Advanced Drug Delivery Reviews 72 (2014) 127–143

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Ultrasound mediated transdermal drug delivery ☆

Aharon Azagury [a], Luai Khoury [b], Giora Enden [b], Joseph Kost [a,*]

[a] Department of Chemical Engineering, Ben-Gurion University, Beer-Sheva 84105, Israel
[b] Department of Biomedical Engineering, Ben-Gurion University, Beer-Sheva 84105, Israel

ARTICLE INFO

Available online 22 January 2014

Keywords:
Sonophoresis
Transdermal drug delivery
Ultrasound
Transport phenomena
Models and simulations
Synergistic effects of ultrasound
Safety

ABSTRACT

Transdermal drug delivery offers an attractive alternative to the conventional drug delivery methods of oral administration and injections. However, the stratum corneum serves as a barrier that limits the penetration of substances to the skin. Application of ultrasound (US) irradiation to the skin increases its permeability (sonophoresis) and enables the delivery of various substances into and through the skin.
This review presents the main findings in the field of sonophoresis in transdermal drug delivery as well as transdermal monitoring and the mathematical models associated with this field. Particular attention is paid to the proposed enhancement mechanisms and future trends in the fields of cutaneous vaccination and gene therapy.
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☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Ultrasound triggered drug delivery".

* Corresponding author at: Department of Chemical Engineering, Ben-Gurion University of the Negev, POB 653, Beer-Sheva 84105, Israel. Tel.: +972 8 646 1212/3; fax: +972 8 646 1023.
E-mail address: kost@bgu.ac.il (J. Kost).

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http://dx.doi.org/10.1016/j.addr.2014.01.007

1. Introduction

Effective therapeutic outcome requires not only proper drug selection but also an effective drug delivery system. The human skin is a readily accessible surface for drug delivery. Transdermal drug delivery—the delivery of drugs across the skin and into systemic circulation—is distinct from topical drug administration, which targets local areas. Transdermal drug delivery offers several important advantages over more traditional dosage forms such as oral delivery and injections, including elimination of first pass metabolism and minimization of pain. The steady permeation of a drug across the skin allows for long-lasting and more consistent serum drug levels, often a goal of therapy [1]. (See Table 1.)

In spite of major research and development efforts in transdermal systems and the many advantages of the transdermal route, low permeability of the human skin remains a major hurdle that limits the usefulness of the transdermal delivery approach. It is well accepted that the stratum corneum (SC), the uppermost layer of the skin, is the major rate-limiting barrier to molecular diffusion through the mammalian epidermis. Due to the fact that most drugs do not permeate the skin in therapeutic quantities, chemical and physical approaches have been examined to transiently lower the SC barrier properties and enhance transdermal transport. Illustrating the problem is the fact that as of today, drugs that are administered across the skin are of low molecular mass (<500 Da) and very lipophilic in nature at low dosages [1]. Hydrophilic solutes generally exhibit poor skin permeability (10^{-7}–10^{-8} cm/s), about one or more orders of magnitude lower than hydrophobic solutes [2].

For protein and peptide drugs, the transdermal route has the potential of being an extremely efficient delivery domain. Topical application avoids the effects of both gastric degradation and hepatic first-pass metabolism; it presents a large surface area for absorption (approximately 2 m^2) and has relatively low proteolytic activity. The skin is undoubtedly one of the most easily accessible organs of the body. Of course, as mentioned above, the molecular size of the transported agents precludes their passive delivery through skin at effective therapeutic concentrations.

The chemical approach using chemical penetration enhancers (CPEs) for enhancement of transdermal mass transport has long been used, especially in cosmetics. CPEs are divided into chemical groups such as: sulfoxides, pyrrolidones, fatty acids, alcohols, surfactants, metabolic interventions, and the only specifically designed material designated to enhance transdermal mass transport, Azone. Most CPEs enhance transdermal mass transport by interacting with the intercellular lipid domain of the SC. Although many chemicals have been evaluated as CPEs in human or animal skins, to-date none has proven to be ideal because of suspected pharmacological activity or unresolved safety issues [3].

Table 1
Absorption coefficients (α) at 1 MHz Ultrasound for various organs [28].

Material	α (dB/cm)
Blood	0.18
Lung	40
Liver	0.9
Brain	0.85
Kidney	1.0
Spinal cord	1.0
Lens of eye	2.0
Skull bone	20
Fat	0.6
Muscle (across fibers)	3.3
Muscle (along fibers)	1.2
Water	0.0022

Several physical approaches for skin penetration enhancement, such as stripping of the SC, micro-needles, heating, iontophoresis, electroporation, and ultrasound have also been evaluated [4].

1.1. Micro-needles

Micro-needles are designed to create a physical pathway through the upper epidermis to increase skin permeability. They are applied to the skin surface and pierce the outer epidermis layer (which contains no nerves) deep enough to increase skin permeability and allow drug delivery, but superficially enough not to cause any pain through the sensory receptors of the dermis. For example, individual silicon needles 150 μm in length and 80 μm in base diameter are fabricated onto arrays of 3 × 3 mm (approximately 400 needles), or needles with hollow centers, each containing a bore of 5–70 μm through which drugs can be administered [5].

1.2. Laser cell-ablation

Laser cell-ablation to remove the SC barrier by controlled ablation has also been investigated as a means of enhancing topical drug delivery. Laser such as erbium – yttrium-aluminum-garnet (YAG) – was found to increase skin permeability. The molecular size, lipophilicity, and sequence of the peptides were found to play important roles in modulating the delivery enhancement. In an in vivo study, mouse skin was treated with laser followed by skin vaccination with a lysozyme antigen. It was demonstrated that laser treatment with no adjuvant or penetration enhancer enhanced the production of antibodies in the serum 3-fold [6].

1.3. Radio-frequency (RF) cell-ablation

Radio-frequency (RF) cell-ablation is performed by placing an array of microelectrodes on a body area (i.e., skin) and passing an alternating electrical current at a frequency of 100–500 kHz (radio frequency) through the area. The ions in the cells adjacent to the microelectrodes vibrate as they try to follow the change in electrical current direction. These vibrations generate heat, which causes water evaporation, cell ablation, and possibly damage of deeper skin layers. RF micro-channels are created by placing a closely spaced array of tiny electrodes with very precise dimensions against the skin. The alternating electrical current is transferred through each of the microelectrodes, ablates the cells underneath each electrode, and forms microscopic passages in the SC and in the outer dermis [7,8].

1.4. Iontophoresis (IP)

The iontophoretic method is based on the repulsion forces of same charges. It involves the application of small electric current (up to 0.5 mA/cm^2) to a drug reservoir wetting the surface of the skin, with the same charged electrode as the solute of interest. This produces repulsion that effectively drives the solute molecules across the SC towards the opposite electrode, which is placed elsewhere on the body [9]. Iontophoresis can enhance the penetration of uncharged molecules into the skin as well. When an electric field is applied to a solution consisting of charged ions, the charged ions are forced to move in the direction of the field. Due to viscous forces the entire solution undergoes a convective flow that carries non-charged particles as well. This process is referred to as electro-osmosis [10].

1.5. Electroporation

Electroporation, originally used to transfect cells with macromolecules such as DNA, involves the application of a pulsating electrical field at high voltage (>50 V, typically 1–100 ms) to the skin. This causes the formation of transient aqueous pores in the SC, through which

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