Transdermal drug delivery technology

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Drug Delivery Strategies for Biologics
BioCity, Nottingham
December-2012
“Transdermal delivery is not sexy...”

Compared to... more interesting subjects, such as:
* Nanomedicines, including liposomes
* Polymer therapeutics, including implants, bioresponsive devices
* Oral, pulmonary, nasal delivery of proteins, peptides, siRNA, etc.
* siRNA, gene delivery
* Oral delivery of poorly-water-soluble drugs

... and so on.

So, is transdermal delivery the ugly duckling of the field... or a swan!
Why transdermal drug delivery?

- Avoid pre-systemic metabolism
  \[\Rightarrow\text{lower daily dose}\]
- Maintain drug level within the therapeutic window for prolonged period
  - extend duration of drug action
  - reduce frequency of dosing
- Reduce inter- and intra-patient variability
- Improved patient compliance and acceptability of drug therapy
- Drug input terminated simply by patch removal

![Graph showing concentration (Cp) vs. area (cm^2) for different drugs: Clonidine, Nitroglycerin, Fentanyl.](graph.png)
Transdermal delivery limitations

Limited to potent drug molecules... \{potency\}³
i.e., daily dose ≤ 50 mg
skin barrier function

Physical chemistry
* size... generally ‘small’ molecules
* lipophilic is good, but some solubility in both oil and water is necessary

Pharmacokinetics/pharmacodynamics
\( t_{1/2}, \) metabolism, dosing regimen, tolerance problems?

Area of patch (≤ 100 cm²)

Drug must not be locally irritating or sensitizing

Efficiency of drug use, expense, justification?

* scopolamine
* nitroglycerin
* clonidine
* estradiol
* fentanyl
* nicotine
* testosterone
* norelgestromin + ethinyl estradiol
* oxybutynin
* selegiline
* methylphenidate
* buprenorphine
* rotigotine
* rivastigmine
* granisetron
Skin structure

**Epidermis:** desquamating epithelium

**Stratum corneum (SC):** 'brick wall', water loss, lipids

**Dermis:** microcirculation, resorption

**Appendages:** hair follicles, sweat glands

<table>
<thead>
<tr>
<th>Layer</th>
<th>Thickness 1</th>
<th>Thickness 2</th>
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<tbody>
<tr>
<td>Stratum corneum</td>
<td>10 μm</td>
<td>0.01 mm</td>
</tr>
<tr>
<td>Epidermis</td>
<td>100 μm</td>
<td>0.10 mm</td>
</tr>
<tr>
<td>Dermis</td>
<td>1000 μm</td>
<td>1.00 mm</td>
</tr>
</tbody>
</table>
Current status

- 15 drugs, multiple systems:
  - scopolamine, nitroglycerin, clonidine, estradiol, fentanyl, nicotine, testosterone, combination norelgestromin-ethinyl estradiol, buprenorphine, oxybutynin, methylphenidate, selegiline, rotigotine, rivastigmine, granisetron

- Successful history (>1980), relative to other non-oral routes of novel drug administration

- Global market ~$6B in 2010

- The "patch" is generally acknowledged and accepted.
Physicochemical and pharmacokinetic properties of some transdermally administered drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>MW (Da)</th>
<th>Log P</th>
<th>Cl (L/hr)</th>
<th>t½ (hr)</th>
<th>F (%)</th>
<th>C_p^eff (ng/mL)</th>
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<tbody>
<tr>
<td>Scopolamine</td>
<td>303</td>
<td>1.24</td>
<td>672</td>
<td>2.9</td>
<td>27</td>
<td>0.04</td>
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<tr>
<td>Clonidine</td>
<td>230</td>
<td>0.83</td>
<td>13</td>
<td>6-20</td>
<td>95</td>
<td>0.2-2.0</td>
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<tr>
<td>Nitroglycerin</td>
<td>227</td>
<td>2.05</td>
<td>966</td>
<td>0.04</td>
<td>&lt;1</td>
<td>1.2-11</td>
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<tr>
<td>Estradiol</td>
<td>272</td>
<td>2.49</td>
<td>615-790</td>
<td>0.05</td>
<td>-</td>
<td>0.04-0.06</td>
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<tr>
<td>Fentanyl</td>
<td>337</td>
<td>2.93</td>
<td>27-75</td>
<td>3-12</td>
<td>32</td>
<td>1</td>
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<tr>
<td>Nicotine</td>
<td>162</td>
<td>1.21</td>
<td>78</td>
<td>2</td>
<td>30</td>
<td>10-30</td>
</tr>
<tr>
<td>Testosterone</td>
<td>288</td>
<td>3.31</td>
<td>-</td>
<td>-</td>
<td>&lt;1</td>
<td>10-100</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>357</td>
<td>4.16</td>
<td>?</td>
<td>2</td>
<td>6</td>
<td>1-5</td>
</tr>
<tr>
<td>Ritalin</td>
<td>233</td>
<td>2.11</td>
<td>20</td>
<td>2-3</td>
<td>5-20</td>
<td>5-25</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>315</td>
<td>4.68</td>
<td>5-7 (T)</td>
<td>n/a</td>
<td>~1</td>
<td>~1</td>
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<tr>
<td>Rivastigmine</td>
<td>250</td>
<td>2.3</td>
<td>108</td>
<td>1.5</td>
<td>40</td>
<td>~10</td>
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</table>
Transdermal drug delivery - rationale

• Topical application of classic formulations for systemic delivery is inefficient and inelegant

• Poor control of dose, area, etc. leads to variation in duration and extent of drug effect

• Transdermal systems aim to deliver drugs to the systemic circulation at a controlled and predictable rate:
  - TDS = drug + device
  - Control from system area and design
Technologies for transdermal drug delivery

- Conventional dosage forms (*ointments, gels*)
  - ? control, elegance, cost

- Transdermal delivery systems
  - adhesive systems
  - layered systems
  - reservoir systems
Characteristics of transdermal delivery

- TDD depends on **area** of contact between patch and skin!!
- TDD is less sensitive to drug loading, especially when skin controls input
  - Compare with oral!!
- Patch design does **not** predetermine degree of rate control
  - ex. nitroglycerin patches
- Drug loading in patch and release mechanism are **inappropriate** measures for bioequivalence
- Ideally (for safety) drug loading is close to amount to be delivered

![Graph showing the concentration vs. area for different drugs (Clonidine, Nitroglycerin, Fentanyl) with different slopes.](image-url)
Fentanyl

Analgesic with very narrow therapeutic index
- post-operative pain, chronic cancer pain
- US market already >$1.2B in 2007!
- 1 - 2 ng/mL = effective $C_p$
- accurate dose titration essential

Multiple systems on market
- Duragesic® = first product, a reservoir system
- labelled fluxes from 12.5 to 100 µg/hr
- up to 3 days application
- newer generics: simple adhesive-type
Design variables and delivery attributes of 100 μg/hr Fentanyl TDDS

<table>
<thead>
<tr>
<th>Brand/Licensee</th>
<th>Duragesic (Liquid Reservoir)</th>
<th>Duragesic D-Trans</th>
<th>Mylan</th>
<th>Teva</th>
<th>Apotex</th>
<th>Nicomed/Mallinckrodt</th>
<th>Ratiopharm</th>
<th>Lavipharm</th>
<th>Helm</th>
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<tbody>
<tr>
<td>Approved In</td>
<td>Innovator</td>
<td>EU/US</td>
<td>US</td>
<td>US</td>
<td>US</td>
<td>EU/US</td>
<td>EU</td>
<td>EU/US</td>
<td>EU</td>
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</tbody>
</table>

### Design Schematic

| Patch size to deliver 100 μg/hour over 3 days (cm²) | 40 |
| Nominal drug content (mg) | 10 |
| Number of layers | N/A |
| Presence of rate-controlling membrane | Yes, EVA |
| State of API in Adhesive | Dispersed |
| Adhesive platform | Silicone |
| Solubilizer or enhancer | None |
| In-vivo release rate (μg/cm²/hr) | 2.50 |
| Drug utilization (%) | 72 |
| Residual drug content in system after 3-day use (mg) | 2.80 |

Thean Yeoh, Pfizer, Groton, CT
Oxybutynin

Maintenance of constant Cp over several days
Significant reduction in daily and weekly incontinence episodes
Avoidance of 1st-pass metabolism
Reduced daily dose
Limited skin irritation observed

Drug delivered + side-effects

Transdermal Oxytrol™
Immediate release (oral)
Neupro: transdermal rotigotine

Neupro = transdermal patches, which release 2, 4, 6, or 8 mg of rotigotine over 24 hours.

Neupro is used to treat early-stage Parkinson’s disease; used w/o levodopa.

First Drug Developed From Outset for Transdermal Delivery
Contributions of transdermal delivery

- Drug administration distinct from oral dosing.
- Avoids the "peaks and valleys" in $C_p$.
- Different patches and release mechanisms... equivalent drug delivery.
- $C_p$ can be manipulated by changing patch area.
- Avoidance of 1st-pass effect; altered metabolite ratios (↓ side-effects).
- Applicable to diverse therapeutic areas.
- Provides sustained drug input from 0.5 to 7 days.
- Delivers difficult-to-formulate drugs.
- Improved patient compliance and drug utilization.
Enhancing transdermal transport

- Passive diffusion of molecules > 1000 da is very inefficient
- Skin's principal function is to provide a barrier
- Efficient transdermal transport $\Rightarrow$ enhancement technology
  - which acts on the molecule
    - iontophoresis
  - which acts on the barrier
    - microneedles, microporation
    - ultrasound
    - other 'permeabilization' approaches (e.g., high-velocity particles)
  - which involves novel formulation
    - liposomes, nanoparticles or other enhancing/targeting moiety
Iontophoresis: Proof-of-principle, ca. 1900

Le Duc ~ 1900

NaCl → le lapin est mort → NaCl

Strychnine Sulfate

NaCl → vive le lapin → NaCl

Strychnine Sulfate
Iontophoresis: facilitated transport across skin

- Small (<0.5 mA/cm²) electric current applied
- Facilitates and controls non-invasive transfer of molecules across skin
- Drug delivery profile adjusted by modifying current profile employed

Graphs showing:

- Migraine treatment with Zolmitriptan concentration over time for Iontophoresis and Oral administration.
- Fertility treatment with Peptide concentration over time for SC and Iontophoresis (3x5 min) administrations.

Vyteris, Inc.
Technology: Lidocaine

* Lidocaine HCl (10%)/Epinephrine (0.1%) iontophoretic patch
* Fast, effective analgesia prior to blood draws, venipunctures, etc.
* Rapid, noninvasive 10-minute application delivers lidocaine deep into skin

LidoSite™ Lidocaine Delivery System

Vyteris, Inc.
Technology: Fentanyl

Serum [fentanyl] following IONSYS compared to IV
(i) during the first hour of treatment, and
(ii) during the last hour and upon termination of treatment

IONSYS: 2 sequential doses of 40 μg over 20 min each hour for 23 h 20 min
IV: 80 μg dose 20 min every hour for 23 h 20 min

http://www.ionsys.net/active/janus/en_US/assets/common/company/pi/ionsys.pdf#zoom=100
Technology: Sumitriptan

Zelrix (NuPathe, Inc.): an active, single-use transdermal system that delivers sumatriptan for the treatment of migraine.

4-hour application results in Cmax of 19-30 ng/mL, sustained from 1 hour post-initiation of current.

Terminal half-life post-treatment is ~3 hr.

NDA submitted
Iontophoretic outlook... good news

- Iontophoresis is a mature and maturing technology
  - Feasibility demonstrated both for drug delivery (lidocaine and fentanyl) and noninvasive monitoring (glucose and...)
  - Other drugs are in development and advances expected in Parkinson's treatment, migraine therapy, fertility...
  - Mechanisms reasonably well-understood
  - Safety, toxicity profile reasonably good
Iontophoretic outlook... bad news

- What are the unmet needs and challenges for iontophoresis?
  - Clear need for a commercial success
  - Clever technology and sound scientific base is not enough
  - Choosing the right drug-disease combination(s) for iontophoresis
  - Overcoming skin irritation
Minimally invasive transdermal technologies

- Laser ablation
- Microneedles
- Thermal poration
- Sonoporation
- PowderJect
- Electroporation
- Microscission
Conventional transdermal drug delivery rate limited by molecular weight.
New technologies can deliver high molecular weight species.

**Macromolecule delivery across skin**

- Fentanyl (336MW)
- Nicotine (162MW)
- Estrogen (272MW)
- Interferon-beta (22,500MW)
- hPTH (4,117MW)
- Insulin (5,916MW)
- Anthrax Vaccine (83,000MW)
Bolus or sustained transdermal delivery of water-soluble biologicals and small drugs

<table>
<thead>
<tr>
<th>Sustained Delivery</th>
<th>Delivery in Humans or Animal Model</th>
</tr>
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<tbody>
<tr>
<td>Exenatide</td>
<td>Enoxaparin Na</td>
</tr>
<tr>
<td>Insulin</td>
<td>Exenatide</td>
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<tr>
<td>Enoxaparin Sodium</td>
<td>BUS.HCl</td>
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<tr>
<td>Interferon-α</td>
<td>FEN.CIT</td>
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<tr>
<td>Fentanyl citrate</td>
<td>PTH</td>
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<tr>
<td>Risperidone tartrate</td>
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</tr>
<tr>
<td>Buspirone HCl</td>
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<table>
<thead>
<tr>
<th>Bolus Delivery</th>
<th>Current patches</th>
</tr>
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<tbody>
<tr>
<td>Parathyroid hormone</td>
<td>RIS.TAR</td>
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<tr>
<td>Insulin</td>
<td>BUS.HCl</td>
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<td>Enoxaparin Sodium</td>
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<tr>
<td>Erythropoietin</td>
<td>PTH</td>
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<tr>
<td>Calcitonin</td>
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<tr>
<td>Human and avian antigens</td>
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Water solubility

Size (daltons)
P.L.E.A.S.E. - painless laser epidermal system

Pantec Biosolutions, AG

Creation of aqueous micro-pores through the epidermis using a laser scanner device

Data from human cutaneous tolerability study, 150 pores on a 6mm circular array (proDERM GmbH, Hamburg)
P.L.E.A.S.E. – painless laser epidermal system

Delivery of triptorelin, a decapeptide (pGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH₂), which is a gonadotropin-releasing hormone (GnRH) agonist

Delivered intact Follicle Stimulating Hormone (MW = 30 Kda) across skin into systemic circulation and achieved therapeutic levels sufficient to induce follicle growth

Pantec Biosolutions, AG
Thermal poration of skin

PassPort system (Altea/Nitto Denko) painlessly creates microscopic channels in stratum corneum and positions a transdermal patch over the openings.

- Bolus or sustained delivery
- Patches 0.25 cm² - 12 cm²
- MW studied = up to 300 kDa
- Aq. solubility studied = up to 300 mg/mL
- Dose achieved per single application
  - 200 mg small molecules
  - 30 mg carbohydrate
  - 10 mg polypeptides
  - 5 mg protein
Sustained glucose-lowering effect for 24 hr

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Glucose Clamp [n=6 normal subjects]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
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<td>6</td>
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<tr>
<td>12</td>
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<tr>
<td>14</td>
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</table>

Transdermal Patch On

Sustained glucose-lowering effect for 24 hr

Bolus delivery of parathyroid hormone (PTH)

Transdermal application of 55 μg PTH (n = 6)

Subcutaneous injection of 20 μg PTH (n = 5)
PassPort® fentanyl citrate multi-dosing

Phase 1 clinical study in healthy subjects; n = 12; 1 cm² patch
New patch worn for 24 h every day for 3 days
Reconstructed 3-D confocal stack

**Red/blue**: Skin autofluorescence

**Green**: Fluorescent nanoparticles

200 nm fluorescent nanoparticles

20 nm fluorescent nanoparticles

Intact skin

Stripped skin

Nanoparticles and thermal ‘poration’

Thermal poration* of skin: skin lipids imaged with CARS (red), nanoparticles with 2-photon fluorescence microscopy (green).

Mid-depth ‘slice’ through a pore

N. Belsey et al., 2011
Nanoparticles and thermal ‘poration’

3-D reconstructions of fluorescent nanoparticle disposition on and into thermally-porated skin.

Skin lipids imaged with CARS (red), deuterated polystyrene 40 nm nano-particles with SRS (blue).

N. Belsey et al., 2011
Nano- and other particles...
Conclusions

- Considerable innovation and progress in transdermal drug delivery technologies since 1980.
  - marked (multi-billion $$$) commercial success
  - opportunities in subcutaneous delivery (patches??)

- Selecting topical/transdermal drug candidates must consider both pharmacology and skin permeability.
  - Lipinski's rules are not irrelevant to skin.

- Delivering biologics is a substantial challenge.
  - iontophoresis can help but is far from a panacea.
  - novel enhancement technologies involving poration of skin barrier can move the barrier out of the way.