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PharmaED's

Transdermal Drug Delivery Systems

*Examine Recent Developments
in Transdermal Drug Delivery*

FEBRUARY 24-25, 2011, RADISSON WARWICK HOTEL, PHILADELPHIA, PA

Key Learning Objectives:

- Practical Considerations for Expanding the Range of Drugs and Vaccines for Delivery Using Transdermal Systems
- Explore Transdermal Drug Delivery Systems as a Viable Alternative to Oral, Intra-Muscular or Intra-venous Injection
- Understand How FDA Regulates Transdermal Drug Delivery Technologies for Investigational and Marketed Products
- Explore Novel Applications of Transdermal Drug Delivery Technologies
- Overcome Obstacles and Achieve Efficacy in Active Transdermal Delivery Platforms
- Cost Considerations in the Development and Production of Transdermal Delivery Systems
- Understand Therapeutic Advantages for Transdermal Delivery of Biopharmaceutical and Vaccines
- Learn How New Technologies are Expanding the Scope of Transdermal Delivery to Include Hydrophilic Macromolecules

Featuring Representation From:

Eakins and Associates, Inc.
BD Technologies
University of Mississippi
Xel Pharmaceuticals, Inc.
AllTranz Inc.
PATH

Biologics Consulting Group
3M Drug Delivery Systems
American Association of Pharmaceutical Scientists
University of Kentucky College of Pharmacy
Polytherapeutics, Inc.



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Thursday, February 24, 2011

8:30 *Chairperson's Welcome and Opening Remarks*

8:45 **Past, Present and Future of Transdermal Drug Delivery Systems**

Michael Eakins, President, Eakins and Associates, Inc.

This opening presentation will cover the rise of transdermal drug delivery systems as a viable alternative to oral, intra-muscular or intra-venous injection. It will provide an overview of the second- and third-generation systems and strategies and evaluate whether the recent rise in the number of drugs administered in transdermal delivery systems will continue at the same pace or slow down due to competition from other drug delivery systems.

9:30 **FDA Regulation of Transdermal Drug Delivery Systems**

Michael Gross, Ph.D., RAC, Senior Consultant, Biologics Consulting Group

This presentation will review, analyze and discuss how FDA regulates transdermal drug delivery technologies. It will cover investigational and marketed products, which are based on a variety of drug delivery technologies that follow a drug development and regulatory pathway (e.g., passive patch) and those that follow a combined drug and device development and regulatory pathway (e.g., iontophoretic patch). The presentation will include product jurisdiction, investigational exemptions and marketing applications, clinical investigations, labeling and post-marketing compliance (e.g., safety reporting, quality systems) as relates to a number of transdermal drug delivery technologies. The presenter will attempt to convey general principles and recommendations on the development of medical products which are based on transdermal drug delivery technologies.

10:30 *Refreshment break*

10:45 **Therapeutic Advantages for Transdermal Delivery of Biopharmaceutical and Vaccines**

Kris Hansen, PhD, MTS Technology & Product Development Manager, 3M Drug Delivery Systems Division

Several new transdermal technologies have been developed to help overcome the barrier properties of the skin to enable delivery of biopharmaceuticals and vaccines. Opening up transdermal delivery to these new classes of compounds has offered new and exciting insights into how to expand the value of transdermal delivery.

Vaccines can be delivered more efficaciously; protein- and peptide-based drugs may be absorbed more readily resulting in faster or more complete pharmacodynamics. Across the field, delivery systems have been developed and optimized for delivery of relatively small amounts of highly potent compounds and larger volumes of biopharmaceutical formulations. Different transdermal technologies offer opportunities for extended release of peptides, highly efficacious delivery of vaccines, and, in some cases, administration of liquid formulations at higher bioavailability than can be achieved by injection. These therapeutic benefits may be achieved while still preserving the key elements of patient satisfaction associated with transdermal delivery: comfort, convenience and needle-free.

11:45 *Luncheon*

1:00 **Novel Applications of Transdermal Drug Delivery Technologies**

Narasimha Murthy, Assistant Professor of Pharmaceutics, Research Assistant Professor in the Research Institute of Pharmaceutical Sciences, University of Mississippi

Transdermal delivery is now considered as one of the well-established Drug Delivery Sciences. Researchers have clearly demonstrated the various pathways of drug absorption across skin, impact physicochemical attributes of drug and dermatokinetics of drugs. The transdermal patch systems of some therapeutic molecules have been very successful commercially. The ongoing research in this area is focusing on exploiting the transdermal delivery technologies for some unique applications. For example, delivery of antifungal drugs into nail apparatus for treating nail disorders or iontophoretic delivery of hematinics for treatment of anemia etc. The recent reports on such novel applications of transdermal drug delivery technologies will be discussed in this presentation.

- Learn about the novel applications of transdermal route of delivery
- Learn about the potential mechanisms of enhancement of drug permeation across the different biological barriers

1:45 **Passive Transdermal Drug Delivery Systems: Challenges and Potential**

Dr. Danyi Quan, Xel Pharmaceuticals, Inc.

Passive transdermal drug delivery systems (TDDS) have been used for decades to successfully deliver small molecule drugs (< 500 Da), which include matrix systems

(drug-in-adhesive) and liquid reservoir system (liquid-in-pouch). Transdermal drug delivery market was, until recently, solely based on passive transdermal delivery systems.

Chemical enhancements are still feasible methods to overcome the skin barrier to deliver drugs transdermally. Various combinations of penetration enhancers and other excipients have been used in passive TDDS.

However, even with the use of enhancers, there is a limited number of drugs can be successfully formulated into passive TDDS because it is a challenge to develop a passive TDDS for drugs with slight larger molecule weights or higher doses.

Nonetheless, a passive delivery system generally is preferred over an active delivery system because it is less expensive to develop and manufacture, easy to use, and has better patient compliance because some patients are uncomfortable to wear active transdermal device on their skin. Therefore, we expect that further innovations in matrix composition and formulation of passive TDDS will expand the number of candidate drugs for passive TDDS.

- Challenges and considerations of passive transdermal delivery systems
- Perspective of chemical enhancements
- Applications of five models for formulation design & development in passive transdermal delivery
- Potential candidate drugs

3:00 *Afternoon Break*

3:15 **New Technologies to Allow Transdermal Delivery of Biopharmaceuticals**

Dr. Ajay K. Banga, Professor and Department Chair, College of Pharmacy and Health Science; Fellow, American Association of Pharmaceutical Scientists

In recent years, there has been increasing interest in enhancement technologies that can expand the scope of transdermal delivery to biopharmaceuticals which are typically hydrophilic molecules and often macromolecules. These molecules do not normally pass through the skin unless enabling technologies are used. Some of the enabling technologies include iontophoresis, phonophoresis, or microporation. Recent innovations in these technologies, especially for iontophoresis and microporation, will be presented. Microporation involves the creation of micron-sized micropores or microchannels in the skin which can then allow the transport of water soluble molecules. Skin microporation can be achieved by microneedles or by using thermal, laser, or radio-frequency ablation. We have used

soluble microneedles made of maltose as well as metal microneedles to demonstrate delivery of human growth hormone and larger proteins like antibodies or even micron sized particulates. Iontophoresis involves the application of small amounts of physiologically acceptable currents to drive ionic drugs into the skin. We have demonstrated iontophoretic delivery of several drug molecules including peptides such as calcitonin. We have also used a combination of iontophoresis and microneedles to show that charged drug molecules can be propelled via microchannels created in the skin by microneedles to achieve delivery flux higher than that could be achieved by either technique alone.

- Learn how new technologies are expanding the scope of transdermal delivery to include hydrophilic macromolecules
- Learn the success and failures of iontophoretic delivery systems developed and marketed over the years
- Learn about the recent excitement and activity centered around bringing a microneedle patch to the market

4:15

Pore Lifetime And Formulation Aspects In Microneedle-Assisted Delivery

M. Milewski, N.K. Brogden, S.L. Banks, and A.L. Stinchcomb, University of Kentucky College of Pharmacy & AllTranz Inc.

Transdermal microneedle systems have become a very popular means of delivering skin impermeable drugs through the stratum corneum at therapeutic rates. Most of the previous research on microneedle systems has focused on optimization of the microneedle geometry. Our approach to microneedle-assisted delivery research has been in the following four areas, which will be presented:

1. Investigation of prodrugs and salt forms with optimal physicochemical properties for drug flux after microneedle treatment
2. Investigation of viscosity and other formulation factors that influence drug flux after microneedle treatment
3. Investigation of micropore lifetime using transepidermal water loss (TEWL), impedance spectroscopy, and pharmacokinetic analysis
4. Investigation of micropore lifetime after treatment with COX inhibitors

4:45

Panel Discussion

5:15

Close of Day One

Friday, February 25, 2011

8:45

Patchless Transdermal Drug Delivery

Dr. Kishore Shah, President and Founder, Polytherapeutics, Inc.

The advent of transdermal drug delivery, as we know it today, can be traced to FDA approval and commercialization of scopolamine (1979) and nitroglycerine (1981) patches. Since then more than a couple of dozen transdermal products have been marketed worldwide and transdermals have become a multi-billion dollar industry. Some of the advantages of transdermal drug delivery include (i) reproducible and prolonged drug delivery rate, (ii) elimination of hepatic "first pass" metabolism, (iii) minimization of undesirable side effects, (iv) patient convenience/compliance, and (v) rapid termination of drug therapy when desired. In spite of these advantages of transdermal medication, only a small percentage of drugs can be delivered transdermally due to essentially two limitations: barrier function of skin and its irritation and sensitization by many drugs. Patchless transdermal drug delivery in the form of topically applied gel, cream, lotion, or solution can to some extent overcome the limitation of skin barrier by application of the drug formulation to a much larger area of skin than would be possible with plastic patches. The patchless delivery may be suitable for treatment of various indications such as pain, hormone replacement therapy, contraception, over active bladder, CNS disorders, male or female sexual dysfunction, and smoking cessation.

Key advantages of patchless transdermal products include:

- Potential for expanding the scope of transdermal delivery to drugs requiring significantly higher dosages than permissible with patches
- Flexibility of dosing
- Lack of occlusion may reduce skin irritation potential of the drug
- Ease of manufacture
- Cost effective
- Cosmetic elegance

The deficiencies of the patchless transdermal delivery are (i) some variability in precision of dosing as compared to patches, and (ii) not suitable for drugs having very high skin permeation rates (e.g. fentanyl and clonidine) and/or a narrow therapeutic window.

Important formulation considerations include selection of appropriate enhancers, retention of drug and enhancers on skin, transfer to clothing or other individuals by contact, drug solubility in the medium, possible crystallization of the drug on skin when the applied formulation dries.

9:45

Intradermal Delivery and the Developing World

Darin Zehrung, Technical Officer, Portfolio Leader, Vaccine Delivery Technologies, PATH

PATH is an international nonprofit organization that creates sustainable, culturally relevant solutions, enabling communities worldwide to break longstanding cycles of poor health. By collaborating with diverse public- and private-sector partners, PATH helps provide appropriate health technologies and vital strategies that change the way people think and act to improve global health and well-being.

For more than 20 years, PATH has worked with immunization technologies for use in low-resource settings. PATH's Vaccine Delivery Technologies Group takes a multi-disciplinary approach to product development, ensuring that new technologies for vaccine administration are acceptable to users, cost effective, and based on sound and tested science.

PATH is currently working to identify current and future applications for intradermal immunization in developing countries, with a particular focus on alternative delivery devices. Intradermal delivery represents potential benefit to international public health, but must be weighed against operational challenges such as reformulation, vaccine presentation, development of intradermal delivery devices, injection safety and health care worker training requirements.

10:45

Refreshment break

11:00

Transdermal Drug Delivery Systems: Dermatologic Issues

Dr. Danyi Quan, Xel Pharmaceuticals, Inc.

An important function of the skin is its barrier properties, which has aided the survival of humans in an environment that offers variable temperatures and humidity; challenges to hydration, and the presence of environmental dangers such as chemicals, bacteria, and allergens. Furthermore, the barrier properties of the skin are due to the outer layer of its epidermis, the stratum corneum, which is a rate-limiting impediment to the percutaneous absorption of drugs. Transdermal drug delivery technology is to overcome the skin barrier to successfully enhance transdermal permeation. Therefore, dermatologic and other skin-related, adverse reactions are the unavoidable disadvantages of transdermal drug delivery systems. These issues can be

major obstacles for the application of a transdermal system if scientists do not design it well during the product-development stage. This presentation discusses the dermatologic issues that transdermal drug delivery systems can cause and the possible methods to minimize these adverse reactions.

- Formulation related factors
- Non formulation related factors
- Skin responses to transdermal patch application
- Dermatologic adverse issues

12:00 *Luncheon*

1:30 **Intradermal Delivery of Therapeutic Drugs and Vaccines Using Stainless Steel Microneedles**

Ronald J. Pettis, Ph.D., BD Technologies

BD has developed stainless steel microneedles that offer the potential for reliable and effective delivery of a wide range of protein-based drugs and various classes of vaccines. Here, we review the pre-clinical and clinical development of this robust drug delivery platform, highlighting work conducted with influenza vaccine and insulin.

Pre-clinical studies of microneedle-based protein delivery have shown consistent differences in pharmacokinetic uptake and distribution compared to other parenteral routes such as subcutaneous (SC) delivery. These animal trials have shown that in almost all cases microneedle ID delivery results in faster uptake, and increased early-phase bioavailability. This effect has also been demonstrated clinically with insulin in both normal subjects using glycemic clamp conditions and in diabetic subjects receiving standardized meals. The microneedle delivery route enables a more physiologically relevant insulin profile and enhanced pharmacodynamics response of blood glucose control. This effect may have substantial benefit for diabetics for both post-prandial control and insulin infusion applications. Pre-clinical studies with influenza vaccine showed that microneedle-based intradermal (ID) delivery can, in many cases, enable dose-sparing and induce stronger humoral immune responses compared to that achieved by intra-muscular (IM) injection using standard needles. A microneedle-based ID injection system, BD Soluvia™, was developed for commercial applications. Through clinical trials it was shown that this delivery system is easy to use and enables accurate and reproducible ID injection in humans. Clinical trials with influenza vaccine demonstrated that microneedle-based ID delivery

induces increased immune responses compared to IM injection, especially in elderly subject populations. The world's first microneedle product, Intanza®/ID Flu® (sanofi-pasteur) has received regulatory approval in Europe.

Microneedle based ID injection offers unique characteristics that are not readily achieved with other more traditional forms of parenteral delivery. These properties have been shown to offer potential clinical benefit for various vaccine and protein formulations, without necessitating substantial changes in drug formulation. With the availability of approved clinical delivery systems, microneedles are poised to enhance patient therapy and offer unique opportunities across a range of injection therapies.

2:30 **Early Stage Technologies of Transdermal Drug Delivery Enhancement**

Narasimha Murthy,

Assistant Professor of Pharmaceutics

Research Assistant Professor in the Research Institute of Pharmaceutical Sciences, University of Mississippi

Despite there is a lot of research ongoing in the area of physical methods of drug delivery, there is more and more technologies being developed on the otherside with an objective of overcoming the limitations of existing technologies. In this direction, some research groups have reported the early stage development data on technologies such as magnetophoresis, electret based techniques, etc.

3:15 *Refreshment break*

3:30 **Pharmacopeial Requirements for Product Performance Testing of Topical and Transdermal Drug Product**

Michael Eakins, President, Eakins and Associates, Inc.

Two new USP general chapters have been published for comment on topical and transdermal product quality tests (USP <3>) and product performance tests (USP <725>). These chapters will be reviewed as well as other relevant USP chapters and compared with the approach of the EP to these issues.

4:15 **Panel Discussion**

5:00 *End of Conference*



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