Calibration services for health care

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Content

• Metrology for Drug Delivery - Overview
• 3 types of primary standards for calibration
  • Gravimetric method
  • Water front tracking in a capillary
  • Liquid thermometer method
• Validation of primary standards by means of inter comparison
Motivation Metrology for drug delivery (MeDD)

1. IV therapy *can* cause adverse patient incidents (various (inter)national studies)
2. Wide spread usage of infusion
3. Characteristics of infusion pumps + accessories not fully known
4. Un(der)developed and underused infrastructure for (low) liquid flow rate calibrations

Unknown characteristics
*Reduced accuracy in delivered doses*

Typically only the infusion pump (plus syringe) is ‘calibrated’ (according to existing written standards)

Adding accessories changes the response time

For a multi-pump set up, the pumps can interact with each other affecting the response behavior
What has MeDD delivered?

1. Metrology: upgraded and validated infrastructure for flow rate calibrations from 600 ml/h down to 0.006 ml/h
2. System characteristics: show cases infusion pump set ups
   - Pump plus accessories: effective flow rate, stability and start up time (compliance)
   - Dependency on fluid and process parameters (temperature, viscosity, flow rate, … )
3. Knowledge and awareness: best practice guide and input to current written standards

MeDD Consortium

1. National Metrology institutes: VSL (NL), CETIAT (FR), CMI (CZ), DTI (DK), IPQ (PT), METAS (CH), UME (TR)
2. University Medical Centre Utrecht (NL)
3. Lübeck University of Applied Sciences (DE)
4. EMRP Grant (2012, Health call)
   - Metrology-focused European programme
   - Accelerate innovation and competitiveness in Europe whilst continuing to provide essential support to underpin the quality of our lives

www.drugmetrology.com
Why calibration? Why traceability to SI-Units?

Uncertainty of calibration has to be 3 (5) times smaller than the stated accuracy of the device under test or the maximum permissible error.

- A sound calibration gives the flow rate error and the uncertainty in that error.
- Traceability is a guarantee for quality of calibration results.

3 Types of Primary Standards

**Gravimetric method**
Flow rates
100 nl/min – 10 ml/min

**Water front tracking in capillary**
Flow rates
5 nl/min – 1 µl/min

**Liquid thermometer method**
Flow rates
30 nl/min – 1.5 µl/min
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**Gravimetric Method**

- 2 types of collecting water in beaker to avoid droplet formation and minimize evaporation
- 2 principles for flow generator

**Water droplet**
Size 50µl
(Pharmacology, Wikipedia)

Flow rate 10 ml/min,
time to get the droplet: 0.3 s

Flow rate 100 nl/min,
500 min (8h 20 min)
working day in Switzerland

Flow rate 5 nl/min,
Full week (24/7)
2 types of collecting water in beaker to avoid droplet formation and minimize evaporation

Water Bridge to waterabsorbing materials in saturated air

- Needle immersed into water
  - with oil cover
  - in saturated air

Flow Generator: 2 principles

Constant pressure drop over capillary tube setting the flow rate

- Pressure controller
- Bellow in watertank
- Capillary tube

Syringe pump setting the flow rate

- MFC setting the flow rate
Gravimetric setup

Flow generator and water collection method

Micro Flow Facility – Gravimetric setup

Characteristics

<table>
<thead>
<tr>
<th></th>
<th>METAS</th>
<th>DTI</th>
<th>CETIAT</th>
<th>IPQ</th>
<th>VSL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow rate range</td>
<td>1 ml/min – 100 nl/min</td>
<td>16 ml/min – 100 nl/min</td>
<td>133 ml/min – 16 µl/min</td>
<td>10 ml/min – 50 nl/min</td>
<td>16 ml/min – 4.2 µl/min</td>
</tr>
<tr>
<td>Uncertainty (k = 2)</td>
<td>0.1 - 0.6 %</td>
<td>0.05 - 0.6 %</td>
<td>0.04 – 1 %</td>
<td>0.15 - 6 %</td>
<td>0.06 - 1.4 %</td>
</tr>
<tr>
<td>Water temperature</td>
<td>Ambient</td>
<td>Ambient</td>
<td>10 - 50 °C</td>
<td>Ambient</td>
<td>Ambient</td>
</tr>
<tr>
<td>Pressure range upstream DUT</td>
<td>0 – 2.5 bar</td>
<td>0 – 5 bar</td>
<td>0 – 10 bar</td>
<td>0 – 2 bar</td>
<td>0 – 5 bar</td>
</tr>
<tr>
<td>Flow generator</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Water collection</td>
<td></td>
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</tbody>
</table>
Water front tracking in a capillary

**Measurement principle: front tracking system**

\[ \dot{V} = \frac{dV}{dt} = \frac{x_1 - x_0}{t_1 - t_0} \cdot \pi \cdot R^2 \]

- \( x_1 - x_0 \): traveling distance
- \( t_1 - t_0 \): measurement time
- \( R \): radius of the capillary

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**Experimental set-up**

- camera, lens and light source
- temperature chamber
- fluidic connections
- capillary
- linear stage

**Contact:**

Martin Ahrens, Martin.Ahrens@fh-luebeck.de

Flow rates:

- 5 nl/min – 1 µl/min

Uncertainties > 2.6 %
Primary standard for nanoflow rates

**Working principle**

- **Liquid thermometer method**
- **Primary standard for nanoflow rates**

**Flow rates**
- 30 nl/min – 1.5 μl/min
- Uncertainties: 3.0 % - 2.5 %

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*Biomedical Engineering / Biomedizinische Technik, Band 60, Heft 4, Seiten 317-335*

**Validation of primary standards by means of inter comparison**

- **EURAMET project 1291 / EURAMET.M.FF-S7**
  « Comparison of primary standards for liquid micro flow rates »

- **Internal report of MeDD (D 2.3.4)**
  « Comparison of primary standards for liquid nano flow rates »
Validation of primary standards by means of inter comparison

EURAMET project 1291 / EURAMET.M.FF-S7
« Comparison of primary standards for liquid micro flow rates »

![Graph showing deviation of primary standards](image)

\[ \text{Degree of Equivalence} < 1 \]

Micro Flow Facility – metrological infrastructure for low flow rate testing

Testing and calibration of

- Flow meters
- Flow generators
  - Syringe pump
  - Peristaltic pump
  - Insulin pump

Within this infrastructure it is possible to perform calibrations for different viscosities, temperatures and back pressure.
Micro Flow Facility - Contacts

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Questions?

BMT 2015, FS: Low Liquid Flows in Medical Technology, 2015, Lübeck, D