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Review article

A review on: Transdermal patches for pain management

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ABSTRACT

Continuous oral medication affected all organ, damage kidney and most hazardous action of NSAID class drug is produce ulcer specially in case of arthritis patient continuously pain persist. 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 cover brief outline components, types, present scenario, transdermal drug approved by FDA, mechanism of action, factors affecting transdermal bioavaibility, advantage, disadvantage, general clinical considerations in the use of TDDS and limitation of TDDS.

Keywords: TDDS, Marked product, Arthritis, NSAIDs.

INTRODUCTION

Merriam Webster dates the word transdermal to 1944 highlighting that it is a relatively recent concept in medical and pharmaceutical practice. Transdermal drug delivery system has been accepted as potential non-invasive route of drug administration, with advantages of prolonged therapeutic effect, reduced side effects, improved bioavailability, better patient compliance and easy termination of drug therapy. Non-steroidal anti- inflammatory drugs (NSAID) represents the most commonly used medications for the treatment of pain and inflammation, but numerous well-described side effects can limit their use. Therefore Transdermal delivery of NSAID has advantages of avoiding hepatic first pass effect, gastric irritation and delivering the drug for extended period of time at a sustained level. On various NSAID by formulated and delivered as Transdermal Patches to decrease the side effects associated with the oral delivery. The skin has attracted much attention as an alternative route for administering systemically active drugs. The potential advantages associated with transdermal drug delivery are well documented. Transdermal therapeutic systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug through the skin, at controlled rate to the systemic circulation. Thus, it is anticipated that transdermal drug delivery system (TDDS) can be designed to maintain suitable plasma drug levels for therapeutic efficacy by using skin as the port of entry of drugs. The goal of Pharmaceutical research is to find drugs with desirable therapeutic and low risk of undesirable side effects. Recent research and development efforts have been channelized into the development of drug delivery systems for controlled drug administration through various routes of administration, for example, the skin, to maximize the bioavailability, to optimize the therapeutic efficacy, and/or minimize the side effects of the drug. The advantages of delivering drugs across the skin for systemic therapy are well documented. Some of the main advantages are to delivery infusion of drug over extended period of time to increase the therapeutic drug of many drug by avoiding specific problems association with the drug e.g. GI irritation, low absorption, decomposition, due to hepatic, first-pass effect, formation of metabolites that cause side effect, short half-life necessitating frequent dosing etc. USFDA approved the first Transdermal Patch in 1979. This Patch delivered scopolamine, a drug which suppresses nausea and vomiting in motion sickness Treatment of chronic disease such as asthma, rheumatoid arthritis by transdermal route of drug administration might prove to have several advantages over the other routes of administration over the last two decades, more than 35 transdermal products have been approved. This rapid increase in market value has led to transdermal drug delivery becoming one of the

fastest growing sectors within Pharmaceutical industry [1].

Components of trans- dermal patches

Release Liner: Protects the Patch during storage.

Drug reservoir: The most important part of TDDS is drug reservoir. It consists of drug particles dissolved or dispersed in the matrix. To make the drug soluble, solvents and co solvents are used.

Adhesive: Serves to adhere the components of the Patch together along with adhering the Patch to the skin. The adhesive must possess sufficient adhesion property so that the TDDS should remain in place for a long time. Commonly used adhesives are silicone adhesives, poly isobutylene adhesives and poly acrylate based adhesives.

Membrane: Membrane controls the release of the drug from the reservoir and multi- layer Patches.

Backing: Protects the Patch from the outer environment. Commonly used backing materials are polyesters, aluminized polyethylene terepthalate and siliconized polyethylene terephthalate [2].

Types of Polymer Used

Polymer Matrix

Natural polymers: Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.

Synthetic Elastomers: Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.

Synthetic polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamiode, polyurea, epoxy.

Drug

Drug solution in direct contact with release liner.

Physiochemical propertie

The drug should have a molecular weight less than 1000 Daltons.

The drug should have affinity for both lipophilic and hydrophilic Phases.

The drug should have a low melting point.

Biological properties

The drug should be potent with a daily dose of the order of a few mg/day.

The half life (t½) of the drug should be short.

The drug must not produce allergic response.

(Permeation Enhancer

The flux J. of drug across the skin can be write as

J = D dc/dx J = the Flux

D = diffusion coefficient

C = Concentration of the diffusing spectes X = Spatial coordinate

Solvent: These compounds increase penetration possibly by swelling the polar pathway. e.g.: Alcohols Methanol & Ethanol, Dimethyl acetemide, Propylene glycol and Glycerol.

Surfactants: The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

Anionic surfactant:-Sodium lauryl sulphate Diacetyl sulphosuccinate

Nonionic Surfactant:-Pluronic F 127, Pluronic F68

Bile Salt:-Sodium taurocholate, Sodium deoxycholate.

Other excipients Adhesives

It should not be irritant

It should be easily removed

It should not leave an un washable residue on the skin

It should have excellent contact with the skin.

Physical & chemical compatibility with the drug

Permeation of drug should not affect [3].

Types of Transdermal Patches

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.

Multi -layer drug in adhesive: This type is also similar to the single layer but it contains an immediate drug release layer and other layer will be a controlled release along with the adhesive layer.

Vapour Patch: Commonly used for releasing of essential oils in decongestion. Various other types of vapor Patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

Reservoir system: The drug releases only through the ratecontrolling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix.

Matrix system:

Drug-in-adhesive system.

Matrix-dispersion system

Microreservoir system:

In this type the drug delivery system is a combination of reservoir and matrix- dispersion system. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents [4].

Transdermal Patches in Present Scenario

Marketed Products

An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally. The table gives detail information of the different drugs which are administered by this route and the common names by which they are marketed; it also gives the conditions which the individual system is used. Today's famous brand is of Transdermal

patche is for smoking sensation.

Ni Quitin patches relieve and prevent craving and nicotine withdrawal symptoms associated with tobacco dependence. They are indicated to aid smokers wishing to quit or reduce prior to quitting, assisting smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them [5].

Advance Development in TDDS

Electroporation which uses short electrical pulses of high voltage to create transient aqueous pores in the skin.

Sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum).

Even magnetic energy, coined magnetophoresis has been investigated as a means to increase drug flux across the skin.

Mechanism of Action Of Transdermal Patch

The application of the Transdermal Patch and the flow of the active drug constituent from the Patch to the circulatory system via skin occur through various methods.

Drug diffusion mechanism through a Transdermal Patch [6].

Popular Uses

The first commercially available vapour Patch to reduce smoking was approved in Europe in 2007. The highest selling Transdermal Patch is the nicotine Patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking.

Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in Patch form: Fentanyl and Buprenorphine.

Estrogen Patches are sometimes prescribed to treat menopausal symptoms as well as post- menopausal osteoporosis. Other Transdermal Patches for hormone delivery include the contraceptive Patche.

Emsam, a transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant approved for use in the U.S. in March 2006.

The anti-hypertensive drug Clonidine is available in Transdermal Patch form under the brand name Catapres-TTS [7].

Transdermal Patches Are Not Used in

For acute pain.

Rapid dose titration is required.

Requirement of dose is equal to or less than 30 mg/24 hrs.

Factors AffectingTransdermal Bioavaibility

Physiological factors

Formulation factors Physiological factors include

Age of the patient

Stratum corneum layer of the skin

Anatomic site of application on the body

Skin condition and disease

Race

Skin metabolism

Desquamation (peeling or flaking of the surface of the skin)

Skin irritation and sensitization.

Evaluation of transdermal patches

Physical evaluation

Drug content uniformity

Folding endurance

Thickness of Patches

Moisture Lost

Moisture Gain

Tensile strength

Drug carrier Interaction

In vitro method

In vitro study of Transdermal Patch through Franz diffusion cell.

Kinetics of drug release

Physical Evaluation

Thickness: The thicknesses of the prepared Patches were measured in 3 different points by using a vernier caliper and determined the average thickness.

Drug content determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of PBS in which drug is soluble and then the solution is placed in magnetic stirrer continuously for 24 h. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated by UV spectrophotometer in 10, 20, 30, 40, 50 µg/ml (dilutions).

Weight Variation: The Patches were subjected to mass variation by individually weighing randomly selected Patches.

Moisture lost: The prepared films were weighed individually and kept in a desiccator. Containing calcium chloride at room temperature for 24 h. The films were weighed again after a specified interval. The percent moisture content is calculated using following formula. % Moisture content = [Initial weight – Final weight / Initial weight] ×100 Moisture gain: The accurately weighed films were kept in desiccators at room temperature for 24 hours, containing saturated solution of potassium chloride in order to maintain 80-90% RH. After 24 hours the films were taken out and weighed again. The percentage moisture uptake was calculated from the formula mentioned below.

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

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.

Tensile strength: Tensile strength can be measured by the % elongation. Strech the membrane until it started to break. To measure,

a breaking point. In this evaluation parameter firstly cut a certain square shaped membrane, in these case, chosen about 3x3 cm length and 3 cm breadth, two different ends of this square shaped part of membrane attach with the help of clip, one end of the clip to be fixed, another end of clip attach with the point note down the weight, till the breaking point. At its breaking point note down the weight.

Flatness: Longitudinal strips were cut out from the prepared medicated film the lengths of each strip were measured. Then variation in the length due to the non- uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness. In-vitro skin permeation studies: The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages. Usually permeation studies are performed by placing the fabricated Transdermal Patch with goat skin or rat skin in between receptor and donor compartment in vertical diffusion cell such as Franz diffusion cell or keshary-chien diffusion cell. (28) The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined using double beam spectrophotometer [8].

ADVANTAGES

They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal Ph, enzymatic activity and drug interaction with food, drink and other orally administration drug.

To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liner when taken orally.

They are noninvasive, avoiding the inconvenience of parenteral therapy.

They can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.

They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Transdermal clonidine 7 day.

The activity of drugs having a start half life is extended and controlled through the reservoir of drug in the therapeutic delivery system.

Drug therapy may be terminated rapidly and easily removal of the patche.

DISADVANTAGES

Some patients develop contact dermatitis at the site of application from one or more of the System components, necessitating discontinuation.

Only potent drugs are suitable candidates for Transdermal Patch because of the natural limits of drug entry imposed by the skin's imperameability.

Some drugs e.g. scopolamine Transdermal Patch placed behind the ear, it is uncomfortable for patient.

Long time adherence is difficult [9].

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