

# Drug Delivery<sup>®</sup> Technology

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## Intelligent TDD Via a Selective Barrier Membrane



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# TRANSDERMAL DELIVERY

## *Intelligent Sustained-Release Using a Selective Charged Barrier Membrane*

**By:** Emma A. Durand

*A new approach to enhancing the transport of drugs across the stratum corneum uses a proprietary selective barrier membrane to prevent the inadvertent transport of drugs by diffusion, even at elevated skin temperatures.*

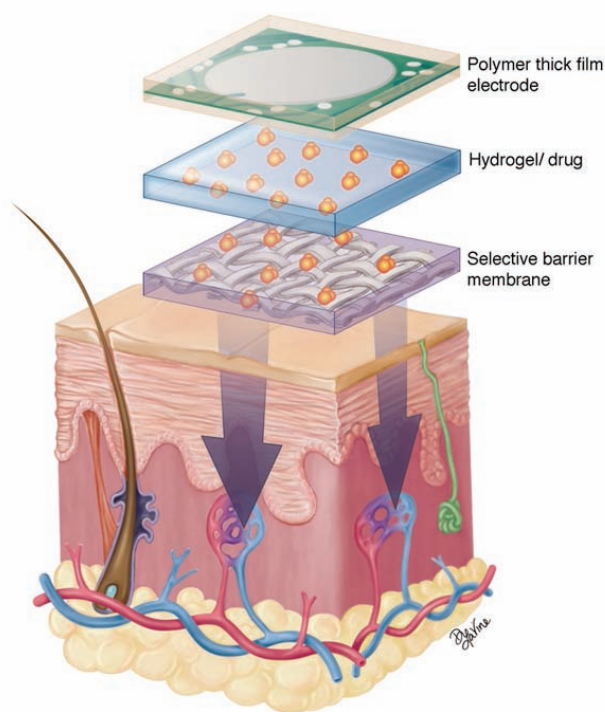
### INTRODUCTION

With the commercial market for transdermal patches now approaching nearly three decades of practical and regulatory precedent, much has been learned and applied from the experience of earlier generation, small molecule “passive” products. Newer, active transdermal drug delivery approaches are on the near-term horizon, promising much more patient- and physician-friendly, as well as more reliable and effective methods of drug administration. The Isis Biopolymer team has combined its experience in advanced polymer development, medical devices and system design to develop the intelligent Isis Patch, currently in preclinical trials. Multiple tests on 75-kg pigs have been completed, and human testing will commence in Q3 2009 at two sites.

As passive and active patches grow in usage, their limitations are now becoming well understood, with patients, healthcare workers and pharmaceutical providers encountering problematic issues ranging from troubles with skin adherence and irritation to lack of physician control. Adding to slowed adoption have been difficulties with under- and over-dosing, as well as problems with portability of power supply and overall cost effectiveness. The Isis Biopolymer approach to transdermal drug delivery uses an intelligent iontophoretic patch and biosensing technology to address many of these shortcomings. Using proprietary, polymer thick film conductive inks, adhesives and dielectrics, along with advanced Radio Frequency Identification Bluetooth LE and battery technology, the Isis approach allows for a more practical application of the transdermal patch in clinical settings. Making the dosing system programmable as well as compact, wireless, portable and user-friendly has allowed for the patch to be more

intelligent, as well as more suitable for ambulatory use. Breakthroughs have been leveraged by the company in both pliable polyester substrate and hydrogels, using technologies not available or applicable to prior-generation patches. This approach will support lower cost development and production and enable delivery of up to three drugs simultaneously, as well as a more diverse spectrum of drugs than is currently available.

**FIGURE 1**



**The Isis Patch combines polymer thick film electrodes with hydrogel-based drug delivery through a selective barrier membrane.**

## ADDRESSING MODULATED RELEASE

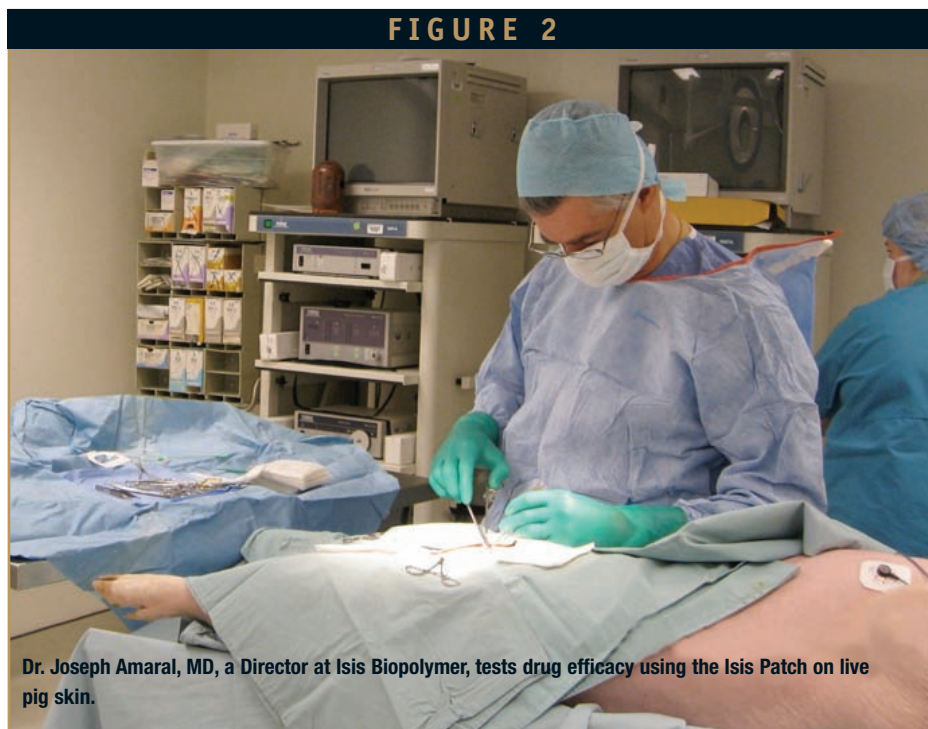
Achieving physician and patient usability together with low cost manufacturing have proven to be challenging. Yet, the major barrier to transdermal delivery of drugs continues to be the skin itself. Permeating the skin's outer layers and enhancing the transport of drugs across the stratum corneum has been the focus of much research and many prior approaches to transdermal products, both active and passive. Significant problems have arisen due to a lack of methodology for ensuring true sustained release, that is, the ability to modulate how much and/or when a drug is released and to control release consistently, over an extended period. This deficiency in intelligence must be addressed by next-generation transdermal drug delivery products for a number of important reasons, including the following:

1. Potentially serious hazards can result from longer than recommended duration of application;
2. Application of more than the recommended number of patches can lead to overdose;
3. Smaller patients can be equally susceptible to overdose; and
4. Elevated body temperature can affect transport.

The following outlines a new approach to overcoming the skin's anatomy and barrier properties, in order to broaden the number and types of drugs deliverable via active transdermal patches and to provide physicians with increased control and dosing compliance.

## TRANSDERMAL ADVANTAGE

For a wide range of reasons, delivering medicine to the general circulation through the skin is a desirable alternative to oral delivery. Many patients forget to take their medicine, while even faithfully compliant patients tire of swallowing pills, especially for those taking multiple medications. Another



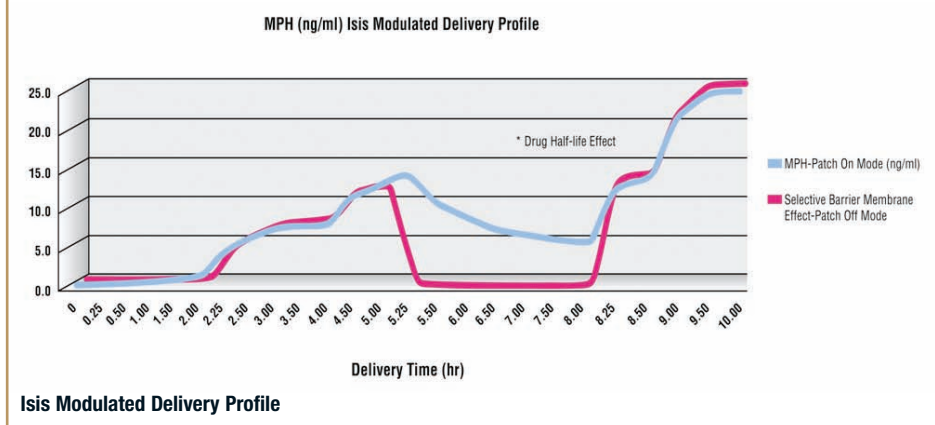
**Dr. Joseph Amaral, MD, a Director at Isis Biopolymer, tests drug efficacy using the Isis Patch on live pig skin.**

advantage is minimizing side effects; bypassing the gastrointestinal tract prevents GI irritation and avoids partial first-pass inactivation by the liver. Further, steady or modulated delivery and absorption of a drug over many hours or even days is usually preferable to the blood level spikes and troughs typically produced by oral dosage forms.

These are clearly among the many advantages of today's transdermal products; however, there continues to be a major drawback to transdermal delivery. Inadvertent delivery caused by changes in body temperature and metabolic rates are problematic, even more so with certain classes of drugs, such as analgesics. The estrogen-progestin patch and the fentanyl patch, which can last for 72 hours, offer real benefits to patients. Yet, while the transdermal approach is highly desirable, there remains the obstacle of the skin itself. Just as the function of the GI tract is to render material suitable for absorption once ingested, the skin's function is to keep substances out of the body. The barrier to transdermal delivery is, of course, the stratum corneum, the top layer of the epidermis. This is the skin's homeostatic and protective barrier, consisting of keratinized, flattened remnants of once-active epidermal cells. By design of nature, it is hydroscopic but impermeable to water, as well as flexible

and tough. The thickness of the stratum corneum is about 10 microns on the back and abdomen, thicker on the palms and soles, and can be as thick as 600 microns. Many drugs that are suitable today for transdermal delivery, including clonidine, estradiol, fentanyl and nicotine, represent potent, low molecular weight molecules that are highly active. To increase the range of drugs available for transdermal drug delivery, a number of chemical and physical enhancement techniques have been developed with the goal of transporting drugs across the skin barrier without irritation. The controlled delivery afforded by iontophoresis involves the application of a small electrical current to maintain a constant current, thus, enabling drug transport. The amount of compound delivered is more or less directly proportional to the quantity of charge involved. In theory, this should give an improved onset time and also a more rapid offset time, so that once the current is switched off, drug transport should stop.

For this article, the issues of drug concentration and the impact of iontophoresis on pH will not be reviewed, as these subjects have been well documented in the literature. The focus here is on the issue of inadvertent drug delivery. This issue can be quite problematic for many drugs, including fentanyl and other analgesics. Iontophoresis

**FIGURE 3****Isis Modulated Delivery Profile**

clearly has vital applications in pain management. Appropriate modulation of the delivery profile means that iontophoresis can provide almost instant relief in response to acute pain episodes. This is important, for example, in applications such as post-operative pain and chronic pain as experienced by cancer patients. Because the input of the drug is current-controlled, kinetics allow non-invasive administration on demand in a manner similar to conventional, patient-controlled anesthesia, but without needles. In addition, maintenance doses, which take into account such parameters as sleep and diet, can be achieved and customized with variable modulated delivery. Finally, in addition to providing systemic pain relief, iontophoresis can be utilized for local pain relief or local anesthesia, such as for minor surgical procedures.

## CURRENT TERMINATION

The major problem that has surfaced with iontophoretic devices dispensing analgesics occurs when drug permeation across the skin continues after termination of current. Iontophoresis, as is known, uses a weak electrical current to stimulate drug-carrying ions to pass through the intact skin, propelling high concentrations of charged medications by repulsive electromotive force.

In many devices, iontophoretic delivery of analgesics is more than able to match IV input kinetics. This is particularly important where the analgesic demonstrates an extensive first-pass effect or has a short half-life and must be given 3 to 4 times per day.

## SELECTIVE BARRIER MEMBRANE

In a typical drug delivery membrane, the drug is contained in a reservoir, surrounded by a membrane. The release of the drug is constant, as long as a consistent concentration of the drug is maintained within the device. But a constant concentration can only be maintained if the reservoir contains a saturated solution and sufficient excess of solid drug. Such systems are only used for low or moderate delivery of drugs.

Isis Biopolymer has developed an intelligent, selective barrier membrane that allows compounds to be transported or blocked from transport. While the appropriate current density is transporting the drug, the Isis selective barrier membrane can be switched to either facilitate or prevent transport. This capability is controlled entirely by the system's microprocessor, without the need for professional (or any type of user) interaction. Similarly, as part of the manufacturing process, openings in the membrane which initiate or prevent drug transport are calibrated to individual drugs. Finally, the density of the current determines the rate of transport.

The Isis Patch utilizes the physics of electrophoresis and dielectrophoresis; these terms imply the interplay between electrical phenomena and motion. Because polymer dispersions contain substantial amounts of liquid, it is possible to formulate a field-sensitive, drug dispersion. Responding to an applied field in the membrane, the drug dispersion properties, such as viscosity and

other physical properties, may be controlled. The response time to those field changes can approach the order of milliseconds. The control field in the membrane is able to increase resistance to flow, thus, allowing cessation of drug transport. In the Isis selective barrier membrane, the rate of transport depends upon the current density and the variable permeability of the membrane to the drug.

## LIFESPAN/ISIS BIOPOLYMER TRIAL

Isis recently completed trials of four drug therapies at Providence, RI-based Lifespan research facilities. Tested drugs included methylphenidate, cefazolin and ibuprofen L-dopa, each based on the use of live pig skin. Extensive ex vivo research using pig skin has demonstrated the ability of a variety of molecules to be absorbed into the skin through the stratum corneum. The purpose of this trial was to evaluate the transdermal delivery of different drugs using the Isis Patch technology in an in vivo animal model by examining serum concentrations achieved for these drugs. The study evaluated molecules with potential widespread human clinical applications that have molecular weights less than 500 Daltons.

Extensive literature review for testing transdermal delivery systems reveals that the pig is a widely accepted model and one favored by researchers because of the similar absorption characteristics of porcine to human skin. Six Yorkshire pigs weighing 30 to 50 kilograms were utilized for the study. The animals were allowed to acclimate for five days at the testing facility, fasted overnight and anesthetized in a sterile operating room. The animals' body hair in the abdominal region was removed and the area prepped in a sterile fashion. The animals were maintained under anesthesia for the duration of the trial.

Four Isis Patches were placed on the abdominal area containing each of the drugs. To eliminate location bias, the exact location of the patches varied in location on each of the six animals. The hydrogel/drug electrode size of all patches was held constant at 5 cm<sup>2</sup>

and allowed for 600 mg to be loaded into the active electrode site. Each patch was loaded with 150 mg of the specific medication, which equates to a 25% loading of the drug in the hydrogel material.

The Isis Patches were programmed with a modulated delivery profile. The patches were not turned on for the first two hours to document the effectiveness of the selective barrier membrane. The patches were turned on for three hours, turned off for three hours, and turned on again for two hours. Three animals had Isis Patches programmed at half maximum voltage, and the other three had patches programmed at full voltage. A baseline blood sample was taken and continuous blood sampling performed throughout the modulated drug delivery process. The 10-ml blood samples were allowed to clot, spun and the serum was separated for testing purposes. All serum samples were initially frozen in liquid nitrogen and then placed at -80°C for storage.

Figure 3 demonstrates the effect of the selective barrier membrane over time. The restrictive effect on the medication when the current is reversed in the barrier membrane is clearly seen. The Isis Patch's selective barrier membrane allows for a modulated delivery profile; thus, rapid uptake and a zero-modularity mode were achieved.

Isis also tested the passive delivery of a compound from a gel formulation with the iontophoretic delivery of the compound contained in a hydrogel. Varying application times were used, including 30, 60 and 125 minutes, after which the skin was tape-stripped and the compound subsequently

extracted from the tapes. The target dosage of the instant compound was 15.5 mg delivered resulting in a blood serum assay of 156 ng/ml.

Notably, on areas of skin contacted by the patches in a passive mode (current off), compound levels were undetectable. Also of importance is this feature's applicability to lidocaine patches for local anesthesia. As recent reports confirm, there are potentially serious hazards in using skin-numbing patch products for relieving pain from medical procedures. These topical anesthetics work by blocking pain sensation in the skin. Some of the medication in a topical anesthetic (or anesthetic contained in a patch reservoir) can pass through the skin into the bloodstream. If skin temperature increases, more anesthetic can be transported. As a result, the amount of anesthetic medication that reaches the bloodstream is unpredictable and may be high enough to cause life-threatening effects, such as irregular heartbeat or breathing difficulties. The Isis Biopolymer selective barrier membrane prevents such inadvertent or unpredictable delivery, even at elevated skin temperatures.

## CONCLUSION

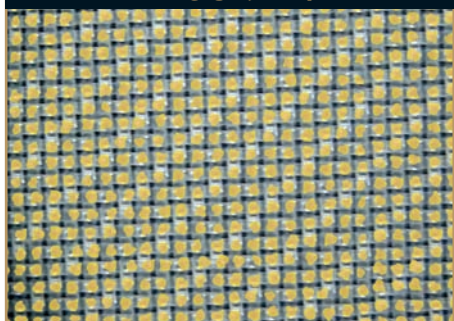
Transdermal administration of drugs has assumed an important place in drug therapy, with many of the shortcomings of previous generations of products now being addressed by more portable, user friendly applications. The issue of inadvertent delivery caused by changes in body temperature or metabolic rates can be addressed by selective barrier membranes, applying principles of facilitated diffusion. Incorporating such functionality into the microprocessor-controlled patch ensures that compounds are transported or blocked from transport, thereby ensuring controllable, predictable and accurate dosing. By preventing inadvertent delivery of current classes of transdermally delivered drugs, Isis has paved the way for improved dosing compliance of new and existing drugs for transdermal delivery.

## BIOGRAPHY



**Ms. Emma A. Durand** is President & Chief Technology Officer at Isis Biopolymer, Inc., founded in 2007 to develop a major advance in intelligent non-invasive drug delivery called the Isis Patch. Ms. Durand holds over 40 US and international patents, covering diverse areas of mechanical, electrical, and chemical engineering, virtually all of which been employed in the development of successful commercial products. Prior to founding Isis Biopolymer, she was Executive Vice President and Chief Technology Officer of American Biophysics Corp.; a Co-founder and Chief Technology Officer of EvaluTech, LLC; and a Founder of Sublimation Systems, Inc., Key-Tech Inc.; and Poly-Flex Circuit Inc. Ms. Durand attended the Massachusetts Institute of Technology, majoring in Mechanical Engineering.

**FIGURE 4**



**This dyed compound shows the effect of an electrical field on a compound within the grid of the selective barrier membrane. This facilitates complete cessation of drug delivery.**