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Review Article

RECENT ADVANCES IN DEVELOPMENT OF TRANSDERMAL PATCHES

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ABSTRACT

Transdermal administration of drugs is an another way of administration that can significantly deliver larger molecules in potent quantities that overcome the problem with the oral administration such as poor bioavailability due to first pass metabolism and sometimes responsible for rapid blood level. Drugs that are given by transdermal route may enhance the potency as well as safety of drugs. One such advance has been the development of transdermal patch delivery systems. Transdermal drug technology specialists are continuing to search for new methods that can effectively and painlessly deliver larger molecules in therapeutic quantities to overcome the difficulties associated with the oral route. Transdermal drug delivery system is the system in which the delivery of the active ingredients of the drug occurs by the means of skin. Skin is an effective medium from which absorption of the drug takes place and enters the circulatory system. Various types of transdermal patches are used to incorporate the active ingredients into the circulatory system via skin. The patches have been proved effective because of its large advantages over other controlled drug delivery systems. New transdermal drug delivery system (TDDS) technologies now have been developed that is considered to be helpful in rate controlled delivery of drug that is difficult to administer.

Keywords: Transdermal Drug Delivery System, Iontophoresis, Electroporation, Electro-Osmosis.

INTRODUCTION

Transdermal drug delivery patches have been in the market for over a decade[1]. The most common available transdermal drug delivery patches are the over-the-counter nicotine patches that help people quit smoking. The words "transdermal drug delivery patch" triggers several questions, such as what material is it made of, how does it work, so on and so forth. Transdermal patches were first introduced for astronauts going in space to cure trouble of motion sickness[2]. Soon after that the transdermal patch for controlling motion sickness was also being used for treating motion sickness in common people.

Significance of Problem

Drugs curing a diseased condition in one part of body can also have an adverse effect on some other part of the body. For instance, most of the drugs available in the market have some or the other side effect associated with using them. The side effects encountered are mainly with the liver, heart, lung, kidney, etc. Some of the oral

medications have an adverse effect on the gastrointestinal system; some make the patient feel drowsy, nauseated, and dizzy. The solution to get over all the side effects might not be available, but there are surely ways and means to reduce them. One way is use of transdermal drug delivery patches that target only the area that needs to be treated. Transdermal drug delivery systems are sometimes preferred over other methods of drug administration because they present lower risk to liver or gastrointestinal track over oral or any other form of drug administration, for instance in the case of estradiol patches, patient's are at lower risk of damaging liver compared to those who take estradiol tablets orally[3].The pharmacokinetics of a compound significantly affects its efficacy and safety. Transdermal delivery has the potential to yield more stable drug plasma levels and to bypass major organs involved in first-pass metabolism[4]. Today, there is a wide spectrum of conditions that are treated with the use of transdermal drug delivery system and to name a few are motion sickness, nicotine drug patches for smokers, Parkinson's disease, angina pectoris, contraception.

TDDS Classification Based on Their Technical Sophistication

a) Rate pre-programmed drug delivery system
b) Activation modulated drug delivery system
c) Feedback regulated drug delivery system
d) Carrier based drug delivery system

a) Rate Pre-Programmed Drug Delivery System

It involves the system design that deliver medicaments by controlling molecular diffusion of drug molecules across the skin barrier within or surrounding the delivery system.

Polymer membrane permeation controlled drug delivery system

It involves the system in which the drug is enclosed within a drug reservoir. This is covered by the semipermeable membrane of polymer that regulates the release and having a specific permeability. There are some potential development with process of membrane permeation are as microporous membrane permeation controlled gastrointestinal delivery device, gastric fluid resistance intestinal targeted controlled release gastrointestinal device and gel diffusion controlled drug delivery system.

Polymer matrix diffusion controlled drug delivery system

It is developed by dispersing drug particles in carrier matrix (in a homogenous manner) that is rate controlling. For e.g. NitroDur. It is designed for application onto intact skin for 24 hrs that provide consistence transdermal infusion of nitroglycerine[5].

Microreservoir partitioned controlled drug delivery system

It involves dispersion of micro particles of suspension of drug (aqueous in nature) in a polymer using high energy dispersion. e.g. Syncromate implant - Engineered to deliver subdermal administration of norgestomet [6].

B) Activation Modulated Drug Delivery System

This type of delivery system can be achieved by

Physical means

Osmotic pressure activated drug delivery system.

- Hydrodynamic pressure controlled drug delivery system.
- Vapour pressure activated drug delivery system.
- Mechanically activated drug delivery system.
- Magnetically activated drug delivery system.
- Electrically activated drug delivery system.
- Ultrasound activated drug delivery system.
- Hydration activated drug delivery system.

Chemical means

- pH activated drug delivery system
- Ion activated drug delivery system
- Hydrolysis activated drug delivery system

Biochemical means

- Enzymes activated drug delivery system

C) Feedback Regulated Drug Delivery System

The release of the drug molecules from the transdermal system is facilitated by an agent that triggers the release of drug, such as biochemicals in the body and also regulated by its concentration through some feedback mechanism.

- Bio-erosion regulated drug delivery system.
- Bio-responsive drug delivery system.
- Self regulated drug delivery system [7].

D) Carrier Based Drug Delivery System (Colloidal particulates carrier system)

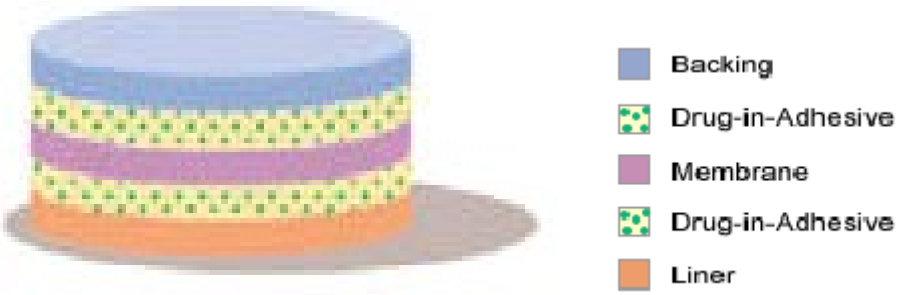
This involves vesicular system like hydrogels, liposomes, niosomes, nanocapsules, nanoparticles, polymeric complexes, microspheres, nanoerythrosomes, transferosomes, dendrimers, aquasomes, etc.[8]

APPROACHES USED IN DEVELOPMENT OF TRANSDERMAL PATCH [9-14]

Single-layer Drug-in-Adhesive

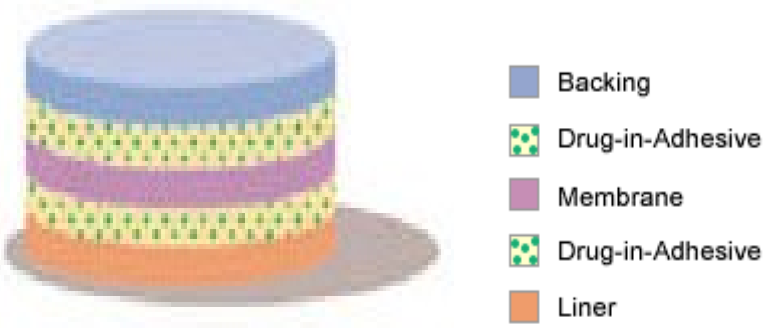
The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and 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



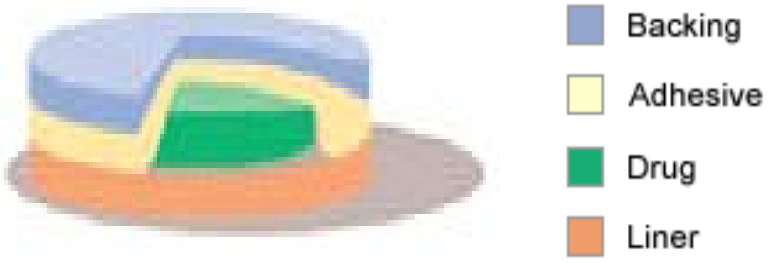
The Multi-layer Drug-in-Adhesive is similar to the Single layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film.

Drug Reservoir-in-Adhesive



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.

GENERATION OF TRANSDERMAL DRUG DELIVERY SYSTEMS

First-Generation Transdermal Delivery Systems

The first generation of transdermal delivery systems is responsible for most of the transdermal patches that have thus far been in clinical use. Significant advances in patch technology, and public acceptance, have enabled the recent surge in first-generation transdermal patches reaching the market. However, this surge will taper off as drugs with suitable properties for such systems are depleted. First-generation delivery candidates must be low-molecular weight, lipophilic and efficacious at low doses. Usually, their transdermal delivery should be more attractive than oral delivery due to low oral bioavailability, the need or desire for less frequent dosing or steady delivery profiles, or other factors.

The first-generation approach to transdermal delivery is limited primarily by the barrier posed by skin's outermost layer called stratum corneum, which is 10 to 20 µm thick. Underneath this layer is the viable epidermis, which measures 50 to 100 µm and is avascular. Deeper still is the dermis, which is 1–2 mm thick and contains a rich capillary bed for systemic drug absorption just below the dermal–epidermal junction. Closer examination of the stratum corneum barrier reveals a brick and mortar structure, where the bricks represent non-living corneocyte cells composed primarily of cross-linked keratin and the intercellular mortar is a mixture of lipids organized largely in bilayers. Drug transport across the stratum corneum typically involves diffusion through the

intercellular lipids via a path that winds tortuously around corneocytes, where hydrophilic molecules travel through the lipid head group regions and lipophilic molecules travel through the lipid tails. This transport pathway is highly constrained by the structural and solubility requirements for solution and diffusion within stratum corneum lipid bilayers.

A variation on the traditional transdermal patch of first-generation delivery systems involves no patch at all, but applies a metered liquid spray, gel or other topical formulation to the skin that, upon evaporation or absorption, can drive small lipophilic drugs into the stratum corneum, which in turn serves as the drug reservoir for extended release into the viable epidermis over hours. For example, testosterone gels have been in use for several years and a transdermal spray has been recently approved for estradiol delivery [15].

Second-Generation Transdermal Delivery Systems

The second generation of transdermal delivery systems recognizes that skin permeability enhancement is needed to expand the scope of transdermal drugs. The ideal enhancer should (i) increase skin permeability by reversibly disrupting stratum corneum structure, (ii) provide an added driving force for transport into the skin and (iii) avoid injury to deeper, living tissues. However, enhancement methods developed in this generation, such as conventional chemical enhancers, iontophoresis and non-cavitational ultrasound, have struggled with the balance between achieving increased delivery across stratum corneum, while protecting deeper tissues from damage. As a result, this second generation of delivery systems has advanced clinical practice primarily by improving small molecule delivery for localized, dermatological, cosmetic and some systemic applications, but has made little impact on delivery of macromolecules [16].

Third-Generation Transdermal Delivery Systems

The third generation of transdermal delivery systems is poised to make significant impact on drug delivery because it targets its effects to the stratum corneum. This targeting enables stronger disruption of the stratum corneum barrier, and thereby more effective transdermal delivery, while still protecting deeper tissues. In this way, novel chemical enhancers, electroporation, cavitational ultrasound and more recently microneedles, thermal ablation and microdermabrasion (Arora, Prausnitz and Mitragotri) have been shown to deliver macromolecules, including therapeutic proteins and vaccines, across the skin in human clinical trials. These advances were made possible in part by the emergence of technologies to localize effects to the stratum corneum combined with recognition that the safety afforded by localization should make these more aggressive approaches medically acceptable [17].

RECENT TECHNIQUES FOR ENHANCING TDDS

Structure-Based Enhancement Techniques

Microfabricated Microneedles

Microfabricated microneedles are devices which are hybrids of the hypodermic needle and transdermal patch through the use of microscopic needles that can deliver the drug effectively (like a hypodermic needle). Their small size offers the potential advantages of delivering large molecules across the stratum corneum without extreme pain to the patients [18].

Macroflux

These are devices having an area of around 8cm as well as 300 micro projections per 2cm with the length of individual micro projection less than 200µm. Three types of Macroflux have been designed. They include,Dry-Coated Macrofluxsystem-this is used for short period delivery that consists microprojection array coated with medicament that adhered to a elastic polymer adhesive backing. D-TRANS Macroflux system-this is alsofor short duration administration that consists of a microprojection array combined with reservoir of drug. E-

TRANS Macroflux system-this is for on demand delivery that involves a microprojection array combined with an electrotransport system [8].

Metered-Dose Transdermal Spray (MDTS)

Metered-dose transdermal spray (MDTSTM), originally developed at the Victorian College of Pharmacy [Monash University (Parkville Campus), Parkville, Victoria, Australia] and currently being commercialized by Acrux Limited [Melbourne, Victoria, Australia] has the potential to expand the growth of TDD systems by broadening patient acceptance and pharmaceutical applications for enhanced TDD (19). The MDTS has the following potential advantages:

- It improves delivery potential without skin irritation due to its non-occlusive nature.
- Increased acceptability.
- Dose flexibility
- Simple manufacture.

Electrically-Based Enhancement Techniques

Iontophoresis

Iontophoresis may be defined as the facilitation of ionizable drug permeation across the skin by an applied electrical potential, the driving force of which may be simply visualized as electrostatic repulsion[20]. A typical iontophoresis device consists of a battery, microprocessor controller, drug reservoir and electrodes[21-23]. The technique involves the application of a small electric current (usually 0.5 mA/cm2) to a drug reservoir on the skin, with the similarly charged electrodes (on the surface of the skin) placed together in the drug reservoir producing a repulsion effect that effectively drives the solute molecules away from the electrode and into the skin [24].

Acoustical Methods

Ultrasonic waves, as well as short-duration shock waves, have been used to facilitate transdermal delivery. Ultrasound at various frequencies in the range of 20 kHz-16MHz has been used to enhance skin permeability by a method called sonophoresis. Traditionally, ultrasound at high frequencies (f>1 MHz, therapeutic ultrasound) was a popular choice for sonophoresis. However, transdermal transport enhancement induced by low-frequency ultrasound (f<100 kHz) is significantly greater than that induced by therapeutic ultrasound. Accordingly, low-frequency sonophoresis has received particular attention during the past decade [25].

In addition to heating, ultrasound is also known to generate cavitation, which is the formation, oscillation and, in some cases, collapse of bubbles in an ultrasonic pressure field. Cavitation is only generated under specific conditions (e.g., low-frequency ultrasound) that differ from those of ultrasonic heating or imaging devices. The opportunity for transdermal drug delivery is that cavitation bubbles concentrate the energy of ultrasound and thereby enable targeted effects at the site of bubble activity. Because bubbles are more difficult to grow and oscillate within densely-packed tissue, cavitation preferentially occurs within the coupling medium (e.g., a hydrogel) between the ultrasound transducer and skin[26-29].

Photomechanical Waves

Photomechanical waves (PW's) are the pressure pulses produced by ablation of a material target (polystyrene) by Q-switched or mode-locked lasers. Photechanical waves are able to render the stratum corneum more permeable to macromolecules via a possible transient permeabilisation effect due to the formation of transient channels. The largest molecule that has been reported to be delivered through the rat skin to date has a molecular weight of 40,000Da. Suggestions have been made that many clinically important proteins such as insulin (6000 Da) and hematoprotien (48000 Da) are within or close to the delivery capability range of PW's. However; this relatively new technique does not yet seem to have produced any human clinical data [30].

Electroporation

It this method, short and high-voltage electrical pulses are applied to the skin thus the diffusion of drug is improved with the increasing permeability. The electrical pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea [23, 31-33].

Electro-Osmosis

If a charged porous membrane is subjected to a voltage difference, a bulk fluid or volume flow, called electro osmosis occurs without concentration gradients, suggesting that this flow is not diffusion. This bulk fluid flow by electro osmosis was found to be of the order of micro liters per hour per square centimeter of hairless mouse skin. The electro-osmotic flow occurs from anode to cathode, thus enhancing the flux of positively charged (cationic) drugs and making it possible to deliver neutral drugs[8,34].

Chemical enhancers

Chemical enhancers can increase skin permeability by various mechanisms, including enhancing solubility, partitioning the stratum corneum, fluidizing the crystalline structure of the stratum cornuem and causing dissolutionof stratum cornuem lipids [35].

Velocity Based Enhancement Techniques

Needle-Free Injections

The highest value, least developed and most technically challenging group of needle-free technologies is prefilled, disposable injectors. The development of such technologies is primarily driven by the demand for a convenient, non-invasive alternative to the conventional needle and syringe injection. The earliest needle free injectors became available as early as 1866, when the French company H. Galante manufactured an “Apparatus for aqua puncture” (8, 36). Some of the needle free injectors under development are:

- Intraject
- Implaject
- Jet Syringe
- Iject
- Mini-ject

Powderject Device

The solid drug particles are propelled across the skin with the aid of high-speed gas flow. This consists of a gas canister that allows helium gas at high pressure to enter a chamber at the end of which drug cassette containing powdered drug between two polycarbonate membranes. After release, the instantaneous rupturation of both membranes usually seen that results in the gas to expand quickly which forms a strong motion like a wave that travels down the nozzle. This takes place at the speed of 600-900 m/s [26].

Other Enhancement Techniques

Transfersomes

This device penetrates the skin barrier along the skin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles (19).

Medicated Tattoos

Med-Tats are a modification of temporary tattoo which contains an active drug substance for trandermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms.

Skin Abrasion

This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substance. In general, one approach is adopted to creates micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules is generally known as Micro-scissuining.

Controlled Heat Aided Drug Delivery (CHADD) System

It facilitates the transfer of drug substance to the blood circulation by applying heat to the skin that increases the temperature and ultimately led to increase in microcirculation and permeability in blood vessel. CHADD system consists a small unit that is used for heating purpose, placed on top of a conventional patch device. An oxidation reaction occurs within the units which tend to form heat of limited intensity and duration.

Laser Radiation

This involves the exposure of the skin to the laser beam that results in the ablation of the stratum cornea without damaging the epidermis which remains in contact with it. Removal of the stratum cornea by this technique is considered to improve the delivery of lipophilic and hydrophilic drugs.

Magnetophoresis

The effect of magnetic field on diffusion flux of drug substance was found to enhanced with increasing applied strength [18].

REGULATORY ASPECTS

A transdermal patch is classified by the U.S. Food and Drug Administration as a combination product, consisting of a medical device combined with a drug or biological product that the device is designed to deliver. Prior to sale in the United States, any transdermal patch product must apply for and receive approval from the Food and Drug Administration, demonstrating safety and efficacy for its intended use[14].

THE FUTURE OF TRANSDERMAL DRUG DELIVERY

Thermal Poration is the formation of aqueous pathways across stratum corneum by the application of pulsed heat, this approach has been used to deliver conventional drugs and to extract intestinal fluid glucose from human subjects [37]. Jet injectors are receiving increased attention now days, which is opening doors for improved device design for controlled, needle-free injection of drug solutions across the skin and into deeper tissue [38]. Small needle is inserted a few millimeters into skin and drug solution is flowed through the needle into the skin at controlled rates using a micro-infusion pump that is contained within a large patch affixed to skin, morphine has been delivered to humans using this approach[39]. During the past decade several theories have been put forward in addressing the combinations of chemicals and iontophoresis; chemicals and electroporation; chemicals and ultrasound; iontophoresis and ultrasound; electroporation and iontophoresis; and electroporation and ultrasound. Two of the better-known technologies that can help achieve significant skin permeation enhancement are iontophoresis and phonophoresis (sonophoresis). Iontophoresis involves passing a direct electrical current between two electrodes on the skin surface. Phonophoresis uses ultrasonic frequencies to help transfer high molecular weight drugs through the skin. A newer and potentially more promising technology is micro needle-enhanced delivery. These systems use an array of tiny needle-like structures to open pores in the stratum corneum and facilitate drug transport [14]. The statical data showed a market of $ 12.7 billion in the year 2005 which is assumed to increase by $ 21.5 billion in the year 2010 and $ 31.5 billion in the year 2015. Almost all the pharmaceutical companies are developing TDDS [40].

CONCLUSION

The development of transdermal delivery systems involves balancing increased transdermal transport with patient's comfort and cost. Because intact skin is not sufficiently permeable to the majority of drugs, enhancement is needed. Extensive research during the past decades, chemical enhancers have achieved only limited success in increasing the transdermal transport of small molecules and have only a relatively poor ability to increase macromolecular transport under conditions likely to have therapeutic action. Physical approaches like ultrasound, iontophoresis, electroporation and microneedles have increased the transdermal delivery form small drugs and macromolecules. Overcoming the hurdles of low

skin permeability using the approaches described in this review will be the crucial advance that in transdermal delivery will realize its great promise.

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