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

Prescription
Production
Quality control
Patient administration

Routine analysis
Stability studies
Incompatibility tests

Physicochemical analysis
Microbiological analysis

Analysis

Activities

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
Low cost of capillaries
Rapid method development
Wide range of compounds
Different detectors

CE-C4D
Experimental conditions
BGE: Tris-phosphate 50 mM, pH 2.5
Injection: 5 s 20 mbar
Voltage: 30 kV
UV: 200 nm

<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>Morphine 10 mg/mL</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>Oxybuprocaine 10 mg/mL</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>
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</tr>
<tr>
<td>120%</td>
<td>100.7%</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Tetracaine 50mg/mL</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>Ketamine 50 mg/mL</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>
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<td>2.4%</td>
</tr>
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</table>

Examples of validation results

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

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


Validation results

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<tr>
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<td>100.9%</td>
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<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 ~10°C without less 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 (80:20, 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

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<tr>
<th>Theoretical concentration</th>
<th>Trueness (CV)</th>
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<th>Intermediate precision (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>suxamethonium 10 mg/mL</td>
<td>100%</td>
<td>100.2%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>


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.
tot. length: 64.5 cm, eff. length: 50 cm
C/0: output frequency: 150 kHz, output voltage: 40 Vpp

Validation

<table>
<thead>
<tr>
<th>Theoretical Conc. [mM]</th>
<th>Trueness (CV)</th>
<th>Repeatability (CV)</th>
<th>Intermediate precision (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>potassium 1</td>
<td>100.6%</td>
<td>1.0%</td>
<td>1.3%</td>
</tr>
<tr>
<td>sodium 1</td>
<td>100.9%</td>
<td>1.2%</td>
<td>1.5%</td>
</tr>
<tr>
<td>calcium 0.5</td>
<td>100.5%</td>
<td>1.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td>magnesium 0.5</td>
<td>99.9%</td>
<td>0.4%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

CE analysis at the Ph. HUG

**CE-UV/DAD**
- Aqueous BGE: tetracaine, ephedrine, ketamine, phenylephrine, lidocaine (IS), codeine, oxybuprocaine, lidocaine, morphine, cocaine, procaine (IS), cefuroxime
- Hydro-organic BGE: scopalamine, 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>Year</th>
<th>CE acquisition % of separation analyses performed</th>
<th>Mean Criteria</th>
<th>Time</th>
<th>Organic solvent consumption</th>
<th>Cost (capillaries or columns, consumables and products)</th>
<th>Quantitative performances (trueness ± 2%, CV &lt;3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000-2004</td>
<td>100</td>
<td>LC</td>
<td>5 h</td>
<td>≥ 100 mL</td>
<td>30 euro</td>
<td>Conform</td>
</tr>
<tr>
<td>2005</td>
<td>80</td>
<td>CE</td>
<td>3 h</td>
<td>0 - 5 mL</td>
<td>7 euro</td>
<td>Conform</td>
</tr>
<tr>
<td>2006</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Quantitative analyse of one formulation batch:
- Mean Criteria: LC, CE
- Time: 5 h, 3 h
- Organic solvent consumption: ≥ 100 mL, 0 - 5 mL
- Cost: 30 euro, 7 euro
- Quantitative performances: Conform, Conform
Conclusion

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

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