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Review Article

RECENT ADVANCEMENT IN TRANSDERMAL DRUG DELIVERY SYSTEM

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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 spikes (both high and low). Drugs that are given by transdermal route may enhance the potency as well as safety of drugs. Most oftenly the medicament containing device remains in contact with the body skin that is required to reduce both the size and frequency of doses required to achieve the plasma concentrations. There are various types of transdermal patches which are further modified to increase the potential of the drug delivery. New Transdermal Drug Delivery System (TDDS) Technologies now have been developed that is considered to be helpful in rate controlled delivery of drug that are difficult to administer. This review article emphasize most of the technologies involved in better permeation through skin into an effective Drug Delivery System.

Keywords: - Transdermal Permeation, Transdermal Patches, Rapid blood level spikes, Iontophoresis.

Introduction
Recently, the TDDS has become one of the most innovative topics for research for administration of those drugs that are trying to administer by transdermal route. The first transdermal device (patch) was approved by FDA in 1981. More than 30 products which can be used transdermally have been approved for sale in the US, and more than 10 API have been taken for approval for use globally. For effective TDDS, the drug must be able to penetrate the skin membrane so that drug easily can reach to target site [1]. The Transdermal Delivery System includes all drug candidates that administer topically, intended to facilitate the drug absorption into the systemic circulation. The controlled and continuous delivery of drugs through the skin to the blood circulation can be achieved by this system [2]. The various combinations have been develop to control drug release which are having different releasing properties. It can be observed in the formulation of Povidone (PVP): Ethyl cellulose (EC) form which sustained level of drug can be attained when taken in the ratio of 1:5 while the PVP: Eudragit formulation was less efficient during controlled release studies [3]. Transdermal patches now have become a great technology to control obesity by reducing the access body weight. This can be done by applying natural weight loss patches containing ingredients like gaurana, yerba mate, zinc pyruvate, flax seed oil, lecithin, l-carnitine, etc. on to the skin it is to possible to reduce the body fat [4]. Due to have an advantage of being non invasive, this delivery has to fulfil some parameters such as high potency, better permeability through skin and non irritation for better compliance [5]. In present time, several advancements have been made for betterment in the technology to control the rate of drug during the course of delivery, and/or targeting the delivery of drug to tissues [6]. TDDS possesses highly significant attributes and improved utilities such as:

- Targeted delivery of drug to the body tissues.
- High safety and effectiveness.
- Reduced dosing frequency and the dose of drug needed.
- Reduction in toxic level of drug.
- Less pain sensation in administration of drug candidates.
- Better patient compliances [7, 8].

There are various considerations used to improve and regulate the delivery of protein therapeutic agents via the skin membrane. The

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delivery of interferon (IFN) α, an antiviral agent that used to treat condylomata acuminata (genital warts) is administered by using lipid-based delivery systems (LBDS). The use of liposomes and fatty acylation are ways to increase IFNα delivery into human skin [9].

Mechanism Of Drug Permeation And Potential Problems

The outer layer of skin named stratum cornea, acts as a physical barrier to those substance that come in contact with the skin membrane. Stratum cornea consists of phospholipids, cholesterol, sulphate, neutral lipids, protein (about 40%) which is mainly keratin. Skin epidermis remains between the stratum cornea and the dermis. The water content is about 90%. Dermis mainly remains just beneath the viable epidermis. It is a structural fibrin and it can be found histologically in normal tissue [10].

Pathway of Transdermal Permeation:

Permeation can occur by diffusion via

-Transdermal permeation, through the stratum corneum.

- Intercellular permeation, through the stratum corneum.

-Transappendaged permeation, via the hair follicle, sebaceous and sweat Glands.

Several molecules are able to penetrate through skin via intercellular micro route and therefore many enhancing techniques aim to disrupt or bypass its molecular architecture [11].

Crystal Reservoir Technology

The way of releasing a medicament effectively is based on the oversaturation of an adhesive polymer with medication, thus propel the drug from reservoir by a partial crystallization of the drug. The presence of both molecular solute and solid crystal Transdermal drug absorption markedly alters drug kinetics and depends on a several parameters including the following-

- Medicament application site
- Thickness and integrity of the stratum cornea epidermidis.
- Size of the molecule that is to be administered.
- Permeability of the membrane for the transdermal drug delivery.
- Hydration state of skin.
- pH of the drug.
- Drug metabolism by skin flora.
- Lipid solubility.
- Drug depot in skin.
- Blood flow alteration in the skin by additives and body temperature

The toxic effect of the drug and problem in limiting drug uptake are major considerable potential for transdermal delivery systems, especially in children because skin thickness and blood flow in the skin usually vary with age. The increased blood supply in the skin along with thinner skin has significant effects on the pharmacokinetics of transdermal delivery for children. In some situations this may be an advantageous, while in others systemic toxicity may occur. This was observed after using scopolamine patches that are used to prevent motion sickness, a eutectic mixture of local anesthetics (EMLA) cream used to minimize the pain, corticosteroid cream applied for its local effect on skin maladies. Episodes of systemic toxic effects, including some fatalities in children, have been documented with each of these, often secondary to accidental absorption through mucous membranes [13].

Advantages of Transdermal Drug Delivery System (TDDS)

The advantages of transdermal delivery over other delivery systems are as follows:

• Avoidance of 'first-pass' metabolism of drugs.

• Reduced plasma concentration levels of drugs , with decreased side effects.

• Reduction of fluctuations in plasma levels of drugs.

Utilization of drug candidates with short half-life and low therapeutic index.

• Easy elimination of drug delivery in case of toxicity.

• Reduction of dosing frequency an enhancement of patient compliance [14].

Limitations for a drug substance to be incorporated into a transdermal delivery system are: -

- Heavy drugs molecules (>500 Da) usually difficult to penetrate the stratum cornea.
- Drugs with very low or high partition coefficient fail to reach blood circulation.
- Drugs that are highly melting can be given by this route due to their low solubility both in water and fat [1].

Many approaches have been attempted to deliver medicament across skin barrier and enhance the efficacy. The major considerations for enhancing transdermal delivery are physical enhancers (ultrasound, iontophoresis, electroporation, magnetophoresis, microneedle), vesicles, particulate systems (liposome, niosome, transfersome, microemulsion, solid lipid nanoparticle) and chemical enhancers (sulphoxides, azones, glycols, alkanols, terpenes etc.) [15].

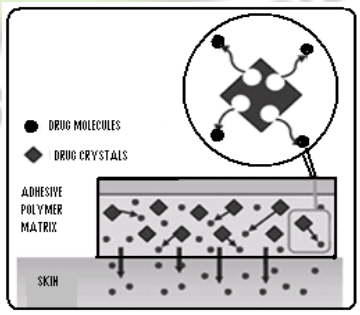

Fig 1-Crystal reservoir technology has resulted in smaller patches with a more controlled and sustained drug release.

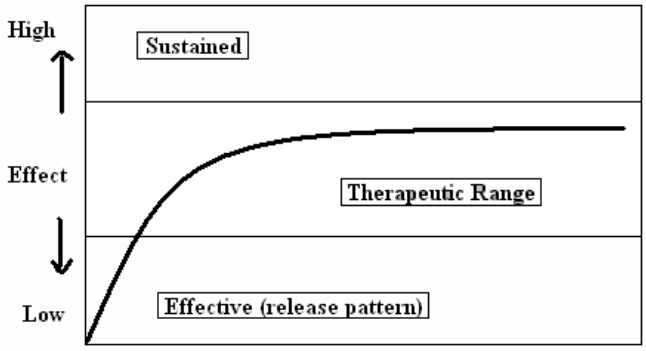

Fig 2- Sustained release is facilitated through the consistent rejuvenation of drug molecules at the surface of skin.

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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 [16].

1-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 [17].

2-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 [18].

B) Activation Modulated Drug Delivery System

This type of delivery system can be achieved by-

1-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**.**

2-Chemical means

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

3-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 a 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 [19].

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.

Recent Techniques For Enhancing Tdds-

A) <u>Structure-Based Enhancement Techniques</u>

1-Transdermal Patches

A transdermal patch or skin adhesive patch is that device which is loaded with drug candidate and usually applied on the skin to transport a specific dose of medication across the skin and into the blood circulation [2]. The adhesive serves two functions: It is glue in nature that keeps the patch adhered to the skin, and it acts as the suspension that holds the drug. The problems associated with this is the concentration of the drug within the adhesive directly affects the "stickyness" of the adhesive so if the large quantities of drug is to be administered , either the size of the patch have to be increased or the patch needs to be reapplied again and again. Several pharmaceuticals usually combined with substances, like alcohol, within the patch to improve their penetration via skin in order to improve absorption [20].

Components of Transdermal Patch

1-Liner - Protects the patch during storage. The liner should be removed before its use.

2- Drug - Drug solution is in direct contact with release liner.

3-Adhesive – It serves to adhere the components of the patch together along with adhering the patch to the skin. E.g.- Acrylic, polyisobutylene (PIB), and silicone are the adhesives have many pharmaceutical applications. For applications in which the adhesive, the drug, and perhaps enhancers are compounded, the selection of a PSA is more complex (e.g., a matrix design).

4-Membrane – It controls the release of the drug from the reservoir and multi-layer patches.

5- Backing – The film protects the patch from the outer environment [21, 22].

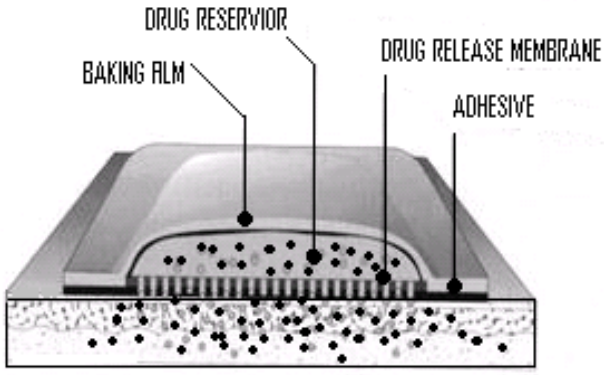

Fig 3 - Different parts of Transdermal Patch

Types of transdermal patches-

The transdermal patches that commonly used are active and passive type. In active one, the applied external forces facilitates the drug penetration accross the skin . In passive type, the drug usually diffused by gradient mechanism in respect of either solubility or concentration of drug. several parameters like the molecular structure, solubility and potency of drugs often determines the effective delivery rate. Passive systems may rely on permeation enhancers that are added to accelerate drug diffusion.

There are four main designs of transdermal patches –

1-Single-layer Drug-in-Adhesive

In this system, the drug is remains in contact with the adhesive which is attached to skin. In this, the adhesive layer helpful in releasing the drug and serves to adhere the various layers together along with the skin.

2-Multi-layer Drug-in-Adhesive

The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in-Adhesive which involves the drug introduction directly into the adhesive. The system has more than one layer of drug-in-adhesive, that are separated by a membrane. This patch also has a temporary liner-layer and a permanent backing.

3-Reservoir

It includes a compartment for liquid that contains a solution or suspension of drugs separated from the liner by a membrane (semipermeable) and adhesive. The adhesive of the product can either be as a continuous layer between the semipermeable membrane and the release liner. [21]

4-Matrix

The system consists a medicament layer of a semisolid matrix that contains a drug as a solution or suspension; this is in direct contact with the liner. The adhesive layer in this device surrounds the drug layer partially overlaying it [21, 22].

Patients with mild to moderate Alzheimer's disease (AD) can be treated by this approach. This is observed by analyzing potency, safety and tolerability parameters of the rivastigmine patch which was compared with placebo were established in a large, international, 24-week, double-blind, randomized clinical trial and subsequent 28-week open-label extension study. [23].

Requirements for pressure-sensitive adhesives (PSAs)

Several classes of PSAs are used for skin contact application include acrylics, polyisobutylene and silicone polymers [24]. The functional properties of PSAs such as tackyness, adhesive property, release force, and cohesive strength as well as adhesive formulations having attributes such as enhanced drug flux and skin friendliness. A PSA must be able to performance effectively under a wide range of temperatures, humidity levels, and application frequency (from 24 hrs for some products to one week for others). The effects of mechanical stresses (e.g., stretching) as well as skin irritation and sensitization also must be considered [21]. The human studies of various commercially available transdermals are examined and reported to assess the relative performance capabilities of each type of transdermal design [24]. Monolithic TTS was fabricated in PSAs- (a) terpolymer (PSA1) of 2-ethylhexyl acrylate, methyl methacrylate, and acrylic acid, (b) copolymer (PSA2) of 2-ethylhexyl acrylate, methyl methacrylate, acrylic acid, and vinyl acetate, and (c) Eudragit E100 pressure sensitive adhesive (PSA3). The transport of nicorandil via skin can be achieved by the skin permeation enhancer i.e. *N*-methyl-2-pyrrolidone (NMP) was investigated at different concentrations (0.05–5%) in PSAs [25].

Drugs used in the Transdermal Patch

(1) Nicotine-used to quit tobacco smoking (2) Fentanyl- used as analgesic for severe pain (3) Estrogen- menopause and osteoporosis (4) Nitroglycerin- angina (5) clonidine- transdermal patch for hypertension treatment . Recent trials have been developed the use of hormonal contraceptives, antidepressants and even pain killers and stimulants for Attention Deficit Hyperactivity Disorder/ADHD by transdermal route. [26, 27, 28, 29].

2-Microfabricated Microneedles

These are the devices which are having the features of both the hypodermic needle and transdermal patch that can deliver the drug that transports the drug effectively across the memberane. The systems consists of a drug reservoir and a some projections (microneedles) extending from the reservoir, these helps in penetrating the stratum cornea and epidermis to deliver the drug

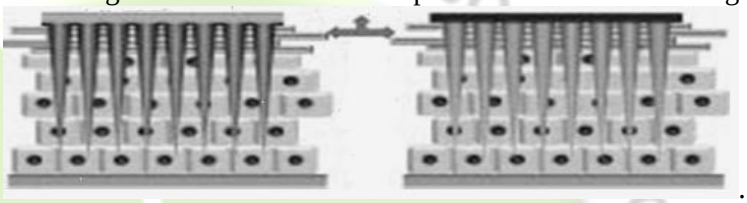

Fig 4- Delivery site for microneedle technology. (a) Hollow microneedles with applied formulation; (b) Solid microneedles

Microneedles are tiny and very sleek devices that are manufactured by the silicon etching technology and micro-mechanical system manufacturing (MEMS) technique, which do not penetrate deep enough into the skin to reach up to the nerve endings and thus there is no pain sensation during the microneedles insertion into the skin. There are number of delivery approaches that have been employed to use the microneedles for TDDS. These includes-

Poke with patch approach- Involves piercing into the skin followed by application of the drug patch at the site of treatment.

Coat and poke approach- Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.

Biodegradable microneedles- Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.

Hollow microneedles- Involves injecting the drug through the needle with a hollow bore. [30].

3-Macroflux

These are devices having an area of around 8cm as well as 300 micro projections per cm^2 with the length of individual micro projection less than 200μm. Three types of Macroflux have been designed . They include,

• Dry-Coated Macroflux system-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 also for 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.

4-Metered-Dose Transdermal Spray (Mdts)

It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come non volatile in nature, which consists the completely dissolved medicament in solution . The use of MDTS reaches the sustained level and better permeation of the drug via skin. The MDTS has the following potential advantages:

- It improve delivery potential without skin irritation due to its non-occlusive nature.
- Increased acceptability.
- Dose flexibility
- Simple manufacture [1].

B)-Electrically-Based Enhancement Techniques

1-Iontophoresis

It involves passing of current (few milliamperes) to skin limited to a certain area using the electrode remains in contact with the formulation which is to be administered. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anesthesia [31, 32].

2-Ultrasound

In this technique, there is a mixing of drug substance with a coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier.

3-Photomechanical Waves

Photomechanical waves significantly led to the stratum cornea highly permeable to drug substance through a possible permeabilisation mechanism due to development of transient channels.

4-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. [31, 33, 34, 35].

5-Electro-Osmosis

To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

C)-Velocity Based Enhancement Techniques

1-Needle-Free Injections

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

2-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.

D)-Other Enhancement Techniques

1-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.

2-Medicated Tattoos-

Med-Tats is 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.

3-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 Microscissuining.

4-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 andpermeability 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 unit which tend to form heat of limited intensity and duration.

5-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.

6-Magnetophoresis-

The effect of magnetic field on diffusion flux of drug substance was found to enhanced with increasing applied strength [1].

The Future Of Transdermal Drug Delivery

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 [36]. TDDS may be ideal for many injected as well as orally given drugs, but many drugs cannot penetrate the skin membrane effectively because of low permeability of skin barrier. Pharmaceutical companies are now developing new adhesives, substances that enhance molecular absorption as well as penetration that will ultimately affect skin permeation and greatly increase the list of drugs which can be delivered transdermally. Well known technologies that are iontophoresis and phonophoresis (sonophoresis) considered to acheive significant plasma concentration levels via skin membrane. A microoneedle technology is more promising for drug administered via skin. These systems use an arrangement of small needle-like structures to open pores in the stratum cornea and facilitate drug transport without any sensation of pain because these are not reachable to nerve endings. These systems are reported to greatly enhance the permeability of macromolecules across skin [22].

Conclusion

A lot of work has been done related to transdermal patches. Recently new researches are going on to introduce newer drugs via this system. Various devices used to increase the absorption rate and penetration of the drug are also being studied. However, due to certain disadvantages like large drug molecules cannot be delivered, large dose cannot be given, the rate of absorption of the drug is less, skin irritation; etc, the use of TDDS has been limited. But day to day increament in the invention of new devices and new drugs that can be administered via this system, the use of TDDS is increasing rapidly in the present time.

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