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APPROACHES TO TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The conventional oral dosage forms has major drawbacks of poor bioavailability due to hepatic first pass metabolism and tendency to produce rapid blood level spikes (Both high and low), leading to a requirement for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. To improve such characters transdermal drug delivery system (TDDS) was emerged which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific) placement within the body thereby reducing both the size and number of doses. TDDS of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. For transdermal delivery of drugs, stratum corneum (SC) is the main barrier layer for permeation of drug. The drug which is to be delivered passively via skin should have suitable lipophilicity and a molecular weight <500 Daltons (Da). So to continue away from the stratum corneum and to increase the flux through skin membrane, different approaches of penetration enhancement are used.

KEYWORDS: Bioavailability, Transdermal drug delivery, Stratum corneum, lipophilicity.

INTRODUCTION

Human skin serves a protective function by imposing physicochemical limitations to the type of permeant that can pass through the barrier. The drug which is to be delivered passively via skin should have suitable lipophilicity and a molecular weight <500 Da. In recent years

various passive and active strategies have emerged to optimize delivery. The passive approach involves the optimization of formulation or drug carrying vehicle to increase skin permeability but the passive methods do not greatly improve the permeation of drugs with molecular weights >500 Da. The active methods, normally involves the physical and mechanical methods for enhancing drug delivery via skin and have been shown to be generally superior.

THE SKIN BARRIER

The barrier function of skin is reflected by its multilayered structured (Fig.1). The top or uppermost layer of skin is known as Stratratum corenum (SC) which comprised of dead cells (corneocytes). It is the "brick and mortar" architecture and lipophilic nature of the SC, which primarily accounts for the barrier properties of the skin.[1] The SC allows only relatively lipophilic drugs to diffuse into the lower layers. Because of the dead nature of the SC, the solute transport across this layer is primarily by passive diffusion in accordance with Fick's law and no active transport processes have been identified.[2]

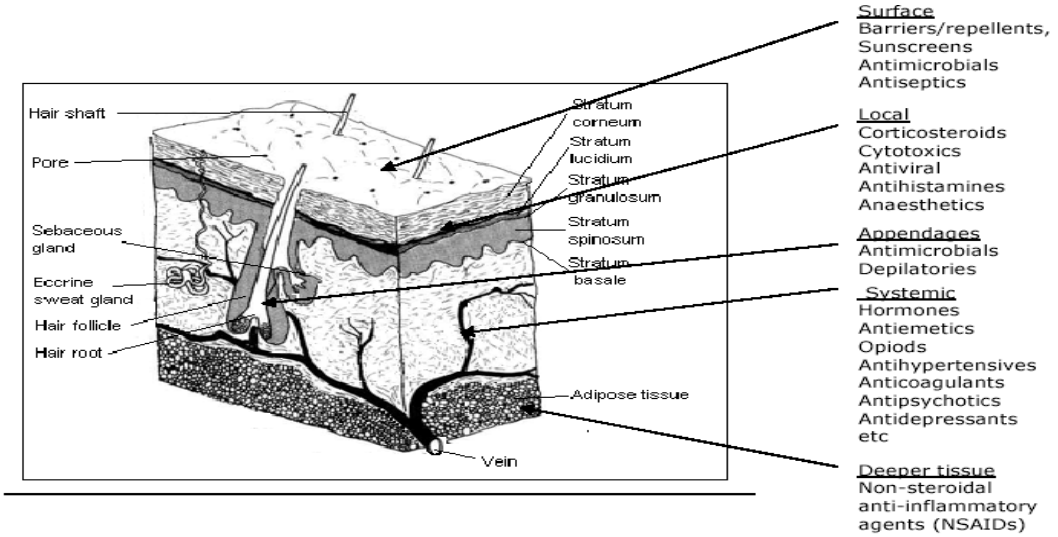

Fig.1: Multilayered structure of the skin

PASSIVE METHODS FOR ENHANCING TRANSDERMAL DRUG DELIVERY

These methods include the use of penetration enhancers[3], supersaturated systems[4], prodrugs or metabolic approach[1, 5] and liposomes and other vesicles.[6, 7] However, the amount of drug that can be delivered using these methods is still limited since the barrier properties of the skin are not fundamentally changed. As such there are still no medicines on the market in the US that contain a labelled penetration enhancer.[8, 9]

ACTIVE METHODS FOR ENHANCING THE TRANSDERMAL DELIVERY

These methods involves the use of external energy which act as driving force to reduce the barrier nature of the SC in order to enhance the permeation of drug molecules into the skin. The large molecular weight (>500 Daltons) polar and hydrophilic molecules, mostly peptides and proteins are delivered by using active methods. The passive methods of skin delivery are incapable for the delivery of above compounds. The active methods are discussed as.

1) Electroporation: Electroporation involves the application of high voltage pulses to induce skin perturbation. High voltages (≥100 V) and short treatment durations (milliseconds) are most frequently employed. [10] The increase in skin permeability is suggested to be caused by the generation of transient pores during electroporation.[11] This technique is widely used to enhanced the skin permeability of molecules with differing lipophilicity and size ((i.e. small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with a molecular weight greater that 7k Daltons (Da).[12]

2) Iontophoresis: This method involves the application of low level electric current either directly to the skin or indirectly (via dosage form) for enhancing the permeation of a topically applied therapeutic agent.[13,14,15] Increase in drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms; electrorepulsion (for charged solutes), electro osmosis (for uncharged solutes) and electropertubation (for both charged and uncharged).The first iontophoretic system is Phoresor™ device approved by FDA in the late 70's as a physical medicine therapeutic device. Other system includes Vyteris and E-TRANS iontophoretic devices.[16, 17, 18]

The limitations of ionotophoretic systems include the regulatory limits on the amount of current that can be used in humans (currently set at 0.5 mA cm^2) and the irreversible damage such currents could do to the barrier properties of the skin. In addition, iontophoresis has failed to significantly improve the transdermal delivery of macromolecules of >7000 Da.[19]

3) Ultrasound (Sonophoresis and Phonophoresis): This method involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre-treatment and is frequently referred to as sonophoresis or phonophoresis. The mechanism which involves in enhancing the skin permeability is the formation of gas cavities within the intracellular lipids on exposure to ultrasound resulting in disruption of SC.[20] The ultrasound parameters which are to be controlled such as treatment duration, intensity and frequency are

all known to affect the percutaneous absorption. Although frequencies between 20 kHz-16 MHz have been reported to enhance skin permeation, frequencies at the lower end of this range (< 100 kHz) are believed to have a more significant effect on transdermal drug delivery with the delivery of macromolecules of molecular weight up to 48 kDa being reported.[21,22]

4) Laser Radiation and Photomechanical Waves: Lasers are widely used for the treatment of dermatological conditions such as acne and to confer 'facial rejuvenation' where the laser radiation destroys the target cells over a short segment of time (~300 ns). Lasers have been used in the clinical therapies for decades; therefore their effects on biological membranes are well documented. There is ablation of the SC without significant damage to the underlying epidermis. Removal of the SC via this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs. [23, 24] The recently found Pressure waves (PW) which can be generated from intense laser radiation, without incurring direct ablative effects on the skin has also been used to enhance the skin permeability.[25] Important parameters affecting delivery such as peak pressure, rise time and duration has been demonstrated.[26]

5) Magnetophoresis: This method involves the application of a magnetic field which acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. The skin exposure to magnetic field may also induce skin alterations that could contribute to an increase in skin permeability. *In vitro* studies by Murthy showed a magnetically induced enhancement in benzoic acid flux, which was observed to increase with the strength of the applied magnetic field.

6) Micro needle based devices: The device consists of a drug reservoir and a plurality of projections extending from the reservoir. These micro needles are 50-110µm in length will penetrate the SC and epidermis to deliver the drug from reservoir. The reservoir may contain drug, solution of drug, gel or solid particulates and the various embodiments of the invention include the use of a membrane to separate the drug from the skin and control release of the drug from its reservoir. The micro projections/ micro needles (either solid or hollow) create channels in the skin, hence allowing the unhindered movement of any topically applied drug. This technology serves as an important and exciting advance in transdermal technology due to the ability of the technique to deliver medicaments with extremes of physicochemical properties (including vaccines, small molecular weight drugs and large hydrophilic biopharmaceuticals.[27, 28]

7) Skin puncture and perforation: These devices are same as that of micro needle devices produced by micro fabrication technology. These include the use of needle like structure or blades, which disrupts the skin barrier by creating holes and cuts as a result of a defined movement when in contact with the skin. One apparatus is described for disruption of the epidermis in a reproducible manner which consists of a plurality of micro protrusions of a length insufficient for penetration beyond the epidermis.[29] The micro protrusions cut into the outer layers of the skin by movement of the device in a direction parallel to the skin surface. After disruption of the skin, passive (solution, patch, gel, ointment etc) or active (iontophoresis, electroporation etc) delivery methods can then be utilised.

8) Needleless injection: It is pain free method of deliver the drug to the skin therefore avoids the issues of safety, pain and fear associated with the use of hypodermic needles. Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source. The device has been reported to deliver successfully testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin.[30, 31]

9) Suction Ablation: This method involves the use of vacuum or negative pressure to remove the epidermis, while leaving the basal membrane intact. The cellpatch® (Epiport Pain Relief, Sweden) is a commercially available product based on this mechanism. [32] It comprises of a suction cup, epidermatome (to form a blister) and device (which contains morphine solution) to be attached to the skin this method which avoids dermal invasively there by avoiding pain and bleeding is also referred to as skin erosion.

The disadvantage of suction method includes the prolonged length of time require to achieve a blister (2.5hr), although this can be reduced to 15-70min by warming the skin at 38ºC. There is no risk of systemic infection in this method as compare to the use of intravenous catheter. [33]

10) Skin Stretching: These devices hold the skin under tension in either a unidirectional or multidirectional manner**.** A tension of about 0.01 to 10 mp results in the reversible formation of micropathways. [34, 35]The efficiency of the stretching process was demonstrated by monitoring the delivery of a decapeptide across the skin of hairless guinea pigs using a micro protrusion array. The other methods which involves the use of skin stretching with subsequent use of delivery devices based on electro transport, pressure, osmotic and passive

mechanisms have also been suggested but the value of skin stretching alone without the benefit of a secondary active delivery device remains to be seen.

VESICULAR SYSTEMS FOR TRANSDERMAL DRUG DELIVERY

Transdermal drug delivery uses the skin as an alternative route for the delivery of systemically acting drugs. This drug delivery route can have several advantages compared with oral drug administration such as.

1) It circumvents the variables that could influence gastro-intestinal absorption such as pH, food intake and gastro-intestinal motility.
2) Prevents the hepatic metabolism therefore suitable for drugs having low bioavailability.
3) The TDDS can give a constant, controlled drug input decreasing the variations in drug plasma levels, thus reducing the side effects particularly of drugs with a narrow therapeutic window.

Despite the many advantages of the skin as a site of drug delivery, only eight drugs are currently in the market in transdermal delivery system namely clonidine, estradiol, nitroglycerine, fentanyl, testosterone, scopolamine, nicotine and oxybutinin. The most important reason for this is the low permeability of drugs in the SC, the outermost layer of the skin acting as the main barrier in the skin which act as brick wall with the coenocytes as the bricks surrounded by the mortar of the intercellular lipid lamellae and these lipid lamellae play an essential role in the barrier properties of SC. Many techniques have been aimed to disrupt and weaken the highly organized intercellular lipids in an attempt to enhance drug transport across the intact skin or to increase the driving force for permeation of drugs across this skin barrier.

CONVENTIONAL VESICLES AS SKIN DELIVERY SYSTEMS

A wide variety of lipids and surfactants can be used to prepare vesicles. Most commonly, the vesicles are composed of phospholipids or non-ionic surfactants (Crommelin *et al*, 1994 and Bouwastra et al., 1994). These are referred to as Liposomes and Niosomes or non-ionic surfactant vesicles, respectively. The composition of the vesicles influences their physico-chemical characteristics such as, size, charge, thermodynamic phase, lamellarity and bilayer elasticity. These physico-chemical characteristics have a significant effect on the behaviour of the vesicles and hence on their effectiveness as a drug delivery system.

RATIONALE FOR USING VESICLES IN TDDS

a. These act as drug carriers to deliver entrapped drug molecules into or across the skin.
b. They also act as penetration enhancers owing the penetration of the individual lipid components into the stratum corneum and subsequently the alteration of the intercellular lipid lamellae with in this skin layer.
c. Serve as a depot for sustained release of dermal active compounds.
d. Serve as a rate-limiting membrane barrier for the modulation of systemic absorption, hence providing a controlled transdermal delivery system.

VESICULAR SYSTEMS

1) Liposomes: Liposomes are colloidal particles, typically consists of Phospholipids and cholesterol. The lipid molecules form a concentric bilayer that may entrap the drug and deliver to the skin. The vesicles accumulate the drug in the upper layer of the skin *i.e* SC and producing the localising effect. Generally, Liposomes are not expected to penetrate into the viable skin, although occasional transport process were reported (Mezei *et al.*, 1992). The mechanism of actions of liposomes is such as.

a) The drug releases from the vesicles and penetrates into the skin through a free drug process.
b) Enhancement due to release of lipids from vesicles and interaction with skin lipids.
c) Improved drug uptake by skin.
d) Penetration of SC by intact liposomes.
e) The different entrapment efficiencies of liposomes controlled the drug input.

Liposomal system also increases the stability of some drugs like Amphotericin B. When Amphotericin B is entrapped in liposomes appeared to be more stable than the free Amphotericin B.[36]

2) Ethosomes: Ethsomes are liposomes containing high amount of ethanol (upto45%).They penetrate into the skin and enhanced compound delivery to deep tissues and systemic circulation. [37, 38, 39] The ethanol fluidises both ethosomal lipids and SC bilayers lipids thus allowing the soft, malleable vesicles penetrate through the disorganised lipid bilayers. The transdermal delivery of Drugs like Minoxidil, testosterone has been studied and comparative study had also been done on ethosomal vs. liposomal system of trihexyphenidyl hydrochloride (THP).The ethosomes prepared was shown to be higher efficient carrier than liposomal system for enhanced THP delivery through the skin. The THP ethosomal system

also enhance the long term stability of THP as compare to classical liposomes and makes it a promissing alternative for transdermal delivery of THP.

3) Niosomes: Niosomes are vesicles mainly composed of non-ionic surfactants that have been evaluated as carriers for various drugs and cosmetic preparations. The noisome have higher chemical stability, lower costs and great availability of surfactant classes. [40] The different properties of niosomes are as follows.

a) The topically applied niosomes can increase the residence time of drugs in the SC and epidermis, while reducing the systemic absorption of the drug.
b) These reduce the transepidermal water loss (TWEL) and increase the smoothness of skin via replenishing lost skin lipids.
c) The sugar based non-ionic surfactants which are used in the preparation of niosomes are less toxic and highly biodegradable in nature.
d) The alkyl Polyglucosides (APGs) have been studied for several type of applications mainly used in dermatological diseases and in cosmetic products

The various studies have been done on niosomal transdermal drug delivery of agents like estradiol Proniosomal formulation), ketorolac (proniosomal formulation), immunological adjutants, Tretenoin for Psoriasis and skin cancer.[41]

4) Solid Lipid Nanoparticles (SLNs): Nanoparticles are colloidal drug delivery systems having a diameter of approximately 200-500nm. These have recently been investigated as carriers for enhanced skin delivery of sunscreens, vitamins A and E, triptolide and glucocorticoids. Their enhanced skin permeation is due to the increase skin hydration which is caused by occlusive film formed on the skin surface by SLN. The various Studies have been done on transcutaneous vaccine delivery, transdermal DNA delivery, minoxidil with block copolymer nanoparticles and in combination with physical methods as iontophoretic delivery of triamcinolone acetonide acetate, iontophoretic administration of triptorelin loaded nanospheres and microneedle mediated delivery of nanoparticles.

5) Transferosomes: These are vesicles containing phospholipids as the main ingredient (upto10-25%) surfactant and 3-10% ethanol. The transfersomes up to 500nm can squeeze to penetrate the SC barrier spontaneously. The 'Transdermal gradiant' act as the driving force for penetration into the skin caused by the difference in water content between the restively dehydrated skin surface (approximately 20% water) and the aqueous viable epidermis (close to100%). Evidence of presence of vesicles between the corneocytes in the outer layers of the

SC has been demonstrated by electron and fluorescence microscopy. The transferosomes work best under *in vivo* conditions where as the liposomes are expected to confine to surface or upper layers of SC, where they dehydrate and fuse with skin lipids. Transferosomes can penetrate the skin and does not cause any changes in semi-permeable barriers that remain unfragmented after delivery. Data indicate that as much as 50% of a topical dose of a protein or peptide penetrates skin *in vivo* in 30 minutes. The transferosomes has some disadvantages such as-

a) These are chemically unstable because of their predisposition to oxidative degradation.
b) Lack of purity of natural phospholipids comes in the way of adoption of transferosomes as drug delivery vehicle.
c) These formulations are expensive to prepare.

6) Pharmacosomes: The limitations of transferosomes can be overcome by' Pharmacosome' approach. These are defined as colloidal dispersions of drugs covalently bound to the lipids and may exist as ultrafine vesicular, micelle, or hexagonal aggregates depending on the chemical structure of the drug lipid complex. The constraints of various classical vesicular drug delivery systems such as problems of drug incorporation, leakage from the carrier, insufficient shelf life can be avoided by this approach. The salient features of the Pharmacosomes are-

a) The high and predetermined entrapment efficiency because drug itself in conjugation with lipids form vesicles.
b) There is no need for removing the free unentrapped drug from the formulation as in case of liposomes which makes the process tedious and time- consuming.
c) The loss due to the leakage of drug does not take place because the drug is covalently linked. However, loss may occur by hydrolysis.
d) No problem of drug incorporation.
e) The drug is release by hydrolysis from pharmacosome.
f) The physiochemical stability of the pharmacosome depends on the physiochemical property of the drug-lipid complex.
g) They can be given orally, topically, extra-or intravascularly.

CONCLUSION

Transdermal drug delivery system is useful for topical and local action of the drug. The drugs which shows hepatic first pass effect and unstable in GI conditions are the suitable candidate for TDDS.

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