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TRANSDERMAL PATCH: A NOVEL ADVANCEMENT IN PAINLESS DRUG DELIVERY

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Abstract

The transdermal drug delivery system is a painless system which is widely accepted due to its numerous advantages as it is a topical drug administration process with prolonged therapeutic effect, reduced side effects, better patient compliance, improved bioavailability and easy termination of drug therapy. Transdermal drug delivery system (TDDS) is one of the systems under the category of controlled drug delivery, in which aims to deliver the drug through skin in predetermined and controlled rate. These are designed to deliver the therapeutically effective dose of medication across the skin. The patches give the patient controlled release of the drug. It functions as a drug carrier, which holds the substance until it is applied. This system has an advantage as it bypass hepatic first-pass effect, gastric irritation and provide extended period of time at a sustained level. The novel technology developed transdermal drug delivery system (TDDS) which delivers drug through skin. They are adhesive drug delivery devices with a specified surface area that release a predetermined amount of medication to intact skin at a pre-programmed rate. This article mainly focuses on the advancements of transdermal delivery drugs that are delivered as transdermal patches to decrease the side effects related to the oral delivery. There are better future prospects for the wider adaptation of transdermal drug delivery as a feasible method for system drug delivery.

Keywords: Transdermal Patch, Polymer, Hypertension, Controlled release

INTRODUCTION

Transdermal drug delivery system (TDDS) is one of the systems under the category of controlled drug delivery, in which aims to deliver the drug through skin in predetermined and controlled rate.

These are designed to deliver the therapeutically effective dose of medication across the skin. The patches give the patient controlled release of the drug. It functions as a drug carrier, which holds the substance until it is applied. The patch is attached to the skin with the help of adhesive. It aids in the penetration process to the skin. On application of transdermal patch, delivers a high dose of medication via the skin and keeps it there for long time, get entered into the blood circulation by diffusion process [1].

Transdermal patches have made a significant contribution to the pharmaceutical sector and medical practice by providing advances in delivery of treatment with existing and novel drugs. Transdermal drug delivery system was come into existence to overcome difficulties of drug delivery by oral route. The drug functions after absorption through skin into

the systemic circulation by capillary action at certain rate. The development of these patches is largely due to breakthroughs in skin science, technology, and knowledge, which have been created via clinical observation, trial and error and evidence-based investigations dating back to the earliest human records.

Transdermal patches are categorized into the following:

- First -generation
- Second generation
- Third generation.

First generation of transdermal patches are utilized in clinics. These contain the medication in a reservoir that is sealed with impermeable adhesives. The transdermal patches used in the second generation made the skin more permeable, which minimizes injury to deeper tissues. Again the third generation of transdermal patches allowed medications to penetrate the skin more deeply by protecting the deeper tissues [2].

Controlled release drug delivery system is a most recent approach in drug delivery that delivers the drug into systemic circulation at a predetermined rate. This method assisted in overcoming the side effects associated with conventional system of medication, which necessitate multidose therapy [8, 9].

The novel technology developed transdermal drug delivery system (TDDS) which delivers drug through skin. They are adhesive drug delivery devices with a specified surface area that release a predetermined amount of medication to intact skin at a pre-programmed rate [10, 11]. The transdermal drug delivery system have greater importance in the recent years which avoids hepatic first pass metabolism, maintaining constant blood levels for longer period of time which results in a reduction of dosing frequency, decreased gastrointestinal irritation, improved bioavailability and patient compliance. Some drugs have already been formulated and evaluated as transdermal patches but most of them still been unexplored. Transdermal patches are now an emerging mode of drug delivery system in pulmonary arterial hypertension.

RISKS ASSOCIATED WITH TDDS

- The drug's systemic bioavailability is increased by bypassing the hepatic metabolism.
- The simplified medication regimen leads to self-medication there by improved patient compliance and comfort with easy, painless, and non-invasive administration.
- Steady permeation of drug across the skin, allowing consistent plasma levels, but non-invasive in nature.
- Duration of action of drug gets prolonged & predictable.
- Drug therapy can be stopped immediately if any toxicity occurs on skin.
- Drugs with a shorter biological half-life may be administered gradually.
- Drugs that cause gastrointestinal upset can be used by this way.
- Drug plasma concentration kept stable.

BENEFITS ASSOCIATED WITH TDDS

- Allergic reactions may occur at the site of application such as rashes, itching, local edema etc.
- Drug with larger molecular size creates difficulty in absorption.
- High manufacturing cost.
- Ionised drugs may cause difficulty in absorption.
- Skin’s impermeability is major restrict in drug access.
- Drugs which require high blood levels to be achieved cannot be delivered by this method.

MECHANISM OF ACTION

A transdermal patch is made up of an adhesive layer which adheres on to the skin; a semi solid to liquid drug is sandwiched between the layers of drug releasing membranes which are exclusively semipermeable in nature. An outermost transparent backing serves as the patch's primary layer of protection during application. An effective connection is formed between the skin and the semipermeable membrane when a transdermal patch is applied to the skin. A strong bond is formed between the skin and the semipermeable membrane when a transdermal patch is applied to the skin.The percutaneous

drug delivery system uses a simple diffusion mechanism to deliver a steady flow of medication from the patch's drug reservoir to the skin [13].

TDDS IS COMPOSED OF:

a) Polymer matrix
b) Drug
c) Permeation enhancers.
d) Pressure sensitive adhesive (PSA).
e) Backing laminate.
f) Release liner.
g) Other excipients like plasticizers and solvents [3] [14].

a) Polymer matrix:it is prepared by dispersing the drug in solid or liquid state synthetic polymer base. It should have

- Biological and chemical compatibility with the drug and other excipients of the system.
- Additionally throughout the product's shelf life they should provide consistent and effective delivery of a drug.

Polymers used in transdermal drug delivery systems are classified as-

a) Natural polymers**:** e.g. Cellulose derivatives, shellac, waxes, zein, gelatin gums, natural rubber and chitosan etc.
b) Synthetic elastomers**:** e.g. polybutadiene, polyisobutylene, acrylonitrile, neoprene,hydrin rubber, silicon rubber, butyl rubber etc.
c) Synthetic polymers**:** e.g. Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene polyacrylate, polyamide etc.

b) Drug:transdermal medications release less medication into the bloodstream over a longer period of time. .some of the patch drugs arenicotine, pain relievers, hormones, and drugs to treat angina and motion sickness. The selection of drug is based on its physiochemical and biological properties [2].

c) Permeation enhancers:the chemicals that enhance the permeability of skin that is stratum corneum so as to attain therapeutic levels of the drug in the blood. By interacting with stratum corneum its permeability is improved. Permeation enhancers used should be
    a) Non-irritating, non- allergic &non-toxic.
    b) Bind specific to the receptor site having pharmacological activity.
    c) Cosmetically acceptable with an acceptable skin feel.

d) Pressure sensitive adhesive (PSA):it aids in the adhesion of the transdermal patch to the skin's surface. It can be readily removed off from the smooth surface without leaving a residue**.** Commonly used PSAs are:

a) Polyacrylates
b) Polyisobutylene
c) Silicon based adhesives

E) Backing laminate: it is a supportive material to the patch which is impermeable to drugs. They should be chemically compatible with the drug, adhesive penetration enhancer, and other excipients. Commonly used are vinyl, polyethylene and polyester films.

F) Release liner: this is the main packing material used to protect the patch during application. It is made up of teflon or silicon. It should be chemically inert & should be permeable to drug, penetration enhancers and water.

It is composed of a base layer that may be

a) Non-occlusive (e.g. Paper fabric)
b) Occlusive (e.g. Polyethylene, polyvinyl chloride)

G) Other excipients like plasticizers and solvents

- Solvents: chloroform, methanol, acetone, isopropanol and dichloromethane.
- Plasticizers: dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol [3].

NOVEL DEVELOPMENTS OF TRANSDERMAL PATCHES

Transdermal patch of diclofenac sodium

An investigation reported that diclofenac sodium patches which are prepared using polymers like chitosan and polyvinyl alcohol (PVA) cross-linked tripolyphosphate sodium to increase the permeation of the drug from the matrix system across rabbit skin. It was done by ultraviolet spectrophotometry. Physical characteristics of the film are determined which includes thickness, weight test, organoleptic observation etc. The ftir data illustrates that an increase in the permeation rate is observed across the rabbit skin.

An ideal patch should have elasticity, flexibility, softness, sufficient strength and also it should adhere for prolonged period on the skin surface for desired therapeutic effect. For better permeation of drug various permeation enhancers and chemicals are used like alcohols, terpenes, and surfactants [15].

Diclofenac sodium, an aryl acetic acid derivative is a non selective cox inhibitor (conventional NSAID) that y inhibits cox enzyme. Postoperative pain is treated with the diclofenac patch. It is used once over the duration of 24 hours to quickly relieve discomfort with less adverse effects. The patch should be placed on the skin, ideally on the area without any hairs. When compared to the oral method, the patch reaches plasma levels that range between 20 and 50 µg/ml.

Transdermal patch of Repaglinide

The Repaglinide transdermal patch were prepared by solvent casting method, it has certain benefits like sustained release, improved bioavailability and patient compliance. This is evaluated for various parameters such as tensile strength, percentage moisture content, percentage drug content and folding endurance. Half-life of Repaglinide is 1 hour and bioavailability is 56% due to first-pass metabolism [16]. Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia due to insulin deficiency, insulin resistance. Repaglinide lies under meglitinide class of drugs used to treat non insulin-dependent diabetes mellitus.

- Dose: 0.5–4 mg (3–4 times) in a day.
- The melting point of repaglinide is 130–131°c.
- Molecular weight: 452.58 [17].

Studies has been proved that after oral administration, repaglinide produces hypoglycemia. The topical or transdermal preparation of repaglinide may be beneficial to the patient since it reduces adverse effects and bypass hepatic first-pass metabolism [2].

Transdermal patch of scopolamine (hyoscine) for the treatment of motion sickness:

Powder of hyoscyamus is the first transdermal patch reached in the market. Scopolamine was first used topically as an antiperspirant [18]. Scopolamine was later used in a study to prevent airsickness but found to be moderately effective. Larger dose show more effect but have dry mouth as an adverse effect.

Scopolamine has a short duration of action [19] as it has short elimination half-life of 4.5 hours. Studies were performed to determine the permeability across the skin. In that best one was found to be a zaffaroni design applied behind the ear.

The transdermal patch had a drug reservoir and a microporous membrane that could control the delivery of scopolamine. Redistribution of scopolamine into the contact adhesive lamina, an initial bolus (loading) dose of scopolamine was released to the skin, which leads to the therapeutic scopolamine plasma levels to be achieved.

Transdermal patch of nitroglycerin for angina pectoris:

Earlier, nitroglycerin ointment was the only product available in the market, until the development of scopolamine patch. Nitroglycerin ointment show more sustained release than sublingual dose forms, the plasma levels of drug depends on the surface area to which a given dose of ointment was applied.

Limitations of semisolid dose forms:

• Applying a particular dose to an area is difficult.

• Frequent dosing is needed lead to patient noncompliance.

Transdermal patch of clonidine for the treatment of hypertension.

Transdermal clonidine was developed to improve patient compliance and to reduce drug side effects like drowsiness and dry mouth. First clinical trials showed that the clonidine transdermal patch was an effective alternative in decreasing BP in healthy volunteers [20] and in patients with essential hypertension. Clonidine patches have shown high rate of dermatological adverse reactions like allergic contract dermatitis.

Transdermal patch of Oestradiol for female hormone replacement therapy

In 1938, Zondek introduced cutaneous application of follicle stimulating hormone, oestrone for amenorrhoea. In 1960, a study reported that 2 g of an ointment containing both radiolabelled oestradiol-17β and progesterone was applied to human subjects. Within 72 hrs about 16.5% to 44% of the radioactivity appeared in the urine [21]. For post-menopausal replacement therapy, transdermal Oestradiol was first applied as a hydroalcoholic gel. However, the dosage control was difficult. In 1983, a us patent disclosed a bandage to be applied to the skin which shows a peak plasma level for administration of Oestradiol within a vehicle ethanol (percutaneous absorption enhancer).The first transdermal Oestradiol system reached in 1984 in the US market. This transdermal device reduces the adverse effects like hot flushes and showed transdermal delivery[22].

Transdermal patch of nicotine for smoking cessation aid:

In 1984, nicotine was first used in a transdermal form as a smoking reduction and cessation aid. One study showed that after the topical application of 9 mg of nicotine significant levels of drug in the saliva is identified. Also an increase in both the pulse and the systolic BP is also identified [23]. Another study showed a reduced craving in 10 cigarette smokers after application of 8 mg of nicotine base in a 30% aqueous solution in a polyethylene patch in comparison to an inactive placebo solution. In this invention, the delivery of nicotine from the transdermal device was controlled by the use of a microporous membrane. Its duration of delivery was noted as 30–45 min, so several patches over the course of a day are required to maintain nicotine plasma levels. Over a million smokers gave up smoking with the help of nicotine transdermal patches[24]. Although transdermal delivery patches had been on the market for around 10 years, it was the arrival of nicotine patches that led to them being widely accepted.

FUTURE OF TRANSDERMAL DELIVERY SYSTEM

- Development of an insulin patch and sufentanil patch for chronic cancer pain.
- A high-dose nicotine patch for fast metabolizers and varenicline patch for smoking cessation.
- Estrogen and testosterone transdermal patches for post-menopausal women.
- Use of clonidine transdermal for the treatment of delerium in trauma patients.

- Selegiline patch for depression in the elderly and cocaine addicted patients.
- For the treatment of tennis elbow, dexamethasone iontophoretic delivery is developed.
- An iontophoreticsumatriptanTDD patch for migraine treatment.
- Transdermal patch of glyceryl trinitrate for acute stroke therapy.

CONCLUSION

This article mainly focuses on the advancements of transdermal delivery drugs that are delivered as transdermal patches to decrease the side effects related to the oral delivery. However, there are currently only a few products on the market in this approach. There are better future prospects for the wider adaptation of transdermal drug delivery as a feasible method for system drug delivery. There are still some obstacles that need to be addressed, including the complexity of applications when employing a combination of transdermal devices and other drug-loaded formulations. Furthermore regulatory control and scaled-up GMP over manufacture are required for some new transdermal techniques [25].

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List of Abbreviations

TDDS - Transdermal drug delivery system

PSA - Pressure sensitive adhesive

PVA - polyvinyl alcohol

BP – blood pressure

NSAID – Non steroid anti-inflammatory drugs

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