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Techniques Aided Transdermal Drug Delivery System

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ABSTRACT

Today about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. The transdermal route has numerous advantages over the more traditional drug delivery routes. Tablets and injections have been the traditional way to take medications; new options are becoming increasingly popular. One highly successful alternative delivery method is the transdermal. Innovations in the area of drug delivery are taking place at a much faster pace as compared to the last two decades. Transdermal delivery is emerging as the biggest application target for these agents, however, the skin is extremely efficient at keeping out such large molecular weight compounds and therapeutic levels are never going to be realistically achieved by passive absorption. Physical enhancement mechanisms including: iontophoresis, electroporation, ultrasound, photomechanical waves, microneedles and jet-propelled particles are emerging as solutions to this topical delivery.

Keywords: TDS, Microneedles, Iontophoresis, Sonophoresis, Electroporation

1. INTRODUCTION

Transdermal drug delivery systems (TDDS), also known as “patches,” are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin. Conventional systems of medication which require multi dose therapy have numerous problems and complications. The design of conventional dosage form, whether a tablet, an injection or a patch, to deliver the right amount of medicine at the right target site becomes complicated if each medication were to be delivered in an optimal and preferred manner to the individual patient.[1] Transdermal therapeutic systems are defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drugs, through the skin, at a controlled rate to the systemic circulation and this delivery system offers an advantageous alternative to common delivery methods such as injections or oral delivery.[2]

2. SKIN AND DRUG PERMEATION

For understanding the concept of TDDS, it is important to review the structural and biochemical features of human skin and those characteristics which contribute to the barrier function and the rate of drug access into the body via skin.[3]

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.

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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.[4]

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.[5]

Classification of physical delivery technologies available for transdermal drug application

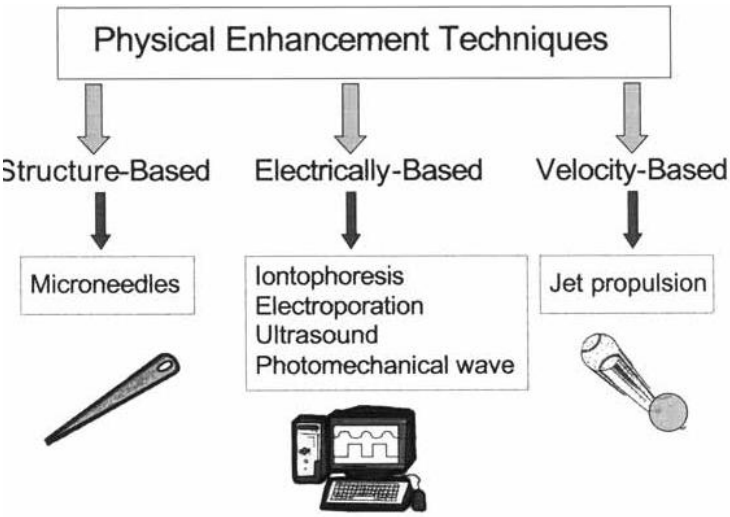

Fig. 1. Classification of the types of physical delivery technologies available for transdermal drug application

Microneedles

Microneedles are designed to be inserted into human tissue and as such they need to be compatible with the local environment, both in terms of toxicity and intended function. The duration of contact with the tissue range from minutes to days at the most (insulin infusion-sets are typically changed every third day). Hence, if the material is non-toxic anther short term, malfunctioning due to biological host response through e.g. biofouling is unlikely to occur. For hollow microneedles there is a risk of blocking the needle bore with cored tissue during insertion into the skin. Concerning toxicity, well-known, bioinert, materials such as titanium, stainless steel or gold, or biodegradable polymers such as PLGA (polylactic-coglycolic acid), may be used with confidence as microneedle material. In the scientific literature, it is often questioned whether silicon (the traditional microengineering material) can be used as microneedle material. Metal microneedles have also been targeted for transdermal drug delivery mainly due to their good mechanical properties.[6,7] Although biocompatibility has not been investigated for silicon microneedles inserted into skin, recent studies show that silicon as a material is biocompatible in prolonged (days to weeks) implantations. [8-10]

Microblades

The need for such a device existed because it was hypothesized that once a drug penetrated through stratum corneum with the aid of the device, permeation through the remaining layers could proceed readily. The apparatus basically consists of a cutter having a plurality of micro protrusions having a height chosen with respect to the layer of skin that is to be disrupted and for preventing the apparatus from penetrating the skin beyond a predetermined distance. As advancement to the basic technique, a microblade device along with negative pressure was patented for the Percutaneous sampling of an agent. The device was designed to optionally include a drug-sensing element. The angle of leading edge was kept between 10º-40º or the convex/ concave shaped microblades were used. It was concluded that curving of microblades tips outside the plane of microblade provided better anchoring. Another device comprising of a piercing member having plurality of microblades with 25-400µm length and provision for applying partial vacuum in the range of 0.1-0.8 atm over a period of about 2-30 sec was designed for piercing the stratum corneum for body fluid withdrawal.

Iontophoresis

Iontophoresis was initially developed to facilitate the delivery of ionised solutes, with inherently low partition coefficients due to their charged state, across tissue membranes. As a non-invasive transdermal drug delivery (TDD) method.[11] This technique involves the application of a small electric current (usually 0.5mA/cm2) to a drug reservoir on the surface of the skin, with the same charged electrode as the solute of interest placed together to produce a repulsion effect that effectively drives solute molecules away from the electrode and into the skin. The first studies using in-vivo iontophoretic transport were published around the turn of the last century, when Ludec successfully demonstrated the iontophoretic delivery of strychnine and cyanide into rabbits. The effect of simple electrorepulsion is known to be one of the main mechanisms by which iontophoresis produces it's enhancement effects, though other factors including the possibility

of increasing the permeability of the stratum corneum in the presence of a flow of an electric current and lectroosmosis of uncharged and larger water soluble molecules. [12] Though it offers numerous advantages, application of iontophoresis is limited to drugs that can be formulated in the ionic form. As long as the current density is less than $0.5mA/cm^2$ there is no disruption of the skin in iontophoresis. [13-16]

Iontophoretic drug delivery systems form a major group of the relatively few physically enhanced transdermal delivery systems that have been successfully developed and commercialised. The electrically driven penetration enhancement provided by this method has succeeded in overcoming the formidable barrier presented by the SC, and has shown to be a promising technique for various agents, including macromolecules. Combination strategies with other physical enhancement techniques such as electroporation or ultrasound or with chemical enhancers have led to the observation of significantly higher flux levels compared with passive transdermal delivery. However, the resulting irritation caused to the skin due to combined strategies may be a cause for concern. Also, electrically assisted delivery systems provide the advantage of controlled drug delivery with customised drug input rates, and an option of ceasing drug transport when desired. In addition, iontophoresis is also finding value in drug delivery via other drug administration routes such as transcorneal and trans-scleral routes and also through bone for delivery of antibiotics to prevent infection during allograft implantation.[17, 18]

1. It is a non-invasive technique could serve as a substitute for chemical enhancers
2. It eliminates problems like toxicity problem, adverse reaction formulation problems associated with presence of chemical enhancers in pharmaceuticals
3. It may permit lower quantities of drug compared to use in TDDS, this may lead to fewer side effects
4. TDDS of many ionized drug at therapeutic levels was precluded by their slow rate of diffusion under a concentration graduation, but iontophoresis enhanced flux of ionic drugs across skin under electrical potential gradient
5. Iontophoresis prevent variation in the absorption of TDDS
6. Eliminate the chance of over or under dosing by continuous delivery of drug programmed at the required therapeutic rate.
7. Provide simplified therapeutic regimen, leading to better compliance.
8. Permit a rapid termination of the modification, if needed, by simply by stopping drug input from the iontophoretic delivery system.
9. It is important in systemic delivery of peptide/protein based pharmaceuticals, which are very potent, extremely short acting and often require delivery in a circadian pattern to simulate physiological rhythm, eg. Thyrotropin releasing hormone, somatotropine, tissue plasminogen activates, interferons, enkaphaline etc.
10. Provide predictable and extended duration of action. [19]

Sonophoresis

Sonophoresis is a process that exponentially increases the, non-invasive, convenient and rapid m ethod of delivering low molecular absorption of topical compounds (transdermal delivery) into the epidermis, dermis and skin appendages by ultrasonic energy. Sonophoresis is a localized weight drugs as well as macromolecules into the skin. Mechanistically, sonophoresis is considered to enhance drug delivery through a combination of thermal, chemical and mechanical alterations within the skin tissue. So, In addition to its effects in delivering compounds into the skin, sonophoresis is being investigated as a way of drawing compounds such as glucose out of the skin.[20-22]

Advantages of using sonophoresis as a physical penetration enhancer

• Enhanced drug penetration (selected drugs) over passive transport
• Allows strict control of transdermal penetration rates
• Low risk of introducing infection as the skin remains intact
• Not immunologically sensitizing
• Reduction of dosing frequency and patient compliance
• Improved control of the concentrations of drugs with small therapeutic indices
• Reduction of fluctuations in plasma levels of drugs [23]
• Avoids hepatic first pass elimination and gastrointestinal irritation
• Substitutes oral administration when the route is unsuitable as in case of vomiting, diarrhoea
• Permit both local and systemic effects
• Less risk of systemic absorption than injection
• Less anxiety provoking and painful than injection
• Easy termination of drug delivery in case of toxicity, through termination of ultrasound. [24]

Sonophoresis is a process that exponentially increases the absorption of topical compounds (transdermal delivery) into the epidermis, dermis and skin appendages. Sonophoresis occurs because ultrasound waves stimulate micro-vibrations within the skin epidermis and increase the overall kinetic energy of molecules making up topical agents. It is widely used in hospitals to deliver drugs through the skin.[25]

Electroporation

Electroporation of skin is associated with a temperature rise within the highly. When an electric field is applied to the skin,

it dissipates energy and heats up (Joule heating). This local temperature rise may affect the barrier function of the skin if the temperature rise induces a phase change in the sphingo-lipids of the stratum corneum, increasing the permeability of skin. Indeed, dramatic decrease of the skin resistance occurs when 65–70 jC are reached [26, 27]. As revealed by temperature sensitive crystals, during the pulse, the temperature did not rise instantaneously over the entire skin surface but started at small spots, resulting in a propagating heat front.[28] Hence, the interior of the localized transport regions was heated above the phase transition temperature, while the localized dissipation regions was also heated but did not reach the phase transition temperature. As the transdermal voltage and pulse time constant increased, the temperature tended to a plateau but did not reach the phase transition of the water.[29] During cooling, the multi lamellar system could not re-establish, leaving the existence of water rich domains, which provided aqueous pathways even long after the pulse. The biological significance of heating of the stratum corneum above the phase transition temperature of sphingo-lipids is not yet understood. However, in vivo experiments using hairless rats showed no significant skin irritation for short and long pulses.[30, 31] The concept of skin electroporation and the supporting preliminary data have motivated a number of subsequent studies, mainly in vitro but also a few in vivo in animals and in humans.[32]. The combination of electroporation with other enhancement methods opens new perspectives.[33] The effect of the physicochemical properties of the drug on transdermal transport by combination of electroporation and iontophoresis was recently highlighted. [34, 35]

3. CONCLUSION

From the above study it is concluded that use of new technologies in transdermal drug delivery system has enhanced the permeation of the drug into skin, hence results in more beneficial outcomes. Modification of transdermal drug delivery systems can enhance the bioavailability of poorly absorbed drugs that leads to rapid increase in market value. Transdermal drug delivery technologies are becoming one of the fastest growing sectors within the pharmaceutical industry. Advances in drug delivery systems have increasingly brought about rate-controlled delivery with fewer side effects as well as increased efficacy and constant delivery.

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