

Drug Delivery Report

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Transdermal Drug Delivery: Time for a Closer Look

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Robert J. Bloder is the Vice President of Business Development for Aveva Drug Delivery Systems (www.avevadds.com), a Nitto Denko company with revenues in excess of US\$5 billion and a leader in Transdermal Drug Delivery Systems. Prior to joining Aveva Drug Delivery Systems, Mr Bloder was a co-founder of ESP Pharma and served as the Vice President of Market Development. Before this, Mr Bloder was the Director of Strategic Partnership Development for Parke-Davis (Pfizer) where he managed the day-to-day operations of an internal business accelerator that focused on Lipitor and the other large, revenue-generating products for the company. During his sales and marketing tenure at Parke-Davis, Mr Bloder launched several blockbuster and 'first in class' products that fulfilled unmet market needs.

Introduction

Transdermal drug delivery has traditionally been considered a niche technology, effective only for a limited number of drugs with unique characteristics. Advances in materials science, the understanding of absorption mechanisms and an increased recognition of the value of effective product life cycle management have changed the landscape forever. While transdermal drug delivery is not a panacea, no longer is anyone questioning the viability of this technology. Today, the important question is: What can 'patches' do for you?

Early Promise, Mixed Reviews

Many of the initial goals for transdermal drug delivery have been selectively achieved with currently marketed products, such as providing a convenient, painless method of drug delivery; improving patient compliance; reducing adverse effects; and maintaining more consistent and prolonged blood levels than those achieved with oral or parenteral dosing. The technology was quickly accepted by patients and clinicians alike, and patches were viewed as a desirable platform for a variety of therapeutic uses, including motion sickness, hypertension, angina, hormone therapy, smoking cessation and pain control.

After the 1981 market introduction of the first patch, Transderm-Scop® (scopolamine), other applications were aggressively pursued. Many met with considerable and sustained success, for example US sales of nitroglycerin patches exceeded 500 million units in 2003 (McManus, 2003). Despite early successes, patches collectively comprise a relatively small portion of available dosage forms, in part due to hurdles that must be overcome for the development of a successful transdermal delivery system. Challenges for patch development include (Cleary, 2004):

- Achieving sufficient skin-permeability to match dose requirements;
- Achieving optimal adhesive performance;
- Avoiding application site skin irritation.

These factors, along with patient compliance and preference, contributed to a perception that patch technology was tapped out and that the inherent problems could not be overcome. By 2001, only a small fraction of the R&D budgets among the major pharmaceutical companies was devoted to alternative drug delivery methods. Now, after more than 20 years in the marketplace, patches account for approximately three-dozen prescription medication products, containing about 16 active drugs (Gordon and Peterson, 2003).

Increasing Pressure for Effective Drug Delivery Alternatives

Drawbacks of both the oral and parenteral drug delivery routes are well established, fuelling a continued search for new options. Currently, the quest for effective alternatives has grown exponentially. Several forces are at work:

- The products of biotechnology, peptides and proteins, generally require parenteral administration due to their large molecular size and complex biopharmaceutical properties (Dubin, 2005);
- Patent expiration for blockbuster drugs, coupled with a decline in new drug pipelines, is placing unprecedented pressure on product life cycle management (Furness, 2004).

According to Ian Sanderson, Pharmaceuticals Analyst at **SG Cowen**: 'After a lull in 2005, the pharmaceutical industry will take a massive unprecedented hit in 2006, when products worth more than \$20 billion in the US will lose patent protection in 1 year alone' (Furness, 2004).

The success of the generics industry has dramatically affected the rate at which brand products lose value after patent expiry, with some brands losing 70% of their worth within 2 or 3 months after loss of patent protection (Furness, 2004). Perhaps the most dramatic example was in 2001 when more than 65% of **Eli Lilly's** Prozac® (fluoxetine hydrochloride) sales were converted to generics in the first month post-patent expiration (Cleary, 2004). Factors contributing to this trend include political pressure

to decrease costs in the face of spiralling healthcare expenditures, authorised generics and a greater willingness by patients and physicians to accept generic alternatives, which is largely attributable to the increased power of managed care to increase formulary adherence and compliance through effective programmes such as tiered Co-Pays.

In addition to both the wave of patent expirations and a healthier, more aggressive generics industry, many pharmaceutical companies are facing a severe drought in their pipelines. For example, in 2003, the FDA approved only 35 new medicines, about half the number it approved in 1996 (Furness, 2004). Understandably, costs of development are substantial, with current estimates for bringing a new drug to market hovering around US\$880 million. In addition, although FDA approval time has improved, the approximate discovery-to-market timeline remains at about 15 years.

By comparison, developing a new delivery system for an already-approved drug requires only 4 to 8 years. Furthermore, screening for the feasibility of developing a new delivery system, such as a transdermal reformulation, may be accomplished within 12 months with an investment of only US\$200,000 to US\$800,000 (Cleary, 2004). Chris Towler, former Director of Global Regulatory Policy, GlaxoWellcome stated: 'There's no doubt that, in the interim between now and capitalizing on the new science of genetics and genomics, we're going to be more dependent on existing product pipelines. The smart companies will look to wring everything they can out of their existing products' (Furness, 2004). Of 74 senior pharma executives surveyed in 2004, 90% believed product life cycle management would become more important in the next 5 years (Cappemini, 2004). Of course, one way to lengthen the life cycle is to introduce a new delivery system.

Additionally, renewed emphasis on finding opportunities to revive development-stage drugs that may have been shelved for dosing regimen limitations is another motivation for a closer look at alternative delivery systems (Hsu *et al.*, 2004).

Based on these issues, a Frost & Sullivan report translates the anticipated growth in transdermal applications to be US\$13 billion before 2008 (Cleary, 2004).

Alternatives in the Pipeline

Along with patch products, considerable attention has been given to other routes and methods of drug delivery. More than 300 US companies are currently engaged in the development and licensing of new drug delivery technologies, while another 1,000 pharmaceutical and medical product manufacturers participate in the drug delivery market to a lesser degree (Kermani and Findlay, 2001). Their mandate is clear (Dubin, 2005):

- Customise delivery to the unique challenges of specific drugs;
- Overcome the macromolecule challenge;

- Improve the dose/duration parameters of alternative drug delivery systems;
- Revive development of drugs that have failed due to a lack of appropriate bioavailability, poor pharmacokinetics or the occurrence of adverse events linked to delivery profile.

New Promise from Transdermal Patch Technologies

While other technologies hold promise for applications in the future, one company has a proven track record in revolutionising the performance of passive transdermal technologies today. **Aveva Drug Delivery Systems**, along with the expertise of its parent company, **Nitto Denko**, a pioneer and one of the largest manufacturers of transdermal drug delivery systems in the world, leverages the most advanced skill sets in polymer synthesis and adhesive technologies to create alternate dosage forms for new chemical entities, as well as life cycle management and product optimisation opportunities for a number of products, including:

- The tulobuterol patch, which garners over US\$200 million in sales per year, while other dosage forms of the drug represent approximately US\$2 million in sales per year;
- Isosorbide dinitrate patches generate annual sales in excess of US\$90 million per year for post-MI patients and the treatment of angina.

Aveva DDS has broad development experience including estradiol, fentanyl, nicotine, nitroglycerine, lidocaine and scopolamine transdermal and topical delivery systems.

Aveva's edge in transdermal drug delivery is exemplified by the revolutionary Gel Matrix Adhesive that, when compared to traditional transdermal products, provides greatly improved patient comfort by minimising the disruption of the stratum corneum during removal.

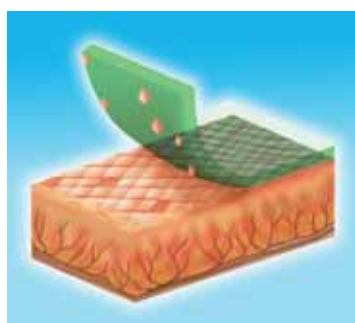


Figure 1 – Surface of adhesive after removal of an Aveva, GelMatrix transdermal patch (area of application: human back; length of application: 8 hours; magnification: 125x).



Figure 2 – Traditional transdermal patch: surface of adhesive after removal (area of application: human back; length of application: 8 hours; magnification: 125x).

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That's the promise of Aveva Drug Delivery Systems, combining innovation and unparalleled industry experience to advance drug delivery and pioneer new frontiers in transdermal drug delivery for new chemical entities and life cycle management opportunities to enhance existing products.

As one of the world's largest manufacturers of transdermal patches offering a full range of research, development and manufacturing capabilities, Aveva transcends traditional limitations of patch technology and business partnerships to achieve new levels of product and corporate performance.

- > Customizing solutions to the unique characteristics of each drug
- > Masterfully balancing the patch properties of adhesion reliability and gentleness that lead to an enhanced patient experience.
- > Managing a higher drug concentration in a smaller patch

A flexible, customer-oriented business philosophy that adds value to projects and exceeds customer expectations.

To license a product or to see how we can add value to your project, call Robert J. Bloder, Vice President Business Development, at **954.624.1374** or visit www.AvevaDDS.com

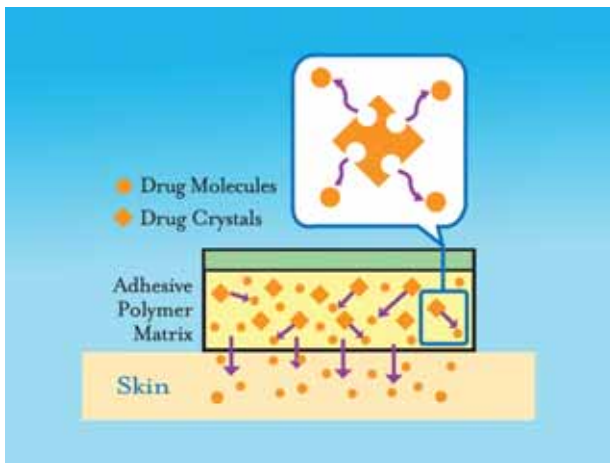


Figure 3 – The Crystal Reservoir Technology results in smaller patches with a more controlled and sustained drug release. This efficiency may minimise the amount of active pharmaceutical ingredients required.

Further, patches with this adhesive can be removed and reapplied with minimal skin irritation (Figures 1 and 2). This enhanced patient experience is especially important in managing chronic conditions when the patch needs to be applied to the same area and where non-compliance over time with other types of delivery systems is a significant issue.

The company's Crystal Reservoir Technology offers additional benefits, making it possible to achieve controlled and sustained drug release, conserving drug requirements and allowing application of smaller size patches. The technology is based on over-saturation of the adhesive polymer with the API, thus forcing a partial crystallisation of the drug. The presence of both molecular solute and solid crystals in each patch allows for a considerably higher drug content and provides a longer lasting and consistent supply of drug. As the skin absorbs the solute, the crystals dissolve to maintain maximum thermodynamic activity at the site of contact (Figure 3).

Together, the Gel Matrix Adhesive and the Crystal Reservoir Technology provide an unequalled balance of adhesion reliability, elegance of design and gentleness for patients, resulting in broader therapeutic applications with improved patient compliance. In addition, Aveva rapidly and cost-effectively generates unique products using customised transdermal delivery systems to meet specialised needs. As importantly, their proprietary technologies open up patent opportunities to protect a pharmaceutical company's revenue stream and extend the life cycle of valuable pharmaceutical agents.

The Partnership Advantage

Clearly, the opportunities for transdermal drug delivery have been greatly expanded through the application of new technologies. Now, a much wider set of drug compounds, including macromolecules, may be delivered transdermally at greater therapeutic levels than was possible just a decade ago. Much of the progress will continue to emerge through synergistic partnering

relationships between pharmaceutical companies and drug delivery companies, such as Aveva Drug Delivery Systems.

Aveva has a wealth of experience partnering with select pharmaceutical manufacturers to develop and manufacture transdermal products that have achieved significant success. Moving forward, the range of proprietary and brand-equivalent transdermal drug delivery systems is expanding, based on the full range of feasibility, research, development and manufacturing capabilities, coupled with the sophisticated technologies, and the following advances that Aveva brings to the table:

- Drug-in-adhesive technology for volatile drugs;
- Exclusive polymer combinations for solubility of crystalline drugs;
- Unique multilayer and membrane designs for controlled delivery profiles;
- Specialised formulations and processing for labile molecules;
- Permeation-enhancer technology;
- 1:1 manufacturing-to-packaging ratio for maximum productivity and commercial supply efficiency.

Furthermore, Aveva also offers other drug delivery technologies, such as transmucosal dissolvable films.

With over 60 issued patents, Aveva offers unique partnering opportunities in the development of novel delivery systems and is currently active in an increasing number of therapeutic applications, including asthma, cardiovascular disease, women's health, nutraceuticals and dermatologicals.

'Our deal configurations are designed for maximum flexibility in accordance with the needs of our partners, and are as unique to each client as are our customized transdermal drug delivery systems', explains Robert J. Bloder (Vice President of Business Development for Aveva Drug Delivery Systems).

A closer look at transdermal technology seems especially timely today, considering the prospect of impending patent expirations, a drought of new drugs in the pipeline, increasing costs of development for new chemical entities, an increasingly aggressive generics industry, and pressures for cost-effective therapies that promise a higher level of efficacy and compliance. Aveva is one company that stands ready for the challenge with the knowledge and experience to see your company through the challenges that lie ahead.

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