

Background & Importance

- **Continuous infusion (CI) of high dose piperacillin/tazobactam** (16/2 g in 264 mL NaCl 0,9%) has been included in the UZ Leuven **OPAT protocol**
- **Elastomeric pumps (Infusor® LV10, Baxter)** were selected as drug delivery device, as by this patient's mobility and comfort is maintained
- Observed problem: **incomplete infusions after 24h related to a reduced flow rate**
 - Mean daily residual volume = 50 ml; corresponding to a dose of 3/0.38 g piperacillin/tazobactam (= **19% of the daily dose**)
 - **Substantial underdosing with risk of treatment failure**

Aim & Objectives:

- **Analyzing two hypotheses:** the reduced flow rate could be a result of
 - **Hypothesis 1: particulate formation of piperacillin dimers** due to the absence of stabilizing excipients (Na-citrate as buffer & Na-EDTA as metal-chelating agent)
 - **Hypothesis 2: high viscosity**

Hypothesis 1

Materials & Methods:

- Comparing the flow rate of Tazocillin® (with stabilizing excipients) vs generic piperacillin/tazobactam (without this excipients)
- Measuring light absorbance (600 nm) by spectrophotometry
- Measuring total piperacillin content of different concentrations piperacillin/tazobactam after storage for 24h at 33°C by 'Liquid Chromatography tandem-Mass Spectrometry' (LC-MS/MS)

Results:

	Tazocillin	Pip/tazo	Blank
Concentration	16 g/264 ml	16 g/264 ml	264 ml NaCl 0,9%
Mean flow rate	8,576 ml/u	8,952 ml/u	11,733 ml/u

Table 1. Mean flow rate of Tazocillin®, generic piperacillin/tazobactam and NaCl 0,9% at 33°C: no difference observed in flow rate between Tazocillin® 16 g/264 ml and generic piperacilline/tazobactam 16 g/264 ml

	Tazocillin	Pip/tazo	Blank
Concentration	16 g/264 ml	16 g/264 ml	NaCl 0,9%
Mean absorbance	0,001 A	0,005 A	0,000 A

Table 2. Light absorbance (600 nm) of Tazocillin®, generic piperacillin/tazobactam and NaCl 0,9%: no difference observed in absorbance between Tazocillin® 16 g/264 ml and generic piperacilline/tazobactam 16 g/264 ml + no difference in absorbance between piperacillin/tazobactam 16 g/264 ml and blank

Tested concentration	% of residual concentration after 24h
60,61 mg/ml	> 100%
72 mg/ml	> 100%
74,42 mg/ml	> 100%
80 mg/ml	> 100%

Table 3. Residual concentration of piperacillin maintained at 33°C over 24h: generic piperacillin/tazobactam seemed to be stable enough for 24h at 33°C

Conclusion:

- Incomplete infusions are probably **not related to particulate formulation**

Hypothesis 2

Materials & Methods:

- Measuring the effect of concentration on the density (pycnometer), kinematic viscosity (Ubbelohde viscometer), dynamic viscosity and flow rate at 33°C
- Evaluating the relation between viscosity and flow rate

Results:

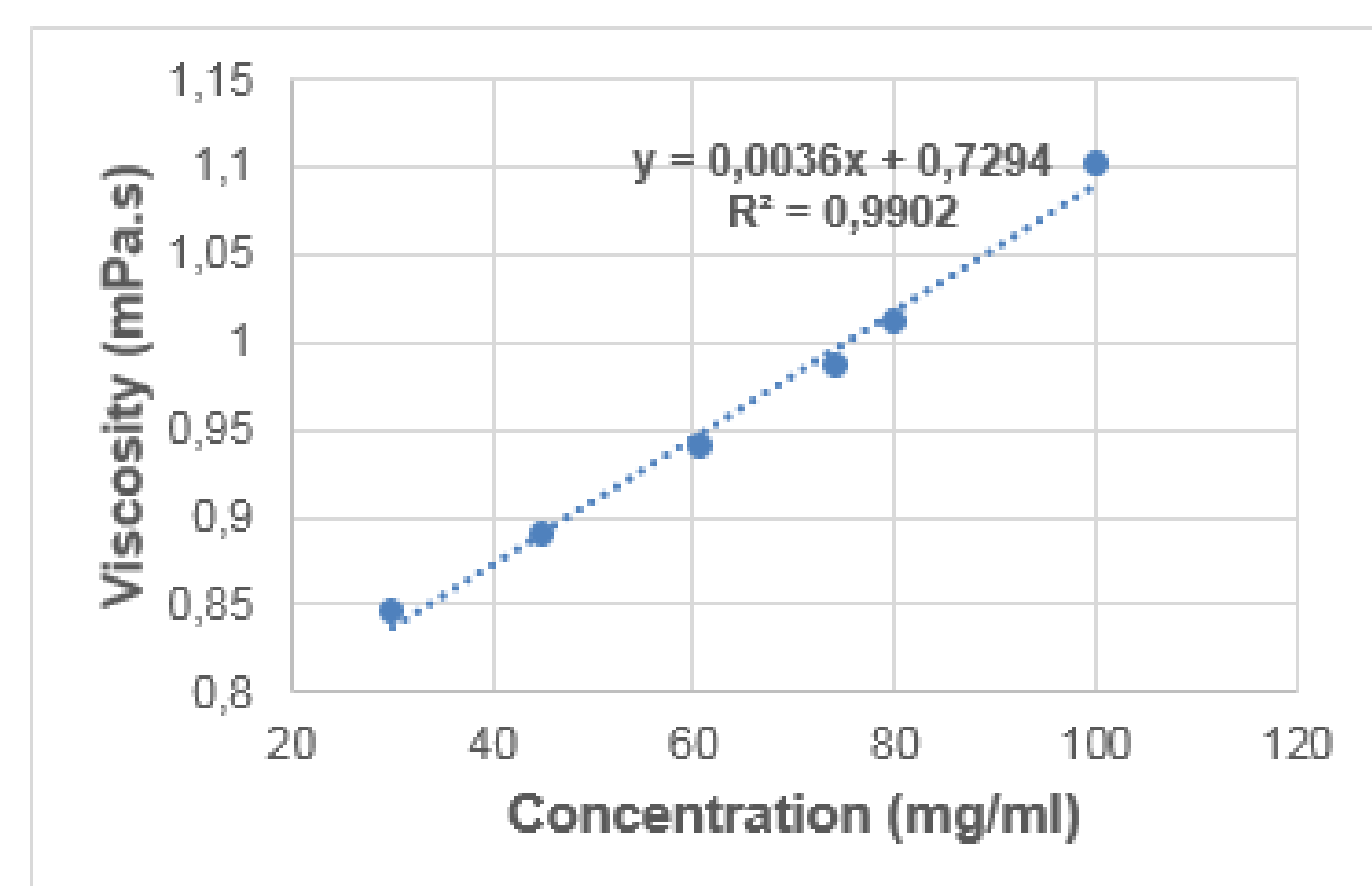


Figure 1. Linear relationship between concentration and viscosity examined at five concentrations between 30-100 mg/ml piperacillin: the higher the concentration, the higher the viscosity

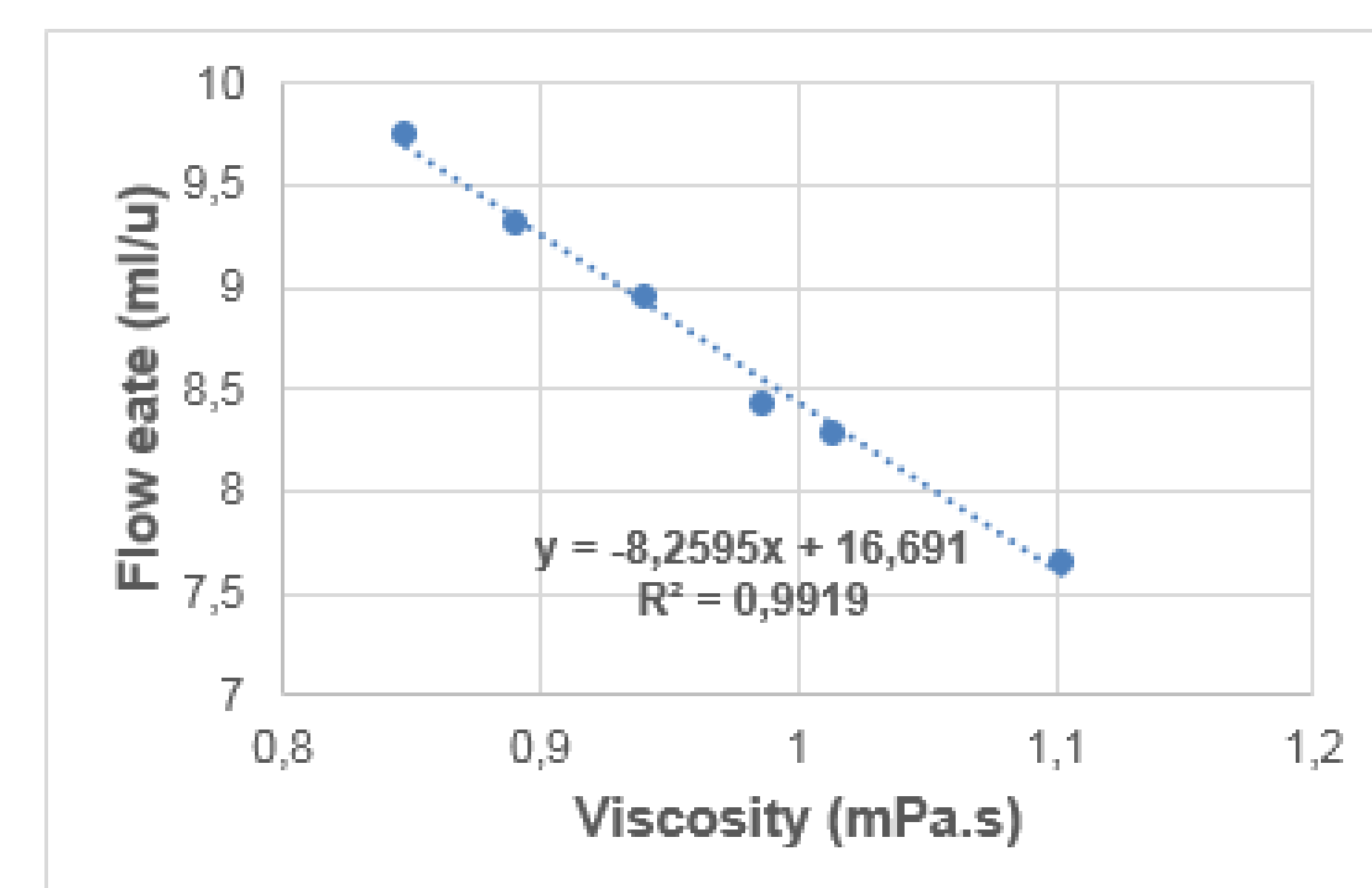


Figure 2. Inverted linear relationship between viscosity and flow rate of piperacillin/tazobactam solutions (examined at five concentrations between 30-100 mg/ml piperacillin): the higher the viscosity, the lower the flow rate

Conclusion:

- Incomplete infusions are related to a reduced flow rate **due to a high viscosity of piperacillin/tazobactam solutions**

Discussion

- The *in vitro* experiments suggest that the **reduced flow rate is a result of high viscosity, related to the concentration** of piperacillin/tazobactam
- Since it is not possible to lower the concentration (maximum volume of the Infusor® LV10 = 264 ml), **the final volume of the solution will be adjusted:**
 - 16/2 g/200 ml (80 mg/ml): based on the above equations and stability data, this will result in complete infusions after 24h
- Before being used in clinical practice for OPAT, this mode of administration will first **be validated in 5 patients during hospitalization**
- In general, **health care teams need to be aware of factors, which may lead to longer flow durations** with these infusion devices
- There is an overall **need for specific administration schedules for each antibiotic in elastomeric devices** for using within OPAT