Pharmaceuticals Charging Through

Transdermal drug delivery offers numerous advantages over other more commonly used techniques. However, the size of a pharmaceutical's molecules has traditionally been a limiting factor in terms of the type of drug that could benefit from this method. Iontophoresis is a technology that increases the size of the molecule that can non-invasively pass into the body through the skin. This article examines this option.

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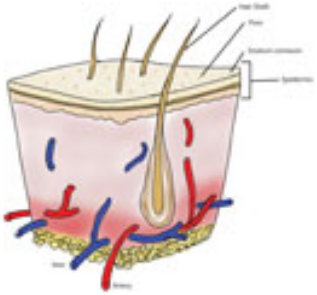


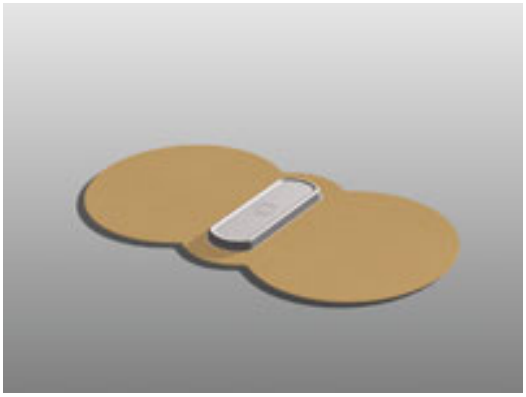
In iontophoresis, a power source is used to drive drug carrying molecules through the skin.

Two of the most common methods for administration of pharmaceuticals are oral and injection. In some cases, however, neither of these administration routes is desirable, leading drug manufacturers to explore alternate forms of drug delivery. Transdermal drug delivery is an increasingly popular drug delivery method, as it has many advantages over the two traditional routes. With transdermal delivery, issues associated with the use or disposal of needles are obviated. Furthermore, since the drug does not pass through the digestive tract, adverse gastrointestinal effects and potential metabolism issues are reduced. Transdermal drug delivery allows for the administration of drugs over a prolonged time period and imposes little burden to the patient.While transdermal drug delivery appears simple in principle, the design of delivery systems for larger, more sophisticated molecules poses a greater challenge. This article describes some of the physiologic limitations and discusses

developmental considerations for advanced transdermal drug delivery systems.

Permeating the Skin

The skin is the body’s first line of defense, preventing the ingress of foreign substances. The outermost layer of the skinthe stratum corneum (the horny layer)consists of approximately 15 to 20 layers of dead skin cells that allow water to pass, keeping the skin hydrated, yet providing a protective barrier to prevent foreign substances from entering the body. In addition to water, however, small proteins and molecules with a molecular weight of up to about 500 Daltons can diffuse through the stratum corneum. This characteristic led to the development of passive patches for treatment of motion sickness in the 1970s, and more recently, nicotine patches for smoking cessation.While passive patches that rely on diffusion are an effective delivery method for small molecules, alternate delivery methods are necessary as the size and complexity of the target molecule increases. Active patches use energy to disrupt the stratum corneum and “actively” drive larger molecules, not ordinarily able to passively penetrate the stratum corneum, into the body. There are numerous methods for enabling large molecules to cross the stratum corneum, including thermal ablation, electroporation, sonophoresis, and iontophoresis. Iontophoresis is of particular interest, as it is a non-invasive method that does not create pores through the stratum corneum, thereby enabling drug delivery without compromising the protective function of the skin.
Iontophoresis relies on the use of an electric current to drive the uptake of an ionized pharmaceutical agent. The pharmaceutical agent, which acts as the current carrier, is contained in an electrode pad which is placed under one electrode (the active electrode). A second electrode (the return electrode) is used to complete the circuit, with the primary current path between the active and return electrodes being the patient’s skin. When power is applied, the active electrode repels the pharmaceutical agent, thereby forcing it into the skin. Since iontophoresis can be used to deliver either positively or negatively charged drugs, the drug formulation determines whether the cathode or the anode electrode is the active or the return electrode.



Iontophoresis works by increasing the permeability of the outer layer of skin to enable migration of therapeutic agents to the bloodstream.

Iontophoresis is well-understood, pain free, needle free, and enables sustained

delivery, giving it distinct advantages over other delivery methods. Additionally, since the drug is a current-carrying charged molecule, the total drug delivery correlates directly to the current applied and can be controlled using the current density, the current amplitude, duration, and modulation of the current delivery profile. The key disadvantage of iontophoresis is that for some patients, minor skin reactions such as erythema, irritation, or itching at the administration site have occurred. Furthermore, depending on the drug formulation and duration of therapy, some hyperpigmentation may occur.

Iontophoretic Products

Many of the iontophoretic products currently on the market including Vyteris' LidoSite and IOMED's OptimA have an external power source that connects to a patch containing the electrodes and pharmaceutical agent. This allows reuse of the comparably expensive programmable power controller. For products intended to be used in a clinical environment, such as a physical therapy suite, the therapist introduces the fluid formulation into the electrode pad immediately prior to therapy initiation. This greatly simplifies packaging challenges associated with preventing moisture permeation between the electrode pad and the control electronics, as well as maintaining the integrity of the drug formulation over the product shelf life.More recently, however, the trend has been towards the development of a completely integrated iontophoretic system, of which ALZA's E-TRANS is an example. There are several companies developing integrated iontophoretic products. Cambridge Consultants has been collaborating with NuPathe Inc, a privately held Pennsylvania-based company for the development of one such product.

The NP101 Migraine SmartRelief

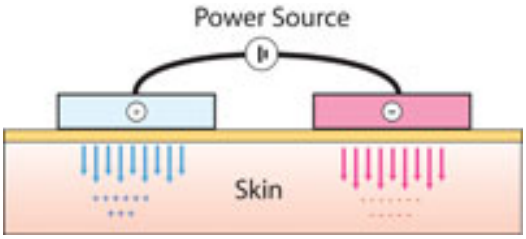
NuPathe is currently in the process of developing its first integrated iontophoretic patch for the delivery of sumatriptan succinnate for acute migraine relief. While NuPathe is working with a multitude of compounds for assorted therapies, its latest-stage product, the NP101 Migraine SmartRelief, is a fully integrated iontophoretic patch. In Phase 1 clinical trials, the NP101 demonstrated successful delivery of therapeutic drug levels over a sustained time period. The successful development of an integrated, single-use disposable iontophoretic product is no small feat, as this combination product requires careful development of the drug formulation, return formulation, electrode pads, electrodes, electronics, and control algorithms. Over the course of the development process, each of these elements must be carefully considered to achieve the design goals while managing complexity.
It is useful to elaborate on the critical elements of an iontophoretic patch, thereby providing a clearer understanding of the design challenges pharmaceutical companies face in expanding transdermal drug delivery therapies.

Formulation

The formulation should be electrically conductive, and typically, should have high water content consisting of a salt solution or a hydrogel formulation with saline components. The active ingredient must have an ionic charge, yet ideally, the remaining components should not have an ionic charge lest they compete with the

active ingredient. The size of the active molecule determines its mobility, which in turn drives uptake and the biologic response to the chemical entity. If there are competing ions in the formulation, it is preferable for them to be larger than the active ingredient to maximize delivery of the drug. Inactive ingredients in the formulation should not unfavorably react with either the skin or the patch electrodes.During iontophoresis, pH changes at the surface of the electrodes can result in damage to the active ingredients, and if uncontrolled, can cause chemical burns. pH changes must be carefully considered during the design process to control this undesirable effect. The inclusion of buffering agents in the formulation can mitigate this risk, but must be added with care, as buffering ions may compete with the active ingredients.
The formulation for the return electrode is less complex; it should include an ionic molecule of the opposite charge to that of the active ingredient. Buffering and minimization of skin irritation should also be considered.

Electrode Pads



NuPathe's NP101 Migraine SmartRelief is designed to be a fully integrated single-use iontophoretic patch.

The electrode pad, the element of the device that carries the drug formulation, must be able to adhere to the electrode as well as the patient and must be of a size and material to carry the formulations. Uniform distribution of the formulation is desirable over the area of the electrode pad.The design complexity of the electrode pads can vary depending on the intended use of the product. If a gel formulation is loaded at the time of manufacture and is packaged until the time of use, the electrode pad and its packaging must prevent pad dehydration, maintain uniform wetness and drug distribution, and not materially degrade or change the composition of the formulation.

Electrodes

The electrode must be of an electrically conductive material, and its geometry should facilitate spreading of the electrical current to enable uniform delivery over the patch area. If the electrode is chemically inert, then electrolysis of water can result in pH changes. The use of active electrodes, comprising an electrochemical cell, in conjunction with a formulation which contains a solution of the ions of the cell (i.e., a Ag-AgCl electrode with a solution containing Cl- ions), results in greater stability of the pH at the skin. If an active electrode is used, then there is an additional design requirement to ensure that a sufficient amount of the reactive elements are chemically available for the desired dosing period.The design of the

electrode geometry determines current density, which in turn, affects delivery efficiency. The current density can have an impact on the biological response. It has been documented that to minimize the likelihood of skin injury, the current density should be less than 1 mA/in2.1

The manufacturing method of the electrodes can also affect the performance of active electrodes. The most common methods for creating electrodes are screen printing or deposition on a substrate. Various process parameters can affect the surface finish, thickness, and uniformity of the electrode, which all in turn affect the electrochemical behavior of the electrodes.

Electronics and Control

The quantity of drug delivered by an iontophoretic patch, determined by the amount of current applied to the patient and the time period over which the current is applied, is typically measured in mA-minutes. The therapeutic effect of the drug delivery, often measured via pharmacokinetic studies of drug level in the blood, also depends on peak current and duration of treatment. The power source typically supplies a constant, voltage-limited current to the electrodes. Although the load resistance varies from patient to patient, the drug delivery profile should remain the same. In applications where it is desirable for the user to have partial control over the dosage, a user interface with current or dosage setting parameters is necessary. In other applications, a bolus dose is delivered immediately to achieve therapeutic levels quickly, and a lower amount of drug is delivered for a prolonged therapy period. For some applications, such as break-though pain control, it is advantageous to offer a bolus on-demand capability.

Vyteris' LidoSite incorporates a reusable external power source to control disposable iontophoretic patches.

In all of these applications, the electronics and software are customized to achieve the desired therapy profile. Design complexity affects the final cost of goods sold, and is often more significant for single-use disposable patches with integrated electronics than for products with a reusable power source.

Conclusion

As drug delivery technology develops, the transdermal drug delivery route is becoming a promising alternative route of administration for pharmaceutical

companies. Transdermal drug delivery is convenient and attractive to the patient, while enabling the effective delivery of large drug molecules. Iontophoresis provides non-invasive delivery of charged particles that otherwise would not permeate the skin. While the principle of iontophoresis is basic relative to other available methods, the successful creation of an iontophoretic product is challenging and requires a deep understanding of the interdependent system elements. As pharmaceutical companies are increasingly looking to combination products to maximize delivery efficiency and patient compliance, it is important to understand and integrate the device development with the traditional formulation work at the earliest opportunity so that the benefits of this technology can be realized.

References

1 Costello, Charles T. and Jeske, Arthur H. “Iontophoresis: Applications in Transdermal Medication Delivery.” *Physical Therapy*. 75:6 (1995): 554.
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