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Editorial

Theme Section: Transdermal Delivery of Proteins

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GUEST EDITOR'S VIEWS ON TRANSDERMAL DELIVERY OF PROTEINS

Where is the field of transdermal delivery of proteins going and how do the articles in the theme section fill the gap?

Transdermal delivery products currently on the market tend to contain small moderately lipophilic drug molecules, which can be delivered through the skin. Opportunities in transdermal delivery can be expanded to include small water soluble drugs as well as macromolecules, such as therapeutic proteins, by several enhancement technologies that are being actively investigated. One promising technique is iontophoresis, which involves the use of a small electric field to push charged drug molecules into the body. Iontophoresis has been used for localized delivery of drugs for many years but recently has seen some success for systemic drug delivery from a pre-filled wearable iontophoretic patch. This has been made possible by the advancement in the field of iontophoretic drug delivery. Several academic groups, especially Professor Richard Guy's group at University of Bath, have contributed significantly to an understanding of transdermal delivery of proteins by iontophoresis as well as by other enhancement technologies. Our laboratory, as well as Dr. Kalia's group, who is a contributor to this theme section, have contributed to this field in addition to excellent contributions from Alza and other companies. Iontophoresis is generally believed to have a size limitation of about 10 kDa for systemic drug delivery. However, one of the papers in this Theme Section reports that delivery of a 12.4-kDa protein by iontophoresis is feasible. There is some clinical literature, which suggests that localized delivery of much larger molecules is possible by iontophoresis.

Iontophoresis cannot deliver all proteins through the skin and researchers are investigating several other enhancement technologies, including thermal microporation, microneedles, and phonophoresis. Recently, considerable excitement has been generated around skin microporation technology, which involves the creation of micron dimension transport pathways in the skin using a minimally invasive technique, such as microneedles, thermal microporation or radiofrequency ablation. This theme section has two articles on skin microporation, one on the development of coated microneedles and the other on the use of thermal microporation for delivery of interferon across skin. Phonophoresis or the use of ultrasound energy is another promising technology for transdermal delivery of macromolecules and is discussed in one of the papers in this theme section. However, the miniaturization of ultrasound systems has not yet advanced to the point of enabling wearable patches as is now possible for iontophoretic patches. The paper in this theme section demonstrates the use of lightweight cymbal arrays, which will help to move towards this goal of miniaturization.

What are the challenges for transdermal delivery of protein drugs and how can these be overcome?

Several protein-based drugs are currently in clinical trials for transdermal delivery. Although transdermal delivery of protein drugs is an exciting opportunity, there are still several challenges to overcome. One challenge is that bioavailability currently tends to be low for some of the enhancement methods and this would be of concern, especially considering the high cost of many protein drug molecules. High bioavailability is desired to meet dosing requirements with a reasonable patch size. Bioavailability can be increased by using coated microneedles, where feasible, or by optimized formulation or device design. Some challenges may be specific to the enhancement technology being used. For example, there is a limit to the size of the molecule that can be delivered by iontophoresis. For iontophoresis, a high isoelectric point is desirable so that the drug does not precipitate within the skin. Technologies involving the creation of physical openings in the skin for protein delivery, may present an increased risk of infection.

As with conventional transdermal patches, irritation, patch fall-off and the effect of heat application will have to be minimized for a product to be successful and achieve FDA approval. Since the skin is an attractive site for immunization, there may be a greater immune response, which will depend on the nature and purity of the protein being delivered. The extent of immune response and how it affects treatment efficacy, needs further investigation. Also, the skin has proteolytic enzymes (though proteolytic activity is less compared to other mucosal routes) that may degrade the protein drug as it travels through the skin. We generally focus on how much of the protein has been delivered intact through the skin. More studies are needed to better understand the proteolytic barrier in the skin and its potential effect on protein drug delivery.

EDITORIAL FOR THEME SECTION/DR. AJAY K. BANGA

Significant strides have been made in drug delivery research in recent years, and several products have been commercialized, especially for oral and parenteral delivery. Of the various other routes investigated, transdermal drug delivery has achieved commercial success, with several drugs now in the market, including clonidine, estradiol, fentanyl, methylphenidate, nicotine, nitroglycerin, oxybutynin, scopolamine, selegiline, and testosterone. In addition, the estrogen/progestin combination patch for birth control is available. These drugs tend to be small moderately lipophilic drug molecules. Many of the new drugs are now protein-based, and these hydrophilic macromolecules do not diffuse through the skin. Some other routes such as pulmonary have shown promise for delivery of proteins and inhaled insulin has been recently commercialized. However, skin is an appealing site for drug delivery and in recent years, nontraditional enhancement technologies are being explored to enable the delivery of these molecules through the skin. These enhancement techniques include the use of electric energy (iontophoresis and electroporation), ultrasound (phonophoresis, also known as sonophoresis) or minimally invasive techniques such as skin microporation (microneedles, thermal microporation, and radiofrequency ablation).

Iontophoresis has been used for localized delivery of steroids or lidocaine using external palm sized power sources for several years. More recently, research has enabled the development of wearable self contained patches for systemic delivery of drugs. One systemically acting drug that has been recently approved for iontophoretic delivery from a pre-filled patch is fentanyl hydrochloride. The compact self contained iontophoretic patch (IONSYS™; Alza) is used in hospitalized patients for short-term management of acute postoperative pain as an alternative to a morphine PCA pump. The patch delivers a 40 μg dose of fentanyl over the course of 10 min when the patient activates dosing by pressing a button on the patch. A partial listing of companies pursuing iontophoresis include Alza, Iomed, Vyteris, Travanti Pharma, and Transport Pharmaceuticals. Other companies may work in collaboration with one of these companies to pursue development of an iontophoretic patch for a specific drug molecule of interest. Hydrophilic charged macromolecules such as polypeptides fit all the criteria needed for iontophoretic delivery. Factors affecting transdermal iontophoretic delivery include size, charge, structure and lipophilicity. Polypeptides, which have a high isoelectric point are ideal candidates as they retain their charge during transport into and across the skin. Iontophoresis is generally believed to deliver polypeptides up to a MW of about 10 kDa. The research paper by Dr. Kalia's group in this theme section documents the delivery of a 12.4-kDa protein by iontophoresis and proposes that polypeptide charge can compensate for molecular weight and that electric mobility is the key parameter in governing peptide electrotransport. The paper also suggests that the three dimensional structure of proteins may also be important in determining transport across the skin. Most of the other skin enhancement technologies rely on permeabilization of skin by use of physical energy, which acts on the outer layers of the skin. However, the electrical current applied during iontophoresis primarily acts on the drug itself.

Skin microporation is an exciting technology that is actively being investigated for transdermal delivery of water soluble small drugs and macromolecules such as proteins and vaccines. It involves the creation of micron dimension transport pathways in the skin using a minimally invasive technique, such as microneedles, thermal microporation or radiofrequency ablation. These micron sized pathways are much smaller than the holes made by hypodermic needles but they are much larger than the size of macromolecules and can allow the delivery of dissolved drug molecules of any size, even DNA or monoclonal antibodies (in limited amounts). This theme section has two articles utilizing this technology, one on the development of coated microneedles and the other on use of thermal microporation for delivery of interferon across skin. Mechanical microneedles are typically made of silicon, metal or polymers and combine the effectiveness of needle-based delivery with the patient-acceptance of patch technology. These microneedles are typically 500 μ long, with a radius of curvature at the tip of about 1 μ, allowing easy penetration into the skin. A partial listing of companies pursuing microneedle technology includes Alza/Macroflux, Becton Dickinson, Corium, 3M, Norwood Abbey, Silex Microsystems, and Texmac. These companies may work in collaboration with pharmaceutical company partners to pursue development of a microneedle patch for specific drug molecules. An applicator can be used to apply the microneedles on the skin to create the micropores followed by patch application. Alternatively, the drug can be coated directly on the microneedles. The latter approach has been used for vaccine delivery since the amount of protein antigen needed to generate immune response is very little and the dose can be accommodated by coating on the microneedles. The paper from Dr. Prausnitz's group in this theme section investigates the coating of model proteins on microneedles using various formulations.

Thermal microporation involves thermal ablation of the stratum corneum to create microchannels in the skin. It is accomplished by the application of a short pulse of electrical current to an array of metallic filaments, which convert electricity to thermal energy. The rapid creation and conduction of thermal energy into the surface of the skin, in an area about the width of a human hair, painlessly ablates the stratum corneum under each filament to create an array of aqueous microchannels. After the microchannels are formed, the protein patch is applied using a simple fold-over

design that aligns it with the newly formed microchannels. This technology is being developed by Altea Therapeutics. This theme section has one paper, which demonstrates delivery of interferon alpha-2b, a 19.3-kDa protein, across the skin using thermal microporation.

Phonophoresis or sonophoresis is another transdermal enhancement technology that can enable delivery of macromolecules across the skin. This technology uses sound waves with a frequency beyond 20 kHz to drive molecules into the skin. A coupling medium is needed and several mechanisms have been proposed for delivery, including cavitation, acoustic microstreaming, heating or radiation pressure. Recently, it has been suggested that phonophoresis also creates micropores in the skin. Companies active in this area include Dermisonics and Sontra Medical. Miniaturization of these ultrasound applicators has not advanced to the point of enabling wearable devices as is now possible for iontophoretic patches. The paper from Dr. Smith's group in this theme section demonstrates the use of lightweight cymbal arrays, which will help to move towards this goal of miniaturization.

Several other enhancement technologies can also be utilized to enable transdermal protein delivery. These are not discussed in this theme section but a partial list includes laser assisted thermal ablation (Norwood Abbey), RF-microchannels (TransPharma), controlled heat assisted delivery (Zars), particle-mediated immunization (PowderMed) or the possible use of dermabrasion, chemical enhancers or carrier molecules like liposomes or cyclodextrins.

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