Transdermal delivery of macromolecules using Macroflux® technology

System requirements with emphasis on microfabrication, surface chemical properties, drug-specific requirements, and the interaction with human skin and systemic biology

NCCAVS – Thin Film Users Group
Bio-Nano-MEMS Technology
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Zosano Pharma
Better products with innovative delivery
Common routes of drug delivery

- Topical
- Oral
- Inhalation
- Injections
  - Intravenous
  - Intramuscular
  - Subcutaneous
  - Intradermal
- Transdermal
  - Passive
  - Active
Advantages of transdermal drug delivery

- Oral delivery is generally preferred but not always possible
  - May be degraded or not be absorbed by the gut
  - Can be irritating
  - Slow uptake
- Injection provides high bioavailability, but …
  - Often requires trained personnel to administer
  - More risk of infection, contaminants / particulates, air boluses
  - Rapid onset can be more addictive
  - Pain and/or phobia
- Transdermal drug delivery
  - Sustained or rapid onset
  - Possible diminished side effects due to reduced metabolites
  - Convenient and flexible dosing without pain
  - Dry formulations possible improving shelf-life and storage
  - Trend is towards faster onset and additional drug candidates
Passive transdermals are well-established

- Most people have used them or know someone who has
- Designed for daily or multi day wear
- Continuous steady state drug delivery profile

- Contain drug reservoir
- Passive, concentration dependent flux
- Slow delivery start up (hours)
- Steady state delivery, 1-7 days continuous
- Small hydrophobic drugs with molecular weights, <500 Da
- Small doses, <10mg/day
- Acceptable skin tolerability
The New Transdermal Delivery Opportunities

- Hydrophilic small drugs with poor or highly variable oral absorption, Class III drugs
- Small hydrophilic drugs requiring rapid delivery or sustained delivery (1 to ? Days)
- Injectables
  - Peptides
  - Biopharmaceuticals
    - (rec proteins, antibodies, RNAi….)
  - Vaccines
    - (protein, glycoconjugates, virus particles and DNA)
Approaches to overcoming skin barrier function

- Most drugs cannot passively diffuse across the waxy stratum corneum skin barrier
- Especially:
  - Hydrophilic
  - Large molecular size
- Approaches:
  - Chemical enhancers: Ethanol, FA & esters
  - Electrotransport
  - Mechanical methods
A number of micro mechanical approaches are in development

- **Radio-frequency - Transpharma - ViaDerm**
  - RF pulse to skin

- **Thermal ablation - Altea - PassPort**
  - “Hot wire” elements applied topically vaporize lipids in stratum corneum to create defects - rapid & local heating

- **Laser Ablation - Pantec Bio**
  - Excimer laser

- **Electroporation - Genetronic Biomedical - MedPulser**
  - Pulse voltage - 10-100 volts/ pulsed for micro-milli secs.

- **Acoustical Waves - Encapsulation Systems - U-Strip, Sontra Medical - SonoPrep**
  - Low frequency ultrasound ( <100 kHz)

- **Microneedles……..**
Skin Biology

Shallow delivery to epidermis avoids vascular bed and majority of pain nerves, reaching stratum spinosum crosses the hydrophobic / hydrophylic gradient.
Short Needles Have Been Known for Decades

- Smallpox vaccination

TB Tine Test
Hollow microneedles are more traditional looking and designed for ID injection (mm length needles)

**BD-Microneedle ID injector,**
- Soluviä microinjection system a prefilled syringe with 1.5 mm needle

1st EMEA application for intradermal influenza vaccine delivery
Announced Feb 13, 2008 by Sanofi Pasteur
Example – Microneedle patch skin pretreatment enhances Naltrexone delivery in clinical study

- 50 ss microneedles 620 micrometers in length
- Skin Pretreatment followed by hydrogel drug patch

Wermeling, DP et al PNAS 105, 2058, 2008
Zosano Patch Delivery System

Drug-coated patch
(size of a US quarter)

Magnified drug-coated microprojections

Individual microprojection

Dead Skin
(10-15 µm)

Epidermis
(50-150 µm)

Dermis
Capillaries & nerve endings

Confidential
Zosano Patch: Comparison to 25 g Needle

Microprojection array

Vaccine-coated microprojection array

Adhesive patch backing
System Requirements

- Self-administration
  - Simple
  - Minimal required dexterity
  - Robust to user variability
  - Room-temperature storage

- Minimal topical effects
  - Relatively short pathway patency
  - Visibly clear in 24 – 48 hours
  - Average stratum corneum turnover time is 14 days, epidermis 26-42 days
Skin Penetration is Controlled by Microprojection Length and Applicator System

5 s application from dip-coated $^{14}$C-OVA microprojection arrays
Microneedle Patch Application on Human Subjects Is Well-tolerated and Efficient

Pre-treatment  Post-treatment  Methylene blue stained
Solid Metal Microneedle Arrays can be Fabricated to Different Sizes, Shapes, and Densities

**Process:**
- Photochemical machining / contact lithography
- Can be scaled to continuous web
- Options for better dimensional control ??
- Options for improved forming tools ??
Zosano PTH Patch Clinical Program

• Extensive Phase 1 program completed to
  - Ensure tolerability
  - Investigate human PK
  - Optimize patch design (projection length & shape)
  - Select optimal patch application site
  - Select range of doses for Phase 2

• Successfully completed Phase 2, 6-month BMD study comparing 3 patch doses to both placebo and Forteo

• Phase 3 one-year BMD study planned for registration
Phase 2 Data in PMW with Osteoporosis Shows ZP-PTH Provides Rapid Pulse and Dose Proportional Delivery

- Patch dose proportionality demonstrated
- Patch delivers faster Tmax, higher Cmax, shorter half life than Forteo injection
- AUC dose variability is comparable to Forteo
- Bioavailability of coated dose administered is ~40% = ~16mcg

Lane et al, ACR/AHRP Ann Scientific Meeting, Oct 24-29, 2008
Following 24 weeks of treatment all active treatment groups increased BMD greater than placebo.

Percent Change from Baseline in LS-BMD (Mean +/- SE)

Percent Change From Baseline Total Hip BMD

Lane et al, ACR/AHRP Ann Scientific Meeting, Oct 24-29, 2008
Volume Manufacturing Capability

- Automated aseptic patch coating and packaging equipment
- Automated forming and assembly of patches subassemblies
- Phase 1-3 clinical supply production capacity
- Highly scalable process for commercial manufacturing
Zosano Transdermal Patch Technology

- Ideal solution for delivery of large and small hydrophilic drugs
  - No molecular size limitation
- Change/improve PK profile / PD outcome
- Simple therapeutic drug delivery
  - High patient acceptance, user friendly, and travel friendly
- Cost effective, alternative to outpatient injection

Additional benefits:
- Ready-to-use drug-coated patch with reusable or disposable low cost patch applicators
- Life cycle management
- Potential elimination of cold-chain (no product refrigeration required)
- Short patch wear time (<1hr); Rapid drug delivery
- Band-Aid like patch removal and disposal