Non-invasive monitoring across the skin

Richard H. Guy
Department of Pharmacy & Pharmacology, University of Bath

Structure of the skin

- **Epidemis**: structure, differentiation
- **Stratum corneum** (horny layer, SC): structure, composition
- **Dermis**: microcirculation, resorption
- **Appendages**: hair follicles, sweat glands

**Optimizing drug delivery…**
- An “ideal” drug delivery system responds to the patient’s needs
  - detects the need for drug input at a certain dose and rate
  - controls delivery precisely in terms of amount per unit time
- The “Holy Grail”
  - a closed-loop ‘biofeedback’ system
- Classic example: diabetes
  - blood glucose levels and insulin administration
- Technological possibilities include:
  - measure drug concentration in blood and infuse dose accordingly
  - implantable sensor and programmable delivery (Microchip technology)
  - noninvasive delivery and monitoring across the skin

**Enhancing transdermal transport ‘in’ and ‘out’**
- Passive diffusion of many molecules (e.g., high MW, low lipophilicity) across skin 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
    - ultrasound, microneedles, microporation
  - other ‘permeabilization’ approaches (e.g., high-velocity particles)
  - which involves novel formulation
    - liposomes, or other carrier/targeting moiety, or enhancers
Iontophoresis: Proof-of-principle, ca. 1900

- Non-invasive technique
- Small electric current applied
  - (< 0.5 mA/cm²)
  - facilitates and controls transfer of molecules across skin

Relevance for drug delivery:
- Steady-state plasma levels are maintained until current is stopped.
- Delivery profile can be adjusted by modifying current profile.

**Transport Number**

\[
t_i = \frac{i_i}{I_{\text{TOTAL}}}
\]

The transport number is the fraction of the total current carried by the ion of interest (the drug).

\[
J_i = \frac{t_i \cdot I}{F \cdot z_i}
\]

The flux of the drug ion is determined by the total current passed and by its transport number.

\[
\sum t_i = 1
\]

There is competition between ions to carry the current across the skin.

\[
t = \frac{z_i \cdot n_i \cdot C_i}{\sum z_i \cdot n_i \cdot C_i}
\]

**Iontophoresis of Lidocaine and Ropinirol**

(Marra et al., Lizarde-Alvarez et al., Pharm. Res., 2005)

**Iontophoresis**

- Drug Reservoir
- Membrane
- Return Reservoir
- Skin
- Blood Vessel

**Graph**

- Lidocaine donor concentration (mM)
- Ropinirol (nmol/cm²/hr)
- Current density (mA/cm²)

**Table**

<table>
<thead>
<tr>
<th>Lidocaine Flux (nmol/cm²/hr)</th>
<th>0</th>
<th>500</th>
<th>1000</th>
<th>1500</th>
<th>2000</th>
<th>2500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD (n = 4-5)</td>
<td></td>
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</table>
Skin negative at pH 7.4/cation permselective

**Electroosmosis**

In vivo, this convective solvent flow:
- Enhances transport of positively charged species → Cationic drugs
- Allows the iontophoretic transport of neutral/hydrophilic species → Glucose (Non-invasive sampling of blood chemistry)

**Iontophoresis and Clinical Chemistry**

- Iontophoresis is a symmetrical process - under the two electrodes, ions are driven both into and out of the skin.
- Therefore, iontophoresis can be used to both deliver and extract material into/from the skin.
- Extraction is non-specific, demands analytical capability.
- But the generality of the procedure implies significant potential for noninvasive clinical chemistry.
- Initial focus: GLUCOSE

**GlucoWatch Biographer** *(Cygnus, Inc.)*

- Monitors glucose levels in diabetics
- Detects trends, tracks patterns in glucose levels
- Frequently automatically
- Non-invasive
- Based on transdermally extracted glucose
- Calibrated to blood glucose
- Iontophoretically extracts glucose, determines concentration and displays results

- Glucomatch has FDA approval and the CE mark
- First marketed in the UK in 2001, US distribution began April 15, 2002
- Pre-market approval for use in juvenile diabetes (7-17 years) from FDA, 08-02
- Improved, next-generation product approved, but not marketed
- Cygnus acquired by Animas in 2005, Animas acquired by J&J in 2006...
Current medical practice versus continuous glucose monitoring with the GlucoWatch Biographer®

- First, a finger-stick calibration
- Glucose readings are then recorded automatically
- ↑↑↑ measures ↑↑↑ information
- Better information ⇒⇒⇒ better control of blood sugar
- Hypoglycemic alarm
- Mild erythema after 12-hour use of device

Glucose and beyond....

- Improve sensitivity by minimizing collection volume?
- Extraction of other analytes of interest: therapeutic drug monitoring (lithium), diagnostics/monitoring (e.g., phenylalanine), metabolism (e.g., lactate, urea, potassium)
- Can the method be made truly noninvasive (i.e., avoid daily calibration)?

Therapeutic drug monitoring

- Typically, via blood sampling:
  - Invasive
  - Risk of infection
  - Poor compliance
- Reverse iontophoresis:
  - “Traffic light” system
  - Portable, home-use
  - Pharmacokinetics in 'difficult' populations (e.g., neonates)
- Examples:
  - Valproic acid
  - Phenytoin
  - Lithium

Predicted [Li]_{serum} in bipolar patients

B. Leboulanger et al., Clin. Chem. 50 (2004) 2091-2100
Lithium: in vivo – in vitro correlation

\[ t_{1/2} = 0.48(\pm 0.04)X_{Li}, \quad r^2 = 0.86 \]

In vivo, slope = 0.54 (± 0.01)


Metabolite monitoring

- Extraction from skin versus extraction from 'central compartment'.
  - Frequently observe higher amounts extracted at short times.
  - Possibility to quantify skin "health", or dermatological disease.
  - Metabolic complications - glucose monitoring variability?

- Examples
  - Eczematous (dry) skin: natural moisturizing factor as a biomarker?
  - Amino acids, lactate.
  - Renal disease: urea, iohexol.
  - Others yet to be identified...

Reverse iontophoresis of amino acids in vivo

8x25-min of iontophoresis (0.3 mA/cm²); LC-MS data compared to blood sampling.

Monitoring renal function by reverse iontophoresis

Patients with kidney failure undergo dialysis.

- Dialysis efficiency is assessed by decrease in urea blood level.
- Urea levels are monitored typically before and after dialysis.

Potential for reverse iontophoresis to:
- (a) noninvasively monitor changes in urea blood levels, and
- (b) track urea concentrations during dialysis.

In vitro experiment

Subdermal [urea] decreased in 5 steps to mimic dialysis procedure.

Urea extraction flux (+) tracks subdermal concentration.

Monitoring renal function by reverse iontophoresis

In vivo, during hemodialysis, urea extraction flux decays exponentially. Extraction fluxes correlate well with blood concentrations. Potassium demonstrates similar behavior.

Glomerular filtration rate: Iohexol

Central compartment

Peripheral compartment

\[
C_{iohexol} = 0.24e^{-0.03t} + 0.17e^{-0.05t}
\]

Mean Dose = 3.2 g

\[
\ln J_{iohexol} = \ln C_{iohexol} \cdot \alpha + \beta (h^{-1})
\]

Initial results encouraging, but glucose extraction much more variable than Na⁺

Alternative, electro-osmotically-extracted internal standards assessed

Urea is a candidate

The "Internal Standard" Concept: GLUCOSE

- Novel technology using an endogenous substance as the "internal standard" obviates need for an invasive calibration step
- Hypothesis:

\[
\frac{J_{Na}}{J_{Glucose}} = K \cdot \frac{[Glucose]}{[Na]}
\]

- Na⁺ = "internal standard" (I.S.)
- In vitro results support hypothesis
- K is constant (0.072 ± 0.011)


**Iontophoresis**

*Summary and outlook*

- **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 and...
  - Mechanisms reasonably well-understood
  - Safety, toxicity profile reasonably good

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