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Review Article

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A COMPREHENSIVE REVIEW ON MATRIX TYPE TRANSDERMAL PATCHES

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ABSTRACT

Transdermal drugs are self-contained, discrete dosage form. Drug delivery through the skin to achieve a systemic effect without producing any fluctuations in plasma concentration of the drug. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. And also provide controlled release of the drug for extended period of the time. This review article covers brief outline advantages, skin pathways for transdermal drug delivery systems (TDDS), various components of transdermal patch, and approaches for preparation of transdermal patches, evaluation of transdermal system, general clinical considerations in the use of tdds and limitation of tdds.

KEYWORDS: skin, Drug delivery, Transdermal, TDDS.

INTRODUCTION

In this system medicated adhesive patches are prepared which deliver therapeutically effective amount of drug across the skin when it placed on skin. They are available in different sizes & having more than one ingredient. Once they apply on unbroken skin they deliver active ingredients into systemic circulation passing via skin barriers. 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.[1]

a) Through hair follicals.
b) Through sebaceous glands.
c) Through sweat duct.

Transdermal drug delivery systems are used in various skin disorders, also in the management of angina pectoris, pains, smoking cessation & neurological disorders such as Parkinson's disease.[2]

Advantages

a) First pass metabolisms of drug get avoided.
b) Gastrointestinal incompatibilities get avoided.
c) Self-medication is possible.
d) Duration of action gets extended & predictable.
e) Unwanted side effects get minimized.
f) Drug plasma concentration gets maintained.
g) Number of doses get reduces which improve patient compliance.
h) Therapeutic value of many drugs get increased by avoiding problems associated with drug like-lower absorption, GI irritation, decomposition due to hepatic first pass metabolism.[3]

Disadvantages

a. Chances of allergic reactions at the site of application like- itching, rashes, local edema etc.
b. Larger molecular size of drug (above 1000) creates difficulty in absorption.
c. Barrier function of skin varies from site to site on the same or different person.
d. Drug with hydrophilic character is less suitable as compare to drug with lipophilic character because of their low permeability.[4,5]

Types of Transdermal Drug Delivery System

Single-layer Drug-in-Adhesive System: In this type of patch the adhesive layer of this system contains the drug. The adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but it is also responsible for the releasing the drug. The adhesive layer is surrounded by a temporary liner.[6]

Reservoir System: In this System the drug reservoir is kept in between backing layer and a rate controlling membrane. And drug releases through microporous rate controlled membrane. Drug can be in the form of a solution, suspension, or gel or dispersed in a solid polymer matrix in the reservoir compartment.[7]

Matrix System: This system is of Two type

a) Drug-in-Adhesive System: For the formation of drug reservoir, the drug dispersed in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesives) on to an impervious backing layer.[8,9,10]

b) Matrix-Dispersion System: In this system the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. And this containing polymer along with drug is fixed onto an occlusive base plate in a compartment fabricated from a drug- impermeable backing layer. In this system the adhesive is spread along the circumference instead of applying on the face of drug reservoir to form a strip of adhesive rim.[11,12]

Micro-Reservoir System

This system is a combination of reservoir and matrix-dispersion systems. In which drug is suspended in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unleachable, microscopic spheres of drug reservoirs.[13]

Components of Transdermal Drug Delivery System

a) Polymer matrix/ Drug reservoir
b) Drug
c) Permeation enhancers.
d) Pressure sensitive adhesive (PSA).
e) Backing laminate.
f) Release liner.
g) Other excipients like plasticizers and solvents.[14]

Polymer Matrix/ Drug Reservoir: It is prepared by dispersing the drug in liquid or solid state synthetic polymer base. It should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers.

Polymers used in Transdermal drug delivery systems are classified as)

a) Natural Polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.

b) Synthetic Elastomers: e.g. polybutadiene, hydrin rubber, silicon rubber, polyisobutylene, acrylonitrile, neoprene, butyl rubber etc.[15]

c) Synthetic Polymers: e.g. polyvinylalcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.

Drugs: Some of ideal properties of drug & some factors to be consider during preparation of Transdermal patches are as follows:

Table 1: Ideal Properties of Drugs.

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

Permeation Enhancers

The chemical compounds that enhance the permeability of stratum corneum so as to attain therapeutic levels of the drug candidate. They improve the permeability by interacting with Stratum corneum.[16]

a) 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.

Pressure Sensitive Adhesive (PSA)

It helps to increase the adherence of transdermal patch to the skin surface. It can easily remove from the smooth surface without leaving a residue on it.

a) Polyacrylates
b) Polyisobutylene
c) silicon based adhesives

Preparation of transdermal patches

Transdermal drug delivery patches can be prepared by various methods

Mercury Substrate Method

In this method required amount of drug is dissolved in predetermined amount of polymer solution along with plasticizer. The above solution is to be stirred for some time to produce a homogenous dispersion and it is keep aside until air bobbles removed completely and then poured in to 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 dried films are to be stored in a desiccator16- 20.[17]

Circular Teflon Mould Method

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Plasticizer added into drug polymer solution. The total contents are to be stirred and then poured into a circular teflon mould. And rate of solvent vaporization controlled with placing inverted glass funnel on teflon mould. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored in a desiccator.[18]

Glass Substrate Method

The polymeric solutions are kept a side for swelling then required quantity of plasticizer and drug solution are

added and stirred for 10 min. Further, it is set-a side for some time to exclude any entrapped air and is then poured in a clean and dry anumbra petriplate. The rate of solvent evaporation is controlled by inverting a glass funnel over the petriplate. After over night, the dried films are taken out and stored in a desiccator.[19]

By Using IPM Membranes Method

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.[20]

By Using EVAC Membranes Method

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. 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.[21]

Aluminium Backed Adhesive Film Method

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom made aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks.[22]

Asymmetric TPX Membrane Method:

A prototype patch can be fabricated by a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene) asymmetric membrane, and sealed by an adhesive.

Evaluation Test of Transdermal Patch

Drug Excipients Interaction Studies

The drug and excipients should be compatible to produce a stable product, and it is mandatory to detect any possible physical and chemical interaction. Interaction studies are commonly carried out using thermal analysis, FT-IR studies, UV and chromatographic techniques by comparing their physiochemical characters such as assay, melting endotherms, characteristic wave numbers, and absorption maxima etc.[23]

Drug Content

A specified area of the patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug content with the suitable method (UV or HPLC technique). Each value represents average of three samples 35-37.

Weight Uniformity

The prepared patches are to be dried at 60°C for 4 hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.[6]

Thickness of the Patch

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.[15]

Flatness Test

Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.[18]

Percentage Moisture Uptake

The weighed films are to be kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.[19]

Percentage moisture uptake = [Final weight-Initial weight/ initial weight] × 100.

Moisture Loss

The prepared films are to be weighed individually and to be kept in a desiccator containing calcium chloride at 40oC. After 24 hrs the films are to be reweighed and determine the percentage of moisture loss.[20-24]

% Moisture Loss = [Initial wt – Final wt/ Final wt] × 100

Application

General clinical considerations in the use of tdds

- The patient should be advised of the following general guidelines.
- Rotating of site of application is important to allow the skin to regain its normal permeability and to prevent skin irritation.

- TDDS should be applied to clean, dry skin relatively free of hair and not oily, inflamed, Irritated, broken.
- Wet or moist skin can accelerate drug permeation time. Oily skin can impair the adhesion of patch.
- If hair is present at the site, it should be carefully cut, not wet shaved nor should a depilatory agent be used, since later can remove stratum corneum and affect the rate and extent of drug permeation.
- Use of skin lotion should be avoided at the application site, because lotions affect the hydration of skin and can alter partition coefficient of drug.
- Patient should not physically alter TDDS, since this destroys integrity of the system.
- The protecting backing should be removed with care not to touch fingertips.[17]
- The TDDS should be pressed firmly against skin site with the heel of hand for about 10 seconds.
- A TDDS should be placed at a site that will not subject it to being rubbed off by clothing or movement.
- TDDS should be left on when showering, bathing or swimming
- A TDDS should be worn for full period as stated in the product's instructions followed by removal and replacement with fresh system.
- The patient or caregiver should clean the hands after applying a TDDS. Patient should not rub eye or touch the mouth during handling of the system. If the patient exhibits sensitivity or intolerance to a TDDS or if undue skin irritation results, the patient should seek reevaluation.
- Upon removal, a used TDDS should be folded in its half with the adhesive layer together so that it cannot be reused.[25-29]

CONCLUSION

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. 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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