USE OF CAPILLARY ELECTROPHORESIS
FOR THE QUALITY CONTROL OF PHARMACEUTICAL FORMULATIONS PRODUCED IN HOSPITAL PHARMACY

CEPharm, Boston, October 12th 2009

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Quality control laboratory
Pharmacy of Geneva University Hospitals
Switzerland
Europe
Switzerland
Geneva
HUG – Geneva University Hospitals - Pharmacy

Geneva University Hospitals
- 2000 beds
- 50'000 hospitalizations/year

Pharmacy
- 50 employees

Distribution
Pharmaceutical assistance
Production

Quality control laboratory
- 3 persons
- ~ 200 m²
- > 20'000 analyses/year
# Missions of Quality Control Laboratory HUG

## Activities

<table>
<thead>
<tr>
<th>Routine analysis</th>
<th>Stability studies</th>
<th>Incompatibility tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw material analysis</td>
<td>New formulation</td>
<td>Physicochemical incompatibilities between drugs</td>
</tr>
<tr>
<td>End-products analysis</td>
<td>Development, validation and application of analytical methods</td>
<td></td>
</tr>
<tr>
<td>Cleanrooms/operators control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Analysis

**Physicochemical analysis**
- Density, refractive index, melting point, boiling point, IR spectra, UV spectra...
- pH, osmolarity, particulate matter identification of drugs/excipients...
- Quantification of active drugs

**Microbiological analysis**
- Sterility test
- Endotoxine determination
- Surface and area control
Production of Drugs at the Hospital Pharmacy

Reasons of production

Not available on the market

Available, but not in an appropriate form
  Dosage (ex. pediatrics)
  Risk of error (ex. dilution)
  Risk of microbiological contamination (ex. intraophtalmics)
  Toxicity (ex. cytotoxics)

Clinical research

Types of Formulations

Injectables
Ophthalmics
Oral, topic solutions
Suspensions
Suppositories
Capsules
Separation techniques used at HUG Ph.

Before 2004

**Illustrated by the recommendation of international pharmacopeias**

- LC-UV
  - High solvent consumption
  - Cost of column: 1 column = 1 compound

After 2004

- High efficiency
- CE-UV
  - Low solvent consumption
- CE-C^4^D
  - Low cost of capillaries
  - Rapid method development
  - Wide range of compounds
  - Different detectors
### CE-UV: Short-end injection, aqueous BGE

#### Experimental conditions
- **BGE:** Tris-phosphate 50 mM, pH 2.5
- **Injection:** 5 s 20 mbar
- **Voltage:** 30 kV
- **UV:** 200 nm

#### Examples of validation results

<table>
<thead>
<tr>
<th>Theoretical concentration</th>
<th>Trueness (CV)</th>
<th>Repeatability (CV)</th>
<th>Intermediate precision (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine 10 mg/mL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td>100.0%</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>100%</td>
<td>99.7%</td>
<td>0.9%</td>
<td>1.3%</td>
</tr>
<tr>
<td>120%</td>
<td>100.3%</td>
<td>1.0%</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>Oxybuprocaine 10 mg/mL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td>100.4%</td>
<td>1.4%</td>
<td>1.5%</td>
</tr>
<tr>
<td>100%</td>
<td>100.2%</td>
<td>1.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td>120%</td>
<td>100.7%</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td><strong>Tetracaine 50mg/mL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td>99.7%</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>100%</td>
<td>100.5%</td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>120%</td>
<td>99.7%</td>
<td>0.4%</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>Ketamine 50 mg/mL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td>99.9%</td>
<td>1.7%</td>
<td>2.0%</td>
</tr>
<tr>
<td>100%</td>
<td>100.8%</td>
<td>2.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td>120%</td>
<td>99.5%</td>
<td>1.4%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

Experimental conditions:
BGE: Tris-phosphate 100 mM, pH 2.5 – acetonitrile (80:20)
Injection: 5 s 20 mbar
Voltage: 30 kV
UV: 200 nm

Hydro-organic BGE

Experimental conditions:
BGE: ammonium acetate 25 mM, acetic acid 1M in MeOH-ACN (10:90, v/v)
Injection: 10 s 40 mbar
Voltage: 30 kV
UV: 200 nm

Non-aqueous BGE

scopolamine (S)
atropine (At)
isoprenaline (I)
adrenaline (Ad)
procaine (internal standard (IS))

homatropine ophthalmic solution
weak ophthalmic injection
(homatropine (H), phenylephrine (P))
procaine (internal standard (IS))

### Stability Study: Cefuroxime 10 mg/mL 0.5mL

**Experimental conditions:**
- **BGE:** Phosphate buffer 20 mM pH 7.2
- **Injection:** 10 s 40 mbar
- **Voltage:** 30 kV
- **UV:** 200 nm

**Validation results**

<table>
<thead>
<tr>
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<tr>
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<td>100.9%</td>
<td>1.3%</td>
<td>1.6%</td>
</tr>
<tr>
<td>120%</td>
<td>99.0%</td>
<td>1.5%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

**Results of stability study**

Syringes of cefuroxime at 10 mg/mL can be stored 4 months at −18°C without loss of potency. After unfreezing, they must be used immediately (fast increase of degradation products at ambient temperature).
**Experimental conditions**

- **BGE:** 100 mM Tris-acetate at pH 4.2, acetonitrile (90:10, v/v)
- **Injection:** 40 mbar 10s
- **Voltage:** 30 kV
- **Capillary:** 50 μm i.d., 375 μm o.d.
  - tot. length: 64.5 cm, eff. length: 50 cm

**Validation**

<table>
<thead>
<tr>
<th>Theoretical concentration</th>
<th>Trueness (CV)</th>
<th>Repeatability (CV)</th>
<th>Intermediate precision (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>suxamethonium 10 mg/mL</td>
<td>80%</td>
<td>98.8%</td>
<td>1.1%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>100.2%</td>
<td>1.3%</td>
</tr>
<tr>
<td></td>
<td>120%</td>
<td>101.1%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

**Stability study**

- ready-to-use solution
- Succinolin, Lysthenon

Quality control of total parenteral nutrition

Experimental conditions

BGE : 100 mM Tris-acetate pH 4.5 : acetonitrile (80:20, v/v)
Injection : 40 mbar 10s
Voltage : 30 kV
Capillary : 50 μm i.d., 375 μm o.d.
  total length: 64.5 cm, effective length: 50 cm
C⁴D: output frequency: 150 kHz, output voltage: 40 Vpp

Validation

<table>
<thead>
<tr>
<th>Theoretical Conc. [mM]</th>
<th>Trueness</th>
<th>Repeatability (CV)</th>
<th>Intermediate precision (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100.6%</td>
<td>1.0%</td>
<td>1.3%</td>
</tr>
<tr>
<td>potassium</td>
<td>2</td>
<td>101.8%</td>
<td>1.2%</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>101.6%</td>
<td>1.1%</td>
</tr>
<tr>
<td>sodium</td>
<td>1</td>
<td>100.9%</td>
<td>1.2%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>100.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>99.7%</td>
<td>0.9%</td>
</tr>
<tr>
<td>calcium</td>
<td>0.5</td>
<td>100.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>100.4%</td>
<td>1.3%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>99.0%</td>
<td>0.4%</td>
</tr>
<tr>
<td>magnesium</td>
<td>0.5</td>
<td>99.1%</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>99.2%</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>98.6%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

CE analysis at the Ph. HUG

**CE-UV/DAD**

Aqueous BGE
- tetracaine
- ephedrine
- ketamine
- phenylephrine
- lidocaine (IS)
- codeine
- oxybuprocaine
- local anesthetics
- procaine (IS)
- cefuroxime

Hydro-organic BGE
- scopolamine
- atropine
- isoprenaline
- adrenaline
- procaine (IS)

Non-aqueous BGE
- homatropine
- opht. solution
- weak ophthalmic injection
- homatropin, phenylephrine
- procaine (IS)

**CE-C⁴D**

capacitively coupled contactless conductivity detection

- suxamethonium
- inorganic cations in parenteral nutrition
- Na⁺, K⁺, Ca²⁺, Mg²⁺
Quantitative analyses achieved by LC and CE

<table>
<thead>
<tr>
<th>% of separation analyses performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE acquisition</td>
</tr>
<tr>
<td>Year</td>
</tr>
<tr>
<td>2000-2004</td>
</tr>
<tr>
<td>2005</td>
</tr>
<tr>
<td>2006</td>
</tr>
<tr>
<td>2007</td>
</tr>
<tr>
<td>2008</td>
</tr>
</tbody>
</table>

Quantitative analyse of one formulation batch:

<table>
<thead>
<tr>
<th>Mean Criteria</th>
<th>LC</th>
<th>CE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>5 h</td>
<td>3 h</td>
</tr>
<tr>
<td>Organic solvent consumption</td>
<td>≥ 100 mL</td>
<td>0 - 5 mL</td>
</tr>
<tr>
<td>Cost (capillaries or columns, consumables and products)</td>
<td>30 euro</td>
<td>7 euro</td>
</tr>
<tr>
<td>Quantitative performances</td>
<td>Conform</td>
<td>Conform</td>
</tr>
<tr>
<td>(trueness 100 ± 2%, CV &lt;3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

1. 20 formulations analyzed by CE successfully by the HUG pharmacy, for routine analysis and stability tests.

2. CE analysis is an attractive alternative to LC for the following reasons:
   - Economical aspects
   - Environment respect
   - Similar performances

Use of CE in quality control laboratories should be strongly encouraged!
Acknowledgement

Dr. Sandrine Fleury-Souverain
Prof. Pascal Bonnabry

Dr. Serge Rudaz
Prof. Jean-Luc Veuthey
Thanks for your attention!