Current and Future Skin Permeation Technologies for Drug Delivery

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Introduction

- More than 35 transdermal patch products have been approved in US over the past 2 decades.
- 2004 patch sales in the US were approximately $3.4 billion.
- Prescriptions for transdermal products have been used by ~12 million people worldwide for ailments ranging from bladder control to heart disease.

- Marketed Products:
  - Transderm Scop® (scopolamine)
  - Transderm-Nitro® (nitroglycerin)
  - Catapres-TTS® (clonidine)
  - Estraderm® (estradiol)
  - Oxytrol® (oxybutynin)
  - Duragesic® (fentanyl)
  - NicoDerm® CQ® (nicotine)
  - Testoderm® (testosterone)
  - Hokunalin® Tape (tulobuterol)
  - Lidoderm ® (lidocaine)

- In 2006:
  - Transdermal Selegiline (Emsam®) - Somerset Pharmaceuticals, Inc.

- In 2007:
  - Transdermal Rotigotine (Neupro ®) - Schwartz Pharma
  - Transdermal Rivastigmine (Exelon ®) - Novartis Pharmaceuticals Corp.
  - Transdermal Methylphenadate (Daytrana ®) - Shire Pharmaceuticals
TRANSDERMAL BASICS

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Skin Anatomy

Key is to cross the stratum corneum - 15 μM

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Routes of Penetration

1. Directly across the stratum corneum
2. Via the hair follicles
3. Through the sweat ducts
Skin Permeability

- Drug transport through skin is the product of skin permeability and drug concentration at saturation in the skin.

- Permeability can be enhanced by altering the structure of the skin or by increasing the solubility of the drug in the skin.

- Enhancers act on skin so that drug diffusivity or drug solubility - or a combination of both – is modified, leading to an increase in transport.
Active Transdermal Delivery
**Evolution of the Market**

**Market Direction Since 1997**

- Since 1997, TDD aligned with Life Science & BioPharmaceutical industries to deliver:
  - Large molecules, peptides, proteins and vaccines
  - Bolus dosing and on-demand dosing
  - Emphasis has been to develop permeation enhancement techniques.

- **Traditional Passive Patches**

- **Permeation Enhancement**
  - **Mechanical**
    - Microneedles
    - Iontophoresis
    - Sonophoresis
    - Electroporation
  - **Chemical**
    - Terpenes
    - Liposomes
    - Azones
    - Lipids
    - Alcohols
  - **Thermal**
    - ZARS®CHADD
    - Altea® Passport System®
Principal strategies for optimizing skin penetration

- **Active/Vehicle Interactions**
  - Drug/Prodrug
  - Chemical Potential
  - Ion Pairs/Coacervates
  - Eutectic Systems

- **Vesicles and Particles**
  - Liposomes and Analogues
  - Microemulsions
  - Lipid Nanoparticles
  - High Velocity Particles

- **Stratum Corneum Modified**
  - Hydration
  - Chemical Enhancers

- **Stratum Corneum Bypassed/Removed**
  - Microneedles
  - Ablation
  - Follicular Delivery

- **Electrically Assisted Methods**
  - Phonophoresis
  - Iontophoresis
  - Electroporation
  - Magnetophoresis
  - Photomechanical Wave
Permeation Enhancers

Chemical permeation research focuses on finding excipients that improve drug solubility and stability in the formulation and enhance the permeation of the drug across the skin.

Two enhancer classes:

1. Enhancers that alter the structure of the skin lipids, decreasing their resistance to diffusion.
2. Those that enhance the solubility of the diffusing drug within the skin.
Permeation Enhancers

- Ethanol
- Dimethyl Sulfoxide
- Isopropyl Myristate
- Propylene Glycol
- Oleic Acid
Permeation Enhancers

- Chemical Permeation Enhancers
  - High boiling alcohols
  - Diols
  - Fatty acids and Fatty acid esters
  - Oleic acid
  - Glyceride-based solvents
**Macrochem**
(www.macrochem.com)

**SEPA® drug delivery technology**

SEPA enhances transdermal drug delivery by temporarily and reversibly disrupting the alignment of the lipid bilayer within the lipid.

**NexMed**
(www.nexmed.com)

NexACT technology utilizes highly effective formulations containing new biodegradable ingredients.
Liposomes & Transfersomes

Structure of nanodispersed vehicle systems

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Iontophoresis

A current passed between the active electrode and the indifferent electrode repelling drug away from the active electrode and into the skin.
IONSYS™
Ortho-McNeil
(www.ionsys.net)

Vyteris’ Lidosite
(www.vyteris.com)

Iomied’s Hybresis
(www.iomedi.com)
Electrokinesis

- Electrokinetic drug delivery is the sum of two processes:
  - Iontophoresis
  - Electroosmosis
- Iontophoresis is the delivery of ions of a drug into the skin by means of an electric field.
- Electroosmosis is the bulk fluid flow associated with cation transport by an electric field. Neutral drug molecules are transported passively by electroosmosis.
SoloVir™ Electrokinetic Transdermal System (ETS) Combination Product for Herpes labialis.
Electroporation

Electroporation is also based on the application of a voltage to the skin. In contrast to iontophoresis where a low voltage is applied, electroporation requires a large voltage treatment for a short period of 10 µs to 100 ms. Electroporation produces transient hydrophilic pores (aqueous pathways) across the skin barrier. These pores allow the passage of macromolecules via a combination of diffusion, electrophoresis and electroosmosis.

Basic principle of electroporation. Short pulses of high voltage current are applied to the skin producing hydrophilic pores in the intercellular bilayers via momentary realignment of lipids.
Sonophoresis (ultrasound technology)

Dermisonics
(www.dermisonics.com)

U-Strip Transdermal
Drug Delivery System

Echo Therapeutics, Inc. (Formerly Sontra Medical)
(www.echotx.com)

Generation 1.5
Generation 2.0
Microneedles

Zosano Pharma
(Formerly The Macroflux Corp.)
(www.macroflux.com)
Thermal Methods

- The use of controlled heat allows drugs to permeate the skin more effectively and efficiently than traditional methods.

- Controlled heat initiates several physiological responses that facilitate drug penetration through the skin, including:
  
  • An increase in skin permeability
  
  • An increase in body fluid circulation
  
  • Dilation of blood vessels, thus improving permeability through the blood vessel wall
  
  • An improvement in the solubility of most drugs
  
  • An increase in the release rate of the drug, from local skin tissue into systemic circulation
Controlled Heat-Assisted Drug Delivery (CHADD™)

- 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.

- Upon contact with oxygen in ambient air, a chemical reaction occurs in the heat-generating medium.

- After an initial rise in temperature, the temperature generated by the CHADD unit will reach and remain within the controlled temperature range for a pre-determined period of time.

- When the heat generating medium is exhausted, the skin temperature gradually returns to baseline.
Altea Therapeutics
(www.alteatherapeutics.com)

PassPortSystem

- Single-use disposable PassPort Patch
- Re-useable handheld Applicator

- A conventional transdermal patch attached to an array of metallic filaments ('porator').
- Pressing the activation button of the Applicator releases a single pulse of electrical energy to the porator, where it is converted into thermal energy.
- The rapid conduction of this thermal energy into the surface of the skin painlessly ablates the stratum corneum under each filament to create microchannels.
- When the Applicator is removed, a simple fold-over design aligns the transdermal patch with the newly formed microchannels.
TheraJect’s TheraJectMAT™
(www.theraject.com)

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“Patchless” Transdermal

Acrux Limited
(www.acrux.com.au)

- The MDTS is placed gently against the skin and depressed releasing a light spray which quickly dries on the skin.

- The ACROSS enhancers allow drugs to pass through the top layers of the skin.

- A once a day application typically delivers consistent amounts through the skin to the blood stream.
FUTURE DIRECTIONS
Crystal Technology

Aviva Transdermal (Nitto Denko)
(www.avevadds.com)

Transform Pharmaceuticals (Johnson & Johnson)
(www.transformpharma.com)

- Drug release from crystals
Radio Frequency Energy

TransPharma Medical™ Ltd.
(www.transpharma-medical.com)
Laser Energy

Norwood Abbey
(www.norwoodabbey.com)

The Epiture Easytouch™ is a revolutionary new drug delivery device that uses a laser to painlessly remove the stratum corneum.
Reverse Iontophoresis & Closed Loop Systems
Animas (Johnson & Johnson)

Glucose molecules being pulled through the skin

\[ g = \text{glucose molecules} \]
\[ - = \text{negative ion} \]
\[ + = \text{positive ion} \]
Technology Hybrids and Micro Systems

Crospon & Hewlett Packard
(www.crospon.com)

- One patch contains about 150 microneedles.
- Enables the drug's dose and time of delivering to be controlled by a microchip.
- The patch also contains 400 cylindrical reservoirs.
Technology Hybrids and Micro Transdermal Systems

Corium & Stratagent
(www.coriumgroup.com)

Dr. Samir Mitragotri
UCSB
Nano-technologies
NanoTechnology Victoria
(www.nanovic.com.au)

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Summary

- Transdermals are still a multi-billion dollar industry and a viable drug delivery platform technology.
- Key is to cross the stratum corneum.
- Traditional “Passive” delivery patches are the mainstay of the industry.
- Topicals and Creams are becoming popular.
- Novel techniques are being invented and developed for transdermal drug delivery.
- Almost all are a combination of active and passive skin permeation technologies.
- The future of dermal and transdermal drug delivery will be the development of pretreatment methods, devices, and topicals.