Microfluidics

Involves the use of microtechnologies to get networks of microscopic channels for chemical processing.

- control of small volumes of liquid (fL to μL),
- reduction of chemicals consumption,
- cheaper process
Available materials

- **Silicon**

- **Glass** (e.g. Pyrex, borofloat)

- **Polymers** (e.g. PMMA, PC, PDMS, etc.)
Device Fabrication

(1) resist deposition by (2) spin-coating

(3) development

Source: U. Staufer (SAMLAB)
Device Fabrication

Pour liquid PDMS over the master and allow to cure

Bond PDMS structure to another flat PDMS layer or to glass and insert tubing

Gently peel off the PDMS from the master
Multiple Internal Reflection Poly(Dimethylsiloxane) Systems for on-line pH Monitoring of Cells
Goal

To develop a method to monitor on-line pH from cell medium, which was in contact with cells.
Human Umbilical Vein Endothelial Cells [HUVEC]
pH monitoring

Phenol red

http://chemistry-1023.wikispaces.com/Acids,+Bases+and+Buffers

http://en.wikipedia.org/wiki/Phenol_red
Propagating Multiple Internal Reflection System (PMIR)

Llobera et al., 2007
Set-up

Incubator:
5% CO₂
37°C
pH monitoring

M.J. Lopez-Martinez et al., MicroTAS 2010
Results

Cells disturb the signal, after introducing them to the chip
Introduce a cavity in the glass slide using HF treatment.
Coat only the cavity with gelatin
Results
Fast Determination of Distribution Coefficients in a Poly(Dimethylsiloxane) Chip
Goal

Calculation of log D at pH = 7.4 for different drugs using a microfluidic device and UV on-line measurements
Distribution coefficient

\[ \text{LogD} = \text{Log} \frac{C_0}{C_w} \]

> The distribution coefficient is the ratio between the concentration of the compound in an organic phase (Co), and the concentration in aqueous phase (Ca) at a certain pH.
Standard method

- Liquid-Liquid extraction
- Presaturation of solvents (24h)
- Volume ratio 1:1, 2:1, 1:2

Cons:
• Time consuming (>30 minutes per sample)
• Labour-intensive procedure
• Large amounts of material are required.
Microfluidics

Slug flow

Side-by-side flow
Aqueous phase

 Slug flow

 Organic phase

 Slug flow

 Aqueous phase outlet

 Narrow channels

 Serpentine Channel

 Organic phase outlet

 Inlets
Set up

UV-Detector: Shimadzu SPD-6A
<table>
<thead>
<tr>
<th>Compound</th>
<th>λ (nm)*</th>
<th>Structure</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol (Mw 151.17 g/mol)</td>
<td>Ac - 245 &lt;br&gt; Alk - 257</td>
<td><img src="image" alt="Paracetamol Structure" /></td>
<td>9.5 -acid</td>
</tr>
<tr>
<td>Salicylic Acid (Mw 138.12 g/mol)</td>
<td>Ac - 236 &lt;br&gt; Alk - 298</td>
<td><img src="image" alt="Salicylic Acid Structure" /></td>
<td>2.97-acid</td>
</tr>
</tbody>
</table>

Standard method

\[ V = 10 \text{ mL} \]
\[ t = 2h 30 \text{ min} \]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Log D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylic acid</td>
<td>-1.68 ± 0.01</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>0.31 ± 0.01</td>
</tr>
</tbody>
</table>
Chip

\[ V = 120 \text{ nL} \]
\[ t < 2 \text{ min} \]

<table>
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</thead>
<tbody>
<tr>
<td>Salicylic acid</td>
<td>-1.69 ± 0.01</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>0.36 ± 0.01</td>
</tr>
</tbody>
</table>
Summary
Acknowledgements

Prof. Dr. E.M.J. Verpoorte
P.P.M.F.A. Mulder
M. Van Dijk
W.I. van Leeuwen-Hangyi
M. Lukkien
J. Meindertsma
Thank you for your attention
Available materials (1)

Silicon
- crystalline
- semiconductor
- transparent at $\lambda > 1.1$ mm
- high mechanical strength
- technology well developed (integrated circuits, early 60’s)
- bulk etching (3-D structures)
- surface micromachining (2-D structures)
- dry or wet processing

Glass (e.g. Pyrex, borofloat)
- amorphous
- electrical insulator
- bulk etching (like silicon)
- large research lab
Available materials (2)

Polymers

- wide variety (PMMA, PC, PDMS, etc.)
- choice of optical / chemical properties

- Replication techniques
  - hot embossing
  - injection molding
  - casting

- resolution: $\mu$m to nm
pH monitoring

Cell Medium contains 2 buffer systems:

- hepes buffer
- carbonate buffer

Measurement will take place in a 5% CO₂ incubator at 37° C

Medium has a pH indicator: phenol red

[*] production information sheet from Sigma-Aldrich
<table>
<thead>
<tr>
<th>Compound</th>
<th>λ (nm)</th>
<th>pH</th>
<th>Log D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>254 (HPLC)</td>
<td>7.4 (35mM phosphate buffer)</td>
<td>-0.62</td>
</tr>
<tr>
<td>Caffeine</td>
<td>254 (HPLC)</td>
<td>7.4 (35mM phosphate buffer)</td>
<td>-0.76</td>
</tr>
<tr>
<td>Salicylic Acid</td>
<td>254 (HPLC)</td>
<td>7.4 (35mM phosphate buffer)</td>
<td>-1.31</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Compound</th>
<th>λ (nm)</th>
<th>pH</th>
<th>Log D (Flow system)</th>
<th>Log D (Batch method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>245</td>
<td>7.4 (20mM phosphate buffer)</td>
<td>0.42</td>
<td>0.38</td>
</tr>
<tr>
<td>Caffeine</td>
<td>272</td>
<td>7.4 (20mM phosphate buffer)</td>
<td>-0.08</td>
<td>-0.32</td>
</tr>
<tr>
<td>Salicylic Acid</td>
<td>296</td>
<td>7.4 (20mM phosphate buffer)</td>
<td>-1.41</td>
<td>-1.44</td>
</tr>
</tbody>
</table>

Carlsson et al. Analytica Chimica Acta 423 (2000) 137-144