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Review

Next generation intra- and transdermal therapeutic systems: Using non- and minimally-invasive technologies to increase drug delivery into and across the skin

Taís Gratieri [a], Ingo Alberti [b], Maria Lapteva [b], Yogeshvar N. Kalia [b,*]

[a] Faculdade de Ciências da Saúde, Universidade de Brasília, Campus Universitário Darcy Ribeiro, s/n, 70910-900 Brasília, DF, Brazil
[b] School of Pharmaceutical Sciences, University of Geneva & University of Lausanne, 30 Quai Ernest Ansermet, 1211 Geneva, Switzerland

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ABSTRACT

The number of drug molecules approved by the regulatory authorities for transdermal administration is relatively modest – less than two dozen. Many other therapies might benefit from the advantages offered by the transdermal route. That they have not already done so is due to the exceptional efficacy of the stratum corneum as a diffusional barrier and its remarkable ability to restrict molecular transport. As a result only extremely potent therapeutics possessing the necessary physicochemical properties can be delivered by passive diffusion across intact skin at pharmacologically relevent rates. This has led to the development of several delivery technologies that might be used to expand the range of medicinal agents that can be administered transdermally with the requisite delivery kinetics. There are essentially two approaches: (i) provide an improved driving force to increase the rate of transport (i.e., act on the molecule) or (ii) modify the properties of the microenvironment through which diffusion must occur (i.e., act on the stratum corneum). The challenge for the latter approach is to compromise the barrier in a reversible and relatively painless manner that minimises irritation, is practical for chronic conditions and has minimal risk of infection. Here, we review some of the physical methods that have been used to either transiently perturb the skin barrier or to provide additional driving forces to facilitate molecular transport with a particular focus on technologies that have either led to marketed products or have at least reached the clinical development stage.

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* Corresponding author. Tel.: +41 22 379 3355; fax: +41 22 379 3360.
E-mail address: yogi.kalia@unige.ch (Y.N. Kalia).

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1. Introduction

Transdermal drug delivery is generally well-liked by patients – it is usually second only to the oral route in terms of preference – and indeed for certain indications it may not only be more convenient but also more efficacious to "put on a patch" rather than to "pop a pill". However, to-date only two dozen or so drugs have been approved by the regulatory authorities for transdermal administration. The problem is that the stratum corneum is an exceptional diffusional barrier whose molecular architecture and composition ensure that only extremely potent therapeutics can be delivered at pharmacologically relevent rates into the body. The lipidic nature of the intercellular space – the principal transport pathway – means that transit of polar, hydrophilic molecules is rendered especially difficult.

As a consequence, several delivery technologies have been developed in order to expand the range of medicinal agents that can be administered transdermally – in particular, with a view to improving the delivery of hydrophilic drugs. A second objective has been to modify the kinetics of drug delivery. One of the principal advantages of the transdermal route is that a zero-order input is easily achieved; this ensures that drug levels in the blood remain relatively constant and avoid the peak-trough variations seen with multiple oral dosing. This can be of significant therapeutic benefit for certain indications where constant stimulation of receptors or continuous interaction with other molecular targets is required and for drugs having a narrow therapeutic index. However, this is frequently coupled with a slow onset of effect – passive transport across the epidermis and the dermis and entry into the systemic circulation is a multistep process that can give rise to significant lag-times before steady state is attained. Thus, not only was there a drive to enable the delivery of different drugs across the skin but also a push to have "faster" transdermal delivery.

It is certainly not difficult to remove the stratum corneum, sandpaper will suffice, but the challenge is to do this in a reversible relatively painless manner that minimises irritation, is practical for chronic conditions and with minimal risk of infection. To be able to increase delivery across intact skin would offer obvious advantages and penetration enhancers have been used in formulations for a long time but their use is an uneasy marriage that balances efficacy with the risk of irritation. Hence, the quest for physical methods to transiently perturb the skin barrier or to provide additional driving forces that facilitate molecular transport.

Here, we provide an overview of some physical methods that have been used to expand the range of molecules that can be considered for transdermal administration and to modify drug delivery kinetics. Emphasis is given to technologies that have either led to marketed products or have at least entered into clinical trials.

2. Non-invasive methods – intact skin

2.1. Iontophoresis

Iontophoresis involves the application of a mild electric potential gradient in order to create a flow of current from the device into the skin. The passage of current necessitates the conversion of an electron flow into an ion flow at the electrode interface. Hence, iontophoresis is ideally suited to facilitate the transport of hydrophilic ionisable molecules that are usually not good candidates for passive transdermal delivery (Kalia et al., 2004).

In simple terms, an iontophoretic system comprises two electrodes – the anode (positive electrode) and the cathode (negative electrode) – a microprocessor, a battery or a power supply and a drug reservoir (Subramony et al., 2006). The "active" electrode compartment contains the drug formulation and the circuit is completed by the "return" electrode placed at an adjacent area on the skin. The application of an electric field results in a flow of current generated by the ordered movement of ions present in the formulation and in the skin. This is referred to as electromigration (EM) and is usually the dominant electrotransport mechanism. Under physiological conditions the skin acts as a cation-selective membrane (with a pI of ~4–4.5) and a convective solvent flow is generated in the anode-to-cathode direction, which is referred to as electroosmosis (EO) and provides a second (minor) mechanism for the electrically-assisted delivery of cations and also enables the electrotransport of neutral molecules from the anode (Pikal, 1990). Anions are delivered exclusively by electromigration from the cathode (Kalia et al., 2004). In addition to expanding the range of drugs that can be considered for administration by the transdermal route, the key advantage of iontophoresis is the control that it affords over delivery kinetics.

Unlike almost all other enhancement methods, it acts principally on the molecule by introducing a second driving force – the electrical potential gradient – in addition to the concentration gradient across the skin (Gratieri and Kalia, 2013). The rate and extent of drug delivery are determined by the duration, intensity and profile of current application. As such, complex drug delivery kinetics – determined solely by the current profile – are feasible without recourse to an infusion pump. This was amply demonstrated in studies carried out in Yorkshire swine investigating the feasibility of delivering zolmitriptan (MW 287.4 Da) – used for the treatment of migraine. An iontophoretic patch system and a complex multistep current profile were used to deliver zolmitriptan at faster rates than those from oral dosage forms. The drug was detected in the blood after only 2.5 min. The study also showed that the drug levels in the blood (7.1 ± 1.7 and 11.9 ± 2.0 ng/ml at $t = 30$ and $t = 40$ min, respectively) closely followed the variations in the applied current (4-step profile with current intensities ranging from 0.35 to 0.05 mA/cm^2) and extrapolation of the results to humans suggested the feasibility of delivering therapeutically relevant amounts of drug (Patel et al., 2009). The ability to modulate delivery via the applied current enables easy individualisation of therapy and the presence of a microprocessor means that the device can serve as a data resource that can be easily tapped to provide information for the clinician in our increasingly "connected" environment.

Iontophoresis is not a new technology and the proof-of-principle was demonstrated early in the last century. Since then several portable power supplies have been developed that are used in combination with fill-on-site patches, which typically consist of an absorbent material that imbibes an aqueous drug solution (e.g., dexamethasone sodium phosphate or lidocaine (Zempsky et al., 1998)); such systems have been frequently used in physical therapy. The challenge has been to develop pre-filled iontophoretic patch systems akin to conventional transdermal patches that are now in routine use. It is fair to say that progress has been slow but nevertheless, three pre-filled iontophoretic patch systems have been approved by the US Food and Drug Administration. This makes, iontophoresis one of the most mature/successful physical enhancement strategies for improving drug permeation across the skin.

The first pre-filled commercial iontophoretic patch systems approved by the FDA was LidoSite™ (Vyteris Inc., Fair Lawn, NJ, USA), which provided rapid local delivery of lidocaine for fast dermal anaesthesia. The system consisted of a disposable pre-filled patch, re-usable battery-powered controller and a flexible interconnect module. The hydrogel matrix patch incorporated Ag/AgCl electrodes and a lidocaine hydrochloride/epinephrine dispersion in the anode. NaCl was also added to the anodal compartment to