

i. They should be non-irritating, non-toxic & non- allergic.

ii. They should not bind to receptor site i.e. not showing any pharmacological activity.

iii. They should be cosmetically acceptable with an appropriate skin feel.[12]

2.4. Pressure sensitive adhesive (PSA)

A PSA maintains an intimate contact between patch and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, and exert a strong holding force. These include polyacrylates, polyisobutylene and silicon based adhesives.The PSA can be positioned on the face

of the device (as in reservoir system) or in the back of the device and extending peripherally (as in case of matrix system) [13]

It can easily remove from the smooth surface without leaving a residue on it

i. Polyacrylates
ii. Polyisobutylene
iii. silicon based adhesives [12]

2.5. Backing laminate

The primary function of the backing laminate is to provide support. Backing layer should be chemical resistant and excipients compatible because the prolonged contact between the backing layer and the excipients may cause the additives to leach out or may lead to diffusion of excipients, drug or permeation enhancer through the layer.

Examples of some backing materials are aluminium vapour coated layer, plastic film

example:

i. polyethylene
ii. polyvinyl chloride
iii. polyester film

2.6. Release liner

During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination.

The release liner is composed of a base layer which may be

i. non-occlusive (paper fabric)
ii. occlusive (polyethylene and polyvinylchloride)

A release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metalized laminate.

2.7. Other excipients

Solvents:

i. Chloroform
ii. Methanol
iii. Acetone
iv. Isopropanol

v. dichloromethane.

Plasticizers:

i. Dibutylpthalate

ii. Triethylcitrate

iii. polyethylene glycol

iv. propylene glycol [14]

3. Types of transdermal patches : [15][16][17][18][19]

3.1. Single layer drug in adhesive

In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

3.2. Vapour patch

The patch containing the adhesive layer not only serves to adhere the various surfaces together but also serves as to release the vapour.

3.3. Reservoir system

In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non porous.

4. Methods of Preparation of TDDS[20]

i. Asymmetric TPX membrane method

ii. Circular Teflon mould method.

iii. Mercury substrate method.

iv. By using “IPM membranes” method

v. By using “EVAC membranes” method.

4.1. Asymmetric TPX Membrane Method:

These are prepared by using the dry or wet inversion process. In this 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 (temperature mantained 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.

4.2. Circular Teflon Mould Method:

It was discovered by Baker and Heller in 1989. Polymeric solution in various proportions is used as an organic solvent. Then that solution is divided in two parts. In one parts calculated amount of drug is dissolved & in another part enhancers in different concentration are dissolved, and then two parts mixed together. Then plasticizer (e.g., Di-Nbutylphthalate) 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 levelled 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. After which a dried film formed & that is to be stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects.

4.3. Mercury Substrate Method:

In this method drug & plasticizer get dissolved in polymeric solution. It stirred for 10- 15 min to produce homogenous dispersion then it is poured into levelled mercury surface, covered with inverted funnel to control solvent evaporation.

4.4. 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 triethanolamine. If 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.

4.5. By Using "EVAC Membranes" Method:

For the preparation of TDS, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membrane is needed as rate control membrane. 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.

5. Evaluation of Transdermal Patches:

5.1. Thickness: [21][22][23]

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

5.2. Uniformity of weight: [24]

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 .

5.3. Drug content determination: [25]

It can be determined by completely dissolving a small area (1 cm^2) of polymeric film in suitable solvent of definite volume. The solvent is selected in which the drug is freely soluble. The selected area is weighed before dissolving in the solvent. The whole content is shaken continuously for 24 h in a shaker incubator followed by sonication and filtration. The drug in solution is assessed by appropriate analytical method.

5.4. Content uniformity test: [26]

The test is applied as the gold standard to determine chemically the content of active constituent for each unit dose. The test is completed by performing assay to find out the content of drug material contained in polymeric film of the patch. According to USP the procedure consists of two stages. First stage consists of assaying the randomly selected ten units. It is followed by second stage to be performed on twenty more units when the first stage fails.

5.5. Moisture content: [26]

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

$$\% \text{ Moisture Content} = \frac{(\text{Initial wt} - \text{Final wt}) \times 100}{\text{Final wt}}$$

5.6. Moisture Uptake: [26]

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

$$\% \text{ Moisture uptake} = \frac{\text{final weight} - \text{initial weight} \times 100}{\text{Initial weight}}$$

5.7. Flatness: [26]

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.

$$\% \text{ constriction} = \frac{(L1 - L2) \times 100}{L1}$$

L2 = Final length of each strip

L1 = Initial length of each strip

5.8. Microscopic studies: [26]

Distribution of drug and polymer in the film can be studied using scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double sided adhesive tape. The sections are then coated with goldpalladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under scanning electron microscope .

5.9. Adhesive studies : [26]

The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure. The adhesive properties of a TDDS can be characterized by considering the following factors:

i. Peel Adhesion properties: [26]

It is the force required to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a single coated tape, applied to substrate at 180° angle. The test is passed if there is no residue on the substrate

ii. Tack properties:[26]

It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer . It includes thumb tack test, rolling ball test, quick stick (Peel tack) test and probe tack test. Thumb tack test is performed by touching the surface of a pressure sensitive adhesive with the thumb and feeling the force required to break the bond. Thus the force required to remove thumb from adhesive is a measure of tack. Rolling ball test involves measurement of the distance that stainless steel ball travels along with an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

iii. Quick stick (Peel tack) test: [26]

The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90◦ at the speed of 12 inch/min. Probe tack test is performed using a probe which is pushed forward into contact with the adhesive surface and then retracted at a predefined speed. The force required to break the bond after a short period of contact is measured. The test may be performed with the help of Texture Analyser

6.CONCLUSION

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream Transdermal drug delivery represents one of the most rapidly advancing areas of novel drug delivery. Due to recent advances in technology and the ability to deliver the drug systemically without rupturing the skin membrane, transdermal route is becoming a widely accepted route of drug administration. TDDS are designed for controlled release of drug through the skin into systemic circulation maintaining consistent efficacy. It offers the delivery of drug at lowered dose that can save the recipient from the harm of large doses with improved bioavailability. In TDDS, there are many methods of preparation of transdermal patches like circular Teflon mould method, assymetric tpx membrane method, mercury substrate methods, IPM membrane methods, EVAC membrane method, aluminium backed adhesive film method, Proliposome/ Proniosome based method, free film method. Cellulose derivative, zein, gelatin, polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene this are the polymers used in the preparation of transdermal patches. This may be achieved by by-passing the hepatic first metabolism. Almost all major and minor pharmaceutical companies are developing TDDS.

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