TRANSDERMAL MARKET

The Future of Transdermal Drug Delivery Relies on Active Patch Technology

By: Jason McKinnie, Frost & Sullivan Analyst

INTRODUCTION

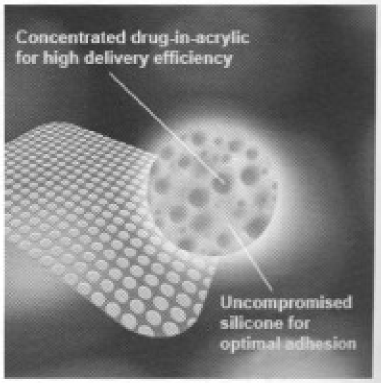
For 25 years, passive patch technology has dominated the transdermal drug delivery industry. Evolving from the simplistic drug reservoir to a complicated matrix design, passive patches have navigated many of the difficulties of transdermal drug delivery and overcome obstacles by utilizing better adhesives, increased drug storage, and better regulated release, all with decreasing overall patch size. Despite these accomplishments, drugs eligible for transdermal delivery must meet certain physical criteria and not require immediate absorption into the body. The specific requirements for delivery limit the type of drugs available and the market potential for this technology. Companies are now finding ways of expanding the portfolio and opening up new markets through development of new passive technologies, and more importantly, through development of active patches that utilize an external energy source.

PASSIVE PATCHES CREATED THE MARKET BUT HAVE LIMITED POTENTIAL

There are multiple indications presently associated with transdermal delivery, such as hormone replacement therapy, contraception, and pain management, but targeting only these indications and applications severely limits the market potential for transdermal drug delivery. Passive patches have advanced in technological capabilities and are now being used to target other indications, such as central nervous system disorders. The DOT Matrix technology developed by Noven Pharmaceuticals revolutionized passive transdermal delivery and enabled patches to become smaller in size with better adhesion characteristics. The patch's unique concept of storing the drug in an acrylic mix and using a thin layer of silicone to provide adhesion allowed for the storage of additional drug and provided the technology for the first estrogen/progestin combination patch. Noven Pharmaceuticals is developing this patch for many other indications and recently launched Daytrana, a patch based on DOT Matrix technology (Figure 1) for the treatment of Attention Deficit Hyperactivity Disorder. The improvements in passive patch technology are leading to development of more small molecules for transdermal drug delivery, but they are still limited to developing compounds within a narrow range of physical characteristics.

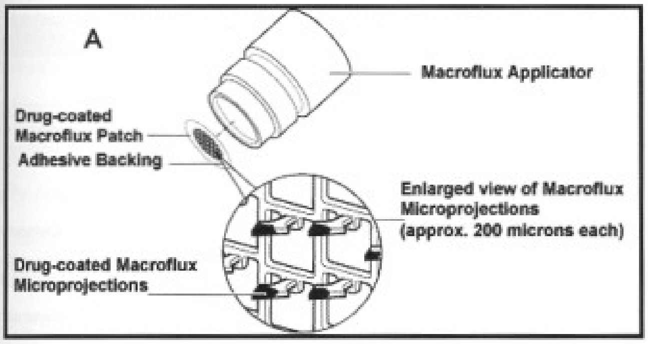
Some companies are attempting to expand the capabilities of passive patches by eliminating the use of the skin as the rate-controlling membrane. Bypassing the stratum corneum allows for the delivery of larger molecules with properties uncharacteristic of typical transdermal drugs. Alza Corporation has developed a device, Macroflux (Figure 2A), which delivers

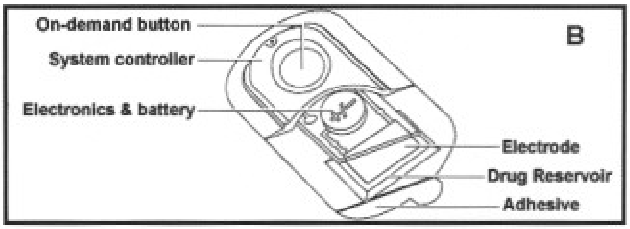
FIGURE 1

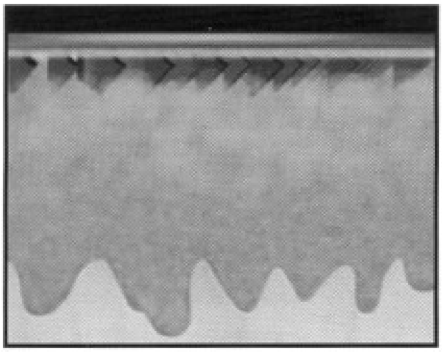


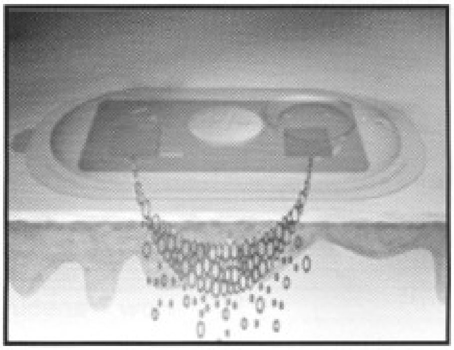
The circular image is a digital photograph of the adhesive layer of a DOT Matrix® patch taken with a scanning electron microscope.

FIGURE 2









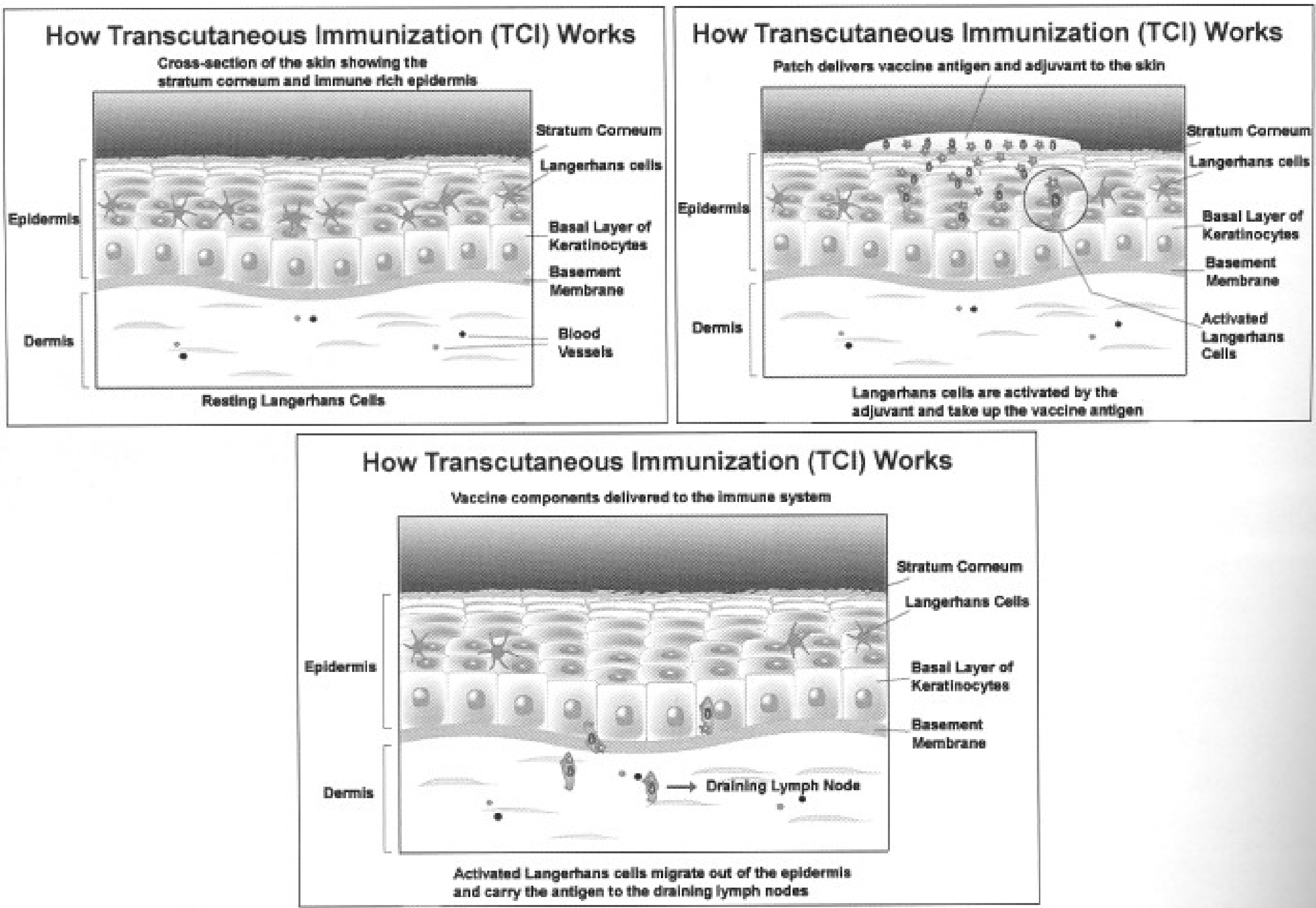
A) Macroflux® technology is designed to enable painless convenient patient administration of therapeutic proteins and vaccines. B) E-TRANS® electrotransport technology enables patient-controlled, pulsatile, and macromolecule delivery through intact skin.

a patch with microprojections on it that extend through the stratum corneum. The projections, ranging from 125 to 175 microns in length, extend past the stratum corneum but do not reach the layers of skin with nerves. The patch causes no pain to the patient, and the mechanism for which the patch is applied can be reused. This method is only ideal for potent drugs, as only 100 micrograms of a compound can be delivered, but it is seen as a potential application for vaccinations. Iomai Corporation is another company seeking to bypass the stratum corneum, but it is accomplishing that with a slight abrasion before patch application. Iomai's Transcutaneous Immunization (TCI) technology (Figure 3) is being developed for vaccination of several diseases, including travelers' diarrhea and anthrax. The system uses a device to remove the stratum corneum through a mild abrasion and then places the patch over the area for 1 to 6 hours. The patch contains an adjuvant LT toxin and disease antigen that work together for activation of the Langerhan's cells. These cells then travel to the lymph nodes where the immunization process takes place. Both technologies circumvent the stratum corneum but still have limitations due to the physical constraints of the molecules capable of delivery and the slight abrasive nature of the methods.

NEW APPROVALS INTRODUCE ACTIVE DELIVERY TO THE MARKET

The active patch delivery era commenced June 2006 with the launch of Synera, a topical patch from Endo Pharmaceuticals and ZARS Pharma. The lidocaine/tetracaine patch is approved for use as local dermal analgesia for superficial venous access and dermatological procedures. Topical lidocaine has been on the market for years, but Synera differs because of the active delivery system it utilizes. ZARS

FIGURE 3

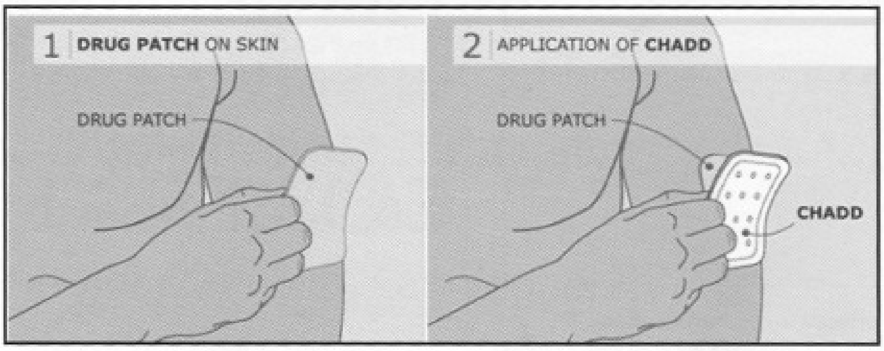


Transcutaneous immunization (TCI) is a new method of vaccination that utilizes the skin. TCI represents a novel combination utilizing established knowledge relating to skin penetration, the potency of adjuvant-based immunostimulation, and data showing that Langerhans cells are highly desirable targets due to their antigen-presenting cell function.

Pharma developed the Controlled Heat-Assisted Drug Delivery (CHADD) technology (Figure 4) to help speed up absorption of the product through heat admission. The technology consists of a pouch filled with a proprietary compound that heats up when exposed to oxygen, and for Synera, the heat admission is approximately 30 minutes. The CHADD technology offers flexibility and can be designed for delivery of heat for up to several hours. ZARS Pharma is currently developing this patch further in different combinations with other topical and systemically delivered drugs.

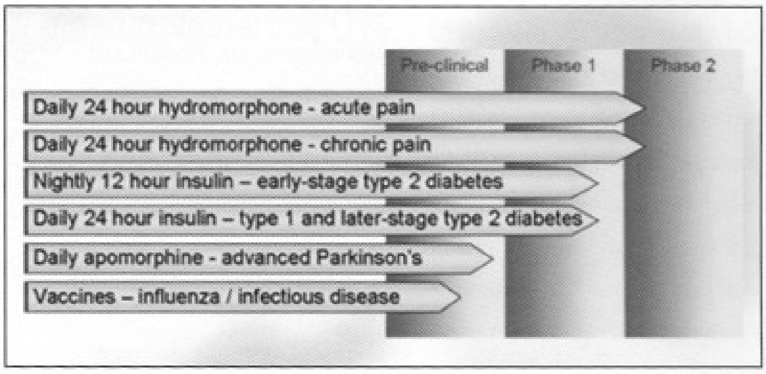
The second active patch delivery system expected to enter the market uses the E-TRANS® (Figure 2B) technology from Johnson & Johnson, developed by their transdermal technology company, Alza Corporation. The E-TRANS fentanyl patch was approved in May 2006 but is not expected to enter the market until early 2007. E-TRANS utilizes electrotransport technology through emission of low-level electrical current. The energy applied allows for fentanyl to quickly enter the body with a similar pharmacokinetic profile to IV-based fentanyl infusion. The most appealing and exciting aspect of this technology is the ability for self-dosing. The patient controls the dose by pushing a button to release the electrical energy, providing similar control to that of an invasive patient-controlled IV pump. In preclinical studies, the device has shown the capability of delivering compounds over 25,000 daltons, making protein delivery a potential application of this technology.

FIGURE 4



CHADD® is a disposable, self-adhesive heating unit that generates heat when exposed to oxygen in the ambient air. The CHADD unit consists of a powder-filled pouch laminated between a top cover film with oxygen-regulating holes and a bottom film with a pressure-sensitive adhesive layer. The heat-generating powder consists of a proprietary chemical mixture.

FIGURE 5

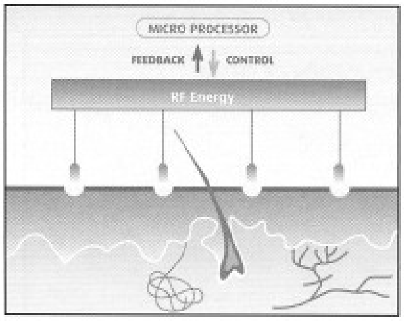


Altea's PassPort® patch opens the way for many more drugs and vaccines to be delivered painlessly via the skin as seen from its pipeline chart.

COMPANIES DEVELOPING NEW TECHNOLOGIES WITH BROAD CLINICAL APPLICATIONS

Altea Therapeutics is developing an active patch capable of delivering compounds over 500 daltons as well as water-soluble drugs. The PassPort technology utilizes rapid bursts of thermal energy to open up microchannels in the skin that bypass the stratum corneum. The technology has a wide array of applications (Figure 5) and is capable of delivering bolus levels, sustained release, and vaccine delivery. The PassPort patch consists of a drug reservoir and screen containing wafer-thin metallic filaments. The application process requires a small hand-held battery device that is used to create the active energy needed for the creation of the microchannels. The patch is attached to the applicator with the metallic screen side of the patch applied to the skin and activated with a click of a button, creating the rapid bursts of thermal energy. This painless process only requires milliseconds and is presently being designed to remain on the skin for up to 24 hours. Once the patch is removed, the microchannels immediately close, returning to the state prior to application. This system shows promise and is in clinical trials for delivery of opioid pain products, insulin, and vaccines. One of the benefits to this

FIGURE 6



TransPharma has applied well-proven RF Technology commonly used in minimally invasive surgery, such as laparoscopic procedures, to create RF-MicroChannels in the skin surface. Each of these RF MicroChannels is of precise dimension to enable reproducible delivery of molecules via a specially formulated patch.

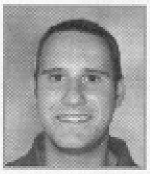
technology is the elimination of heat as a complication because the microchannels eliminate the use of skin as a rate-limiting membrane. Most passive patches rely on the skin as a transfer point of the drug, and when the skin heats up, absorption also increases, which can lead to deadly consequences. Additionally, the company's polymer system enables use of approximately 90% of the drug, helping reduce manufacturing cost and reducing the possibility of abuse in opioid drugs.

TransPharma Medical is developing its own proprietary system that also utilizes the formation of microchannels for transdermal delivery. The ViaDerm system uses radio frequency technology (Figure 6) to create channels in the skin via skin ablation of the stratum corneum. These channels can be 50 microns in diameter, big enough for the largest drug molecules to enter and are stable for up to 24 hours. TransPharma Medical uses a hand-held battery-operated device to create the radiofrequency needed for formation of the microchannels. Through this device and its feedback system, the ViaDerm system can custom create the depth and number of microchannels needed depending on the drug to be delivered and the individual's skin type. These controls make the device safe for human use as well as providing a valuable and accurate transdermal delivery mechanism. The system is capable of delivering a variety of hydrophilic and large molecular weight compounds, but TransPharma Medical is currently focusing on delivery of proteins, specifically parathyroid hormone (PTH) and an undisclosed protein. The protein is placed on the patch in dry powder form and relies on the interstitial fluid, created from the microchannels, to dissolve it and allow for systemic delivery.

SUMMARY

Transdermal drug delivery is still a relatively new field in the pharmaceutical market. The first drugs to utilize patches were of simple design and did not yield much technological creativity until the mid-1990s. Despite the progress in passive patch design, they are only able to adequately deliver small molecular weight compounds with favorable physical properties. Advanced transdermal drug delivery through utilization of an external energy source is now beginning to overcome many of these challenges with potential market availability in 5 years. Once thought to be impossible, active patches are proving they are capable of delivering proteins and providing an alternative to needle delivery, much to the desire of patients and physicians.

BIOGRAPHY



Mr. Jason McKinnie is a Pharmaceutical Research Analyst for Frost & Sullivan in the Healthcare and Life Sciences division. He primarily works in the emerging cancer therapeutics industry, providing insight into pipeline analysis, market forecasts, and industry trends. Mr. McKinnie has worked studies involving emerging cancer therapeutics, which includes creating and distributing surveys with oncologists around the US and conducting interviews with key industry participants. He came to Frost & Sullivan with extensive scientific research in biochemistry in both the academic and industry realm. In addition to his research background, he brings with him real-world healthcare knowledge through his work in a cardiology lab and through his graduate education. Mr. McKinnie graduated in 2004 with a Master of Public Health from Texas A&M University Health Science Center School of Rural Public Health and also earned a BS in Genetics from Texas A&M University.