INTRODUCTION

When you hear the words transdermal drug delivery, what comes to mind? More than likely, you think about a simple patch that you stick onto your skin like an adhesive bandage, such as the nicotine patch. And for good reason, because adhesive transdermal patches, which utilize passive diffusion of drugs across the skin as the delivery mechanism, have been available on the US market for more than 20 years to treat systemic illnesses, and are the predominant transdermal drug delivery (TDD) technology that has been approved by the FDA.

Throughout the past 2 decades, the transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms. Because transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood-level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms.1 In addition, because transdermal patches are user-friendly, convenient, painless, and offer multi-day dosing, it is generally accepted that they offer improved patient compliance.2

Although transdermal drug delivery patches have a relatively short regulatory history compared to other, more traditional dosage forms, the technology has a proven record of FDA approval. Since the first transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness, the FDA has approved, throughout the past 22 years, more than 35 transdermal patch products, spanning 13 molecules.3 The US transdermal market approached $1.2 billion in 2001 and was based on 11 drug molecules: fentanyl, nitroglycerin, estradiol, ethinyl estradiol, norethindrone acetate, testosterone, clonidine, nicotine, lidocaine, prilocaine, and scopolamine.4 Two new, recently approved transdermal patch products (a contraceptive patch containing ethinyl estradiol and norelgestromin, and a patch to treat overactive bladder, containing oxybutynin) should help to expand the US transdermal market.

Clearly, the clinical benefits, industry interest, strong market, and regulatory precedence show why transdermal drug delivery has become a successful and viable dosage form. Yet, the pharmaceutical industry tends to view TDD as a limited technology that serves a niche set of drugs. Certainly, transdermal drug delivery is not suited nor clinically justified for all drugs. And the skin barrier limits the number of drugs that can be delivered by passive diffusion from an adhesive patch. Yet, TDD is viewed to be much more limited than it actually deserves. Several misconceptions exist about transdermal drug delivery that fuel the view that TDD is a limited technology. A recent article in this publication dispelled several myths about the function and capabilities of metered dose inhalers.5 A similar format is used in this article to provide a review of transdermal drug delivery technologies, while dispelling four myths about the function and capabilities of TDD systems and the TDD market.
MYTH 1

The transdermal drug delivery market is stagnant.

In fact, the market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. While it is true that product approvals for new TDD products have not exploded as some predicted following the rapid success of TDD nicotine products in the early and mid 90s, an increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally. TDD product sales in the US have increased by 23% from 2000 to 2001 and by 9% over the same time period in Europe.4

The Japanese market is also strong, despite a lesser number of product approvals compared to the US and European markets. The total market for TDD products in the US, major European markets, and Japan was approximately $2.5 billion in 2001 (this does not include a $1.4 billion market for plaster/poultice products in Japan). The approximate split of global sales among the TDD products is shown in Figure 1. The clear signal from the market is that physicians and patients value the benefits TDD products can provide.

The recent launch of a 7-day contraceptive TDD product (OrthoEvra™) in the US provides an example of the benefits that TDD can provide to a relatively mature
therapeutic area. As shown in Figure 2, total prescriptions for this product continue to show a significant increase, demonstrating the way that patients are responding to the option of a once-weekly TDD product in a market previously dominated by once-daily oral products. In 2002, this contraceptive patch became the second-biggest selling prescription contraceptive on the market.\(^6\)

The outlook for continued growth of the TDD market is very optimistic. Market analysts forecast a low double-digit compound annual growth rate for the US TDD market throughout the next decade. Given the recent trend and product pipeline, this may actually underpredict the potential of the TDD market throughout this time period. The TDD products in late-stage development should continue to fuel the growth of the TDD market and could expand TDD usage into a number of new therapeutic categories, including attention deficit and hyperactivity disorder, Parkinson’s disease, and female sexual dysfunction. New and improved TDD products are also under development that will expand the number of therapeutic options in pain management, osteoporosis, and hormone replacement.

\[\text{FIGURE 2}\]

Total prescriptions of a 7-day contraceptive TDD product (OrthoEvra\textsuperscript{™}) in the U.S

\[\text{Total U.S. Prescriptions for OrthoEvra\textsuperscript{™} 3 Patch Cartons}\]

**MYTH 2**

_Transdermal drug delivery is an old technology._

Interest exists in expanding the function and capabilities of transdermal drug delivery, with many significant innovations in TDD technologies occurring only over the past
decade. A keyword search using the term transdermal drug delivery was performed on the Micropatent Patsearch FullText™ database to obtain the number of transdermal-related US patents granted between 1971 and 2002 and the Medline® (Dialog file 155; covering 1966 to 2003), Embase® (Dialog file 73; covering 1974 to 2003), Biosis® (Dialog file 5; covering 1969 to 2003), and International Pharmaceutical Abstracts (Dialog file 74; covering 1970 to 2003) databases (all provided by Dialog) to obtain the number of transdermal-related research articles published between 1971 and 2002

As Figure 3 illustrates, use of the phrase transdermal drug delivery anywhere in the text of granted US patents has increased continuously since 1977. Figure 3 also shows that use of the phrase transdermal drug delivery in the text of research articles grew continuously in the 1980s, and has remained constant throughout the past decade. These data suggest that innovations in TDD technologies continue to occur at a positive rate, making the technology a fertile and vibrant area of innovation, research, and product development.

Where are the innovations in transdermal drug delivery occurring? Most can be divided into two categories: system innovations and formulation innovations. Most system innovations involve technologies that use various energy sources to increase drug flux across the skin. Formulation innovations involve chemical systems that increase the flux of drug across the skin and improve TDD system performance and stability. For passive drug-in-adhesive (DIA) transdermal patches, the workhorse of current transdermal
technologies, the formulation tends to be a major focus of research because it is a challenge to integrate adhesive, drug(s), and excipient(s) into a single, simple, elegant system and achieve product stability and optimal system performance throughout the duration of the wear period.

A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. These so-called “active” transdermal technologies include iontophoresis (which uses low voltage electrical current to drive charged drugs through the skin), electroporation (which uses short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules). Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin. Of these technologies, only iontophoresis has been successfully developed into a marketable product, albeit for local pain relief.

Several other iontophoretic systems are in late-stage clinical development and FDA review for systemic delivery of drugs. Sonophoretic devices and thermal patch systems are in developmental stages.

A new area of intense transdermal research and development is the development of devices that create micropores in the stratum corneum, the topmost layer of the skin that serves as the greatest barrier to drug diffusion. Such devices include microstructured arrays, sometimes called microneedles, that, when applied to the skin, painlessly create micropores in the stratum corneum without causing bleeding. These micropores offer lower resistance to drug diffusion than normal skin without micropores. Several companies are developing this technology and are in preclinical or early stage clinical development. Laser systems are also being developed to ablate the stratum corneum from the epidermal layer. As with microneedles, the ablated regions offer lower resistance to drug diffusion than non-ablated skin. One company has recently received FDA approval to market this device with a lidocaine cream.

An area of continued interest is the transdermal patch formulation. Because drug-in-adhesive technology has become the preferred system for passive transdermal delivery, two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch.

Excipient research focuses on finding excipients that improve drug solubility and stability in the DIA formulation and enhance the permeation of the drug across the skin. Much research has been performed on chemical permeation enhancers, and many chemical
permeation enhancers have been reported throughout the years that enhance the flux of drugs across the skin compared to the drug flux without the chemical permeation enhancer.\textsuperscript{22-25} Chemical permeation enhancers are divided into two classes (depending on their mechanism of action): those that alter the structure of the skin lipids, decreasing their resistance to diffusion, and those that enhance the solubility of the diffusing drug within the skin.\textsuperscript{26}

An older technology that is attracting some renewed interest is the use of gels and creams for the systemic delivery of drugs.\textsuperscript{27} Gels and creams have a long history in topical and local dermal applications, and prior to the development of nitroglycerin patches, a nitroglycerin ointment was used for the treatment of angina. While these systems rely on the same passive diffusion of the drug across the skin as drug-in-adhesive patches, they offer the advantage of application to a larger surface area than the patch. Their disadvantage lies in the inability to precisely control the dosing to each patient. Recently, testosterone gels have found market acceptance and fast growth with this “reborn” transdermal technology.

Transdermal drug delivery is hardly an old technology, and the technology no longer is just adhesive patches. Rather, transdermal drug delivery is a thriving area of research and product development, with many new diverse technology offerings both within and beyond traditional passive transdermal technologies.

**MYTH 3**

*All drugs that can be delivered transdermally are already on the market.*

In the first section, it was discussed that the transdermal drug delivery market is growing and that there is a prospect for higher growth in this market over the next several years based on the strong pipeline of transdermal products in clinical development in the US. Table 1 provides a snapshot of the pipeline of transdermal products, based on our research. One striking element of Table 1 is the number of new compounds in development. Whereas 13 compounds currently exist in approved transdermal products in the US, six new (i.e., new to the transdermal market) low molecular weight molecules are currently in either preclinical or clinical development. Certainly, this suggests that more drugs can be delivered transdermally than what is already on the market.
Another noteworthy element of Table 1 is that several of the compounds (macromolecules and vaccines) in development are outside of the normal niche for TDD. Usually, that niche is limited to those compounds with the right mix of physiochemical properties ideal for transdermal permeation (without considering clinical needs, which are also important in selecting transdermal drug candidates). It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be nonionic, low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1 to 3), a low melting point (less than 200°C), and are potent (dose is less than 50 mg per day, and ideally less than 10 mg per day). Given these operating parameters, the number of drug candidates for passive transdermal patches is low, owing to the challenge of diffusing across the bilayers in the tortuous stratum corneum. But, as discussed earlier, many new opportunities still exist for novel passive transdermal patch products.

The new transdermal technologies that were introduced in the previous section challenge the paradigm that there are only a few drug candidates for transdermal drug delivery. Table 2 shows a summary of the TDD technologies and the types of molecules that these technologies enable for transdermal delivery. With the active and micropore-creating transdermal technologies, molecular size is not a limiting factor. The same applies for other physiochemical drug properties, such as ionization state, melting point, and solubility. Finally, the active and micropore-creating technologies also enable therapeutic delivery of drugs at doses higher than 10 mg.
Clearly, the opportunities for transdermal drug delivery have been greatly expanded through the application of new formulation technologies and active delivery systems. Now, a much wider set of drug compounds, including macromolecules, have the possibility to be delivered transdermally at therapeutic levels than was possible just a decade ago. Of course, the use of a TDD technology for any drug must be clinically beneficial.\textsuperscript{32} We believe that it is safe to say that in the next 10 to 15 years the transdermal drug delivery market will include many drug compounds that currently are not being delivered transdermally.

**MYTH 4**

*Transdermal drug delivery systems are not suitable for delivery of biotechnology drugs, such as protein/peptide pharmaceuticals.*

New transdermal technologies are being developed that greatly expand the range of molecules that can be delivered transdermally. While it is true that the molecular size and solubility characteristics of biopharmaceuticals, such as proteins, peptides, and carbohydrates, prevent their passage through the skin, which is a quite efficient membrane for preventing transport of macromolecules, and preclude their use within typical passive transdermal systems, newer transdermal technologies are making progress in overcoming this barrier.\textsuperscript{33,34} Several new transdermal technologies incorporate mechanisms to transiently circumvent the normal barrier function of the skin and to allow the passage of macromolecules.

Two of the better-known technologies are iontophoresis and sonophoresis. Both of these technologies have been known for some years, but the rate of product development has been relatively slow as these technologies have emerged. There is currently only one product approved specifically for iontophoretic delivery, and there are no sonophoretic products on the market. These systems can achieve significant skin permeation enhancement, enabling the delivery of proteins, such as insulin and calcitonin.\textsuperscript{35,36} They also potentially offer significant improvements in control over the rate of drug delivery, but the resulting systems are more complex than passive transdermal systems, and their adoption, at least early on, is likely to be limited to specific applications. Still, they provide an alternative for macromolecular delivery that did not exist 10 years ago.
A newer and potentially more promising technology for macromolecule delivery is microneedle-enhanced delivery. These systems use an array of tiny needle-like structures to open pores in the stratum corneum and facilitate drug transport. An example of this system, 3M’s Microstructured Transdermal System (MTS), is shown in Figure 4. The structures are small enough that they do not penetrate into the dermis and thus do not reach the nerve endings, so there is no sensation of pain. The structures can be either solid (serving as a pretreatment prior to patch application), solid with drug coated directly on the outside of the needles, or hollow to facilitate fluidic transport through the needles and into the lower epidermis. These systems have been reported to greatly enhance (up to 100,000 fold) the permeation of macromolecules through skin.\textsuperscript{33}

For example, Figure 5 shows the increase in \textit{in vitro} skin permeation of a model protein following microneedle pretreatment. The combination of the microneedle systems with iontophoresis has also been reported and may offer additional control over the delivery of macromolecules.\textsuperscript{37}
Transdermal delivery of vaccines has also been recently reported. In this case, the goal is to deliver the antigen to the immune responsive Langerhans cells within the epidermis rather than to the systemic circulation. Typical antigens are very large proteins, or even whole cells, which have long been considered unsuitable for administration through an intact stratum corneum. However, quite impressive immune response has been observed with extremely large antigens, such as tetanus toxoid when co-administered with an adjuvant. Relatively simple skin pretreatments, such as hydration, have been shown to improve the immune response. More recently, microneedle arrays have been used as a simple mechanism to pretreat the skin prior to application of the vaccine.

Improved methods of drug delivery for biopharmaceuticals are important for two reasons: these drugs represent a rapidly growing portion of new therapeutics, and they are most often given by injection. The skin offers a highly accessible, convenient, and very large surface area point-of-entry for these therapies. Existing small molecule products have proven that transdermal drug delivery is a more patient-friendly and preferred method of administration compared to injection and offers the additional benefit of sustained release. Newer technologies, such as microneedle enhancement, are demonstrating that these benefits can be extended to macromolecules as well.

**SUMMARY**

Hopefully, a few common misconceptions have been dispelled in this article, showing that transdermal drug delivery technology extends well beyond the passive adhesive
patch. While this proven technology still offers significant potential for growth, with many new product offerings in the coming years, next-generation TDD technologies will enable much broader application of TDD to the pharmaceutical industry. Technologies, such as microneedle enhancement, will reshape the way we think about transdermal drug delivery and open up the benefits of TDD technology to a much broader range of therapeutic areas.

REFERENCES


BIOGRAPHIES
Dr. Ryan D. Gordon is a Sr. Development Engineer at 3M Drug Delivery Systems in St. Paul, Minnesota. He earned his PhD in Chemical Engineering from the University of Minnesota in 1998 and his BS in Chemical Engineering from the University of Wisconsin in 1993. After working at ALZA developing iontophoretic transdermal systems and Seagate Technologies developing photolithography manufacturing processes, Dr. Gordon joined 3M’s Transdermal Drug Delivery group in 2001. Currently, he is responsible for leading the formulation development of drug-in-adhesive transdermal patches and HFA metered dose inhalers.

Tim A. Peterson earned his BS in Chemical Engineering from the University of Minnesota and his MS in Chemical Engineering from the University of Virginia. For the past 15 years, he has contributed in a variety of capacities to transdermal product development within 3M’s Drug Delivery Systems Division. His experience ranges from the development of new polymer materials for use in TDD systems, to complete transdermal system development and the development of new technologies to enable future generations of transdermal drug delivery products. His most recent assignment is Group Leader of 3M’s new transdermal technology development and feasibility group. Among other responsibilities and objectives, this group is pursuing the development of microneedle-enhanced transdermal delivery systems to enable sustained delivery of macromolecules.