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Parenteral Drug Association

Needle clogging of stacked-in-needle PFS with high concentration protein therapeutics

Pre-Conference Workshop: Impact of Pre-filled Syringe Packaging Components on Biopharmaceutical

Vienna/Austria, 6 November 2017

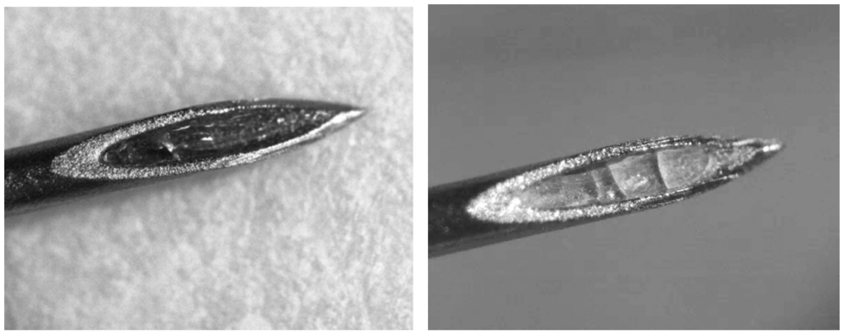
Presentation Overview:

- Introduction to the topic
- What is needle clogging?

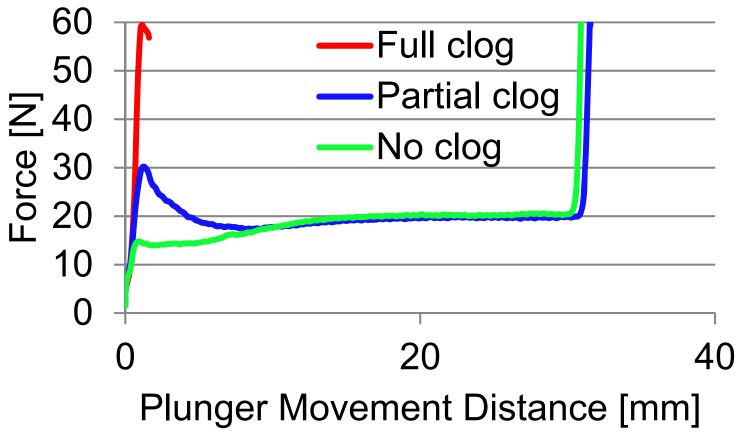
- Study design
- Mechanism of liquid entering in the needle
- Solidification process

- Summary and conclusions

What is needle clogging?

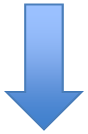


DPs on needle eye, liquid (left) and solidified (right)



Observation of peak forces during injection force testing or even complete blockage of the liquid path

- Jelly-like/solid clog at needle tip

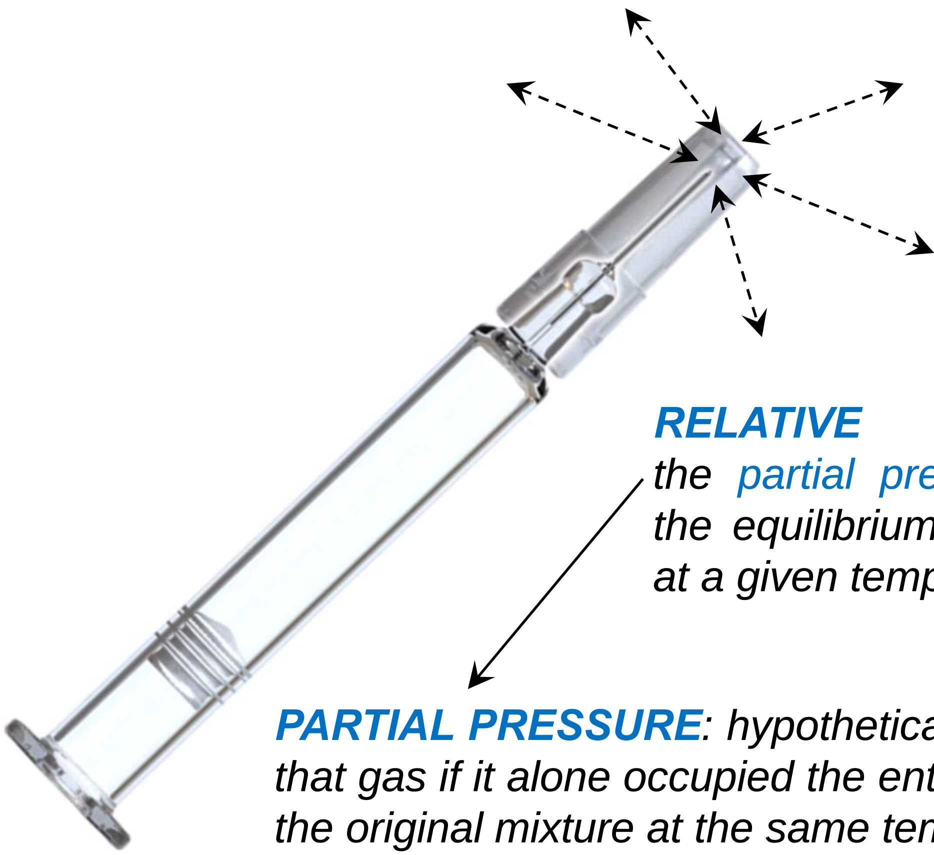


- Difficult injection
- Auto-injector failure

- Understanding of the phenomenon
- Minimize the occurrence
- Increase patient compliance

Some clarifications on needle shield:

- **Gas permeable →** To facilitate the sterilization (steam, EtO)



Factors:
T°: Temperature
rH : Relative Humidity
t : time

***RELATIVE HUMIDITY**: ratio of the partial pressure of water vapor to the equilibrium vapor pressure of water at a given temperature*

***PARTIAL PRESSURE**: hypothetical pressure of that gas if it alone occupied the entire volume of the original mixture at the same temperature*

Liquid enters the needle ← Study of the mechanism: factors and kinetics

↓

Solidification process ←
- Evaporation of the solvent through RNS elastomer
- Increase of DPS concentration and viscosity

↓

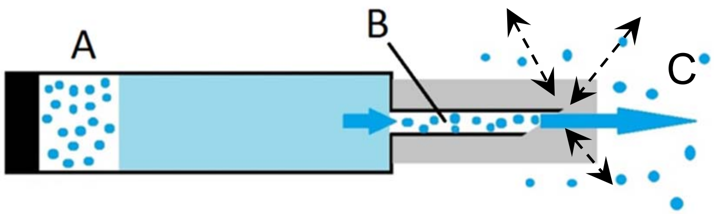
Liquid can not be correctly injected

Goal:
Understanding clogging mechanism for high conc DPS in PFS
Identify root causes

Explanation of the mechanism: theory

→ After filling, needles are <u>empty</u>

What is happening then?



No gas exchange

Slow gas exchange via rubber

Ideal gas law:
PV=nRT

- Mechanical P,
- Atmospheric pressure fluctuations etc.

Temperature variation (ΔT)
ex: T° increase

→ Pressure increase in A and B ($P_{A,B}>P_C$)

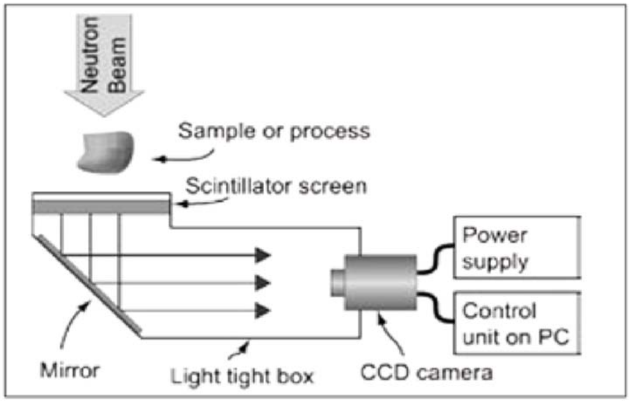
→ Fluid in B is expelled, due to the ΔP between inside and outside (C)

→ DP solution can enter the needle

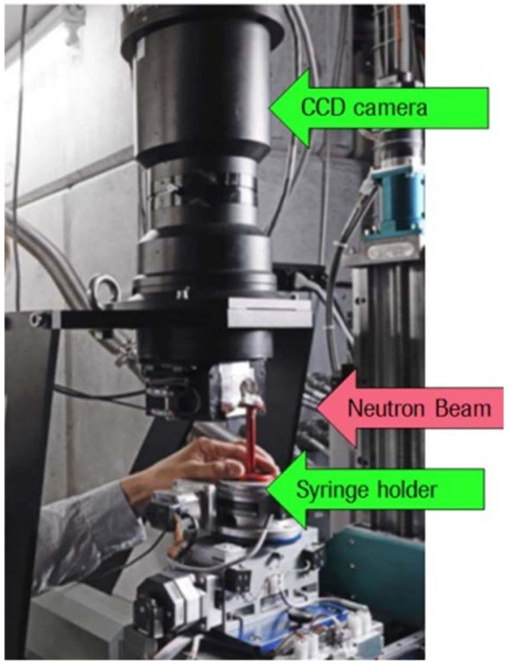
How can we look inside the needle?

Challenges:
- Presence of the needle (metal wall → X-Ray CT not suitable)
- Presence of the RNS

Neutron imaging (N.I.)
- ➢ Higher transmittance of metals
- ➢ High contrast for hydrogenous material (DPs solvent)

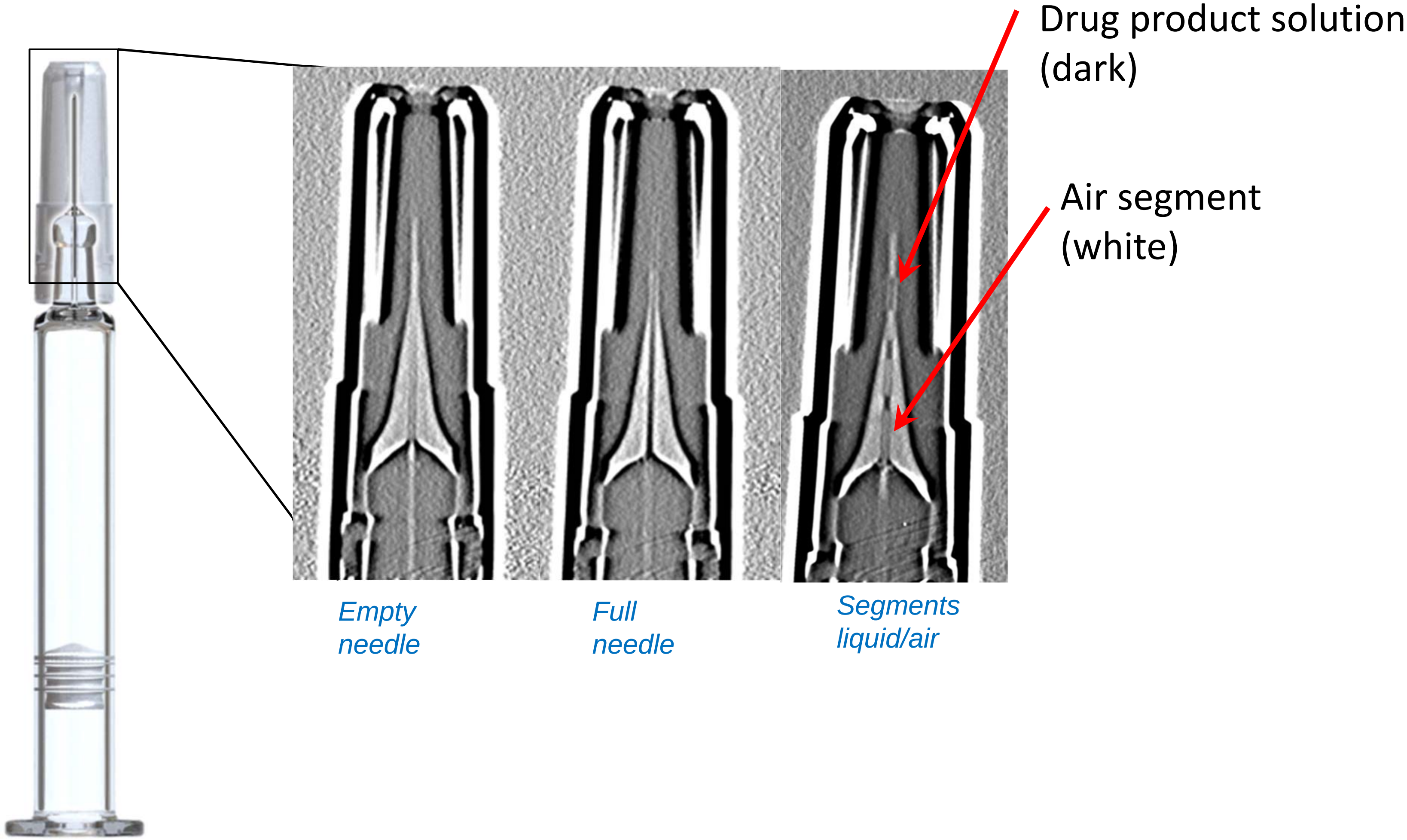


Neutron Imaging: acquisition scheme



Facility at Paul Scherrer Institute (PSI, Switzerland)

Neutron Imaging results:



Measurement performed at
Paul Scherrer Institute (PSI)

N. I. study: Identify the potential critical factors:

- After filling, needles are empty -

Filling (room T°) → Storage (2-8°C) → Inspection (room T°) → Storage (2-8°C) → Assembly (room T°) → Storage (2-8°C) → Packaging (room T°) → Storage (2-8°C) → Pharmacy/ home (room T°) → Storage (2-8°C) → Administration (room T°)

1. Stress PFS under accelerated conditions: high T° cycles, shaking etc. → **2.** Check presence of liquid in the needle → **3.** Identify critical stress factors

Results:

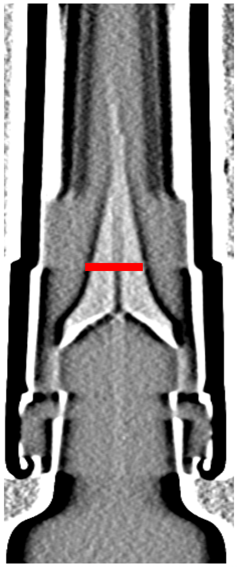
DoE study

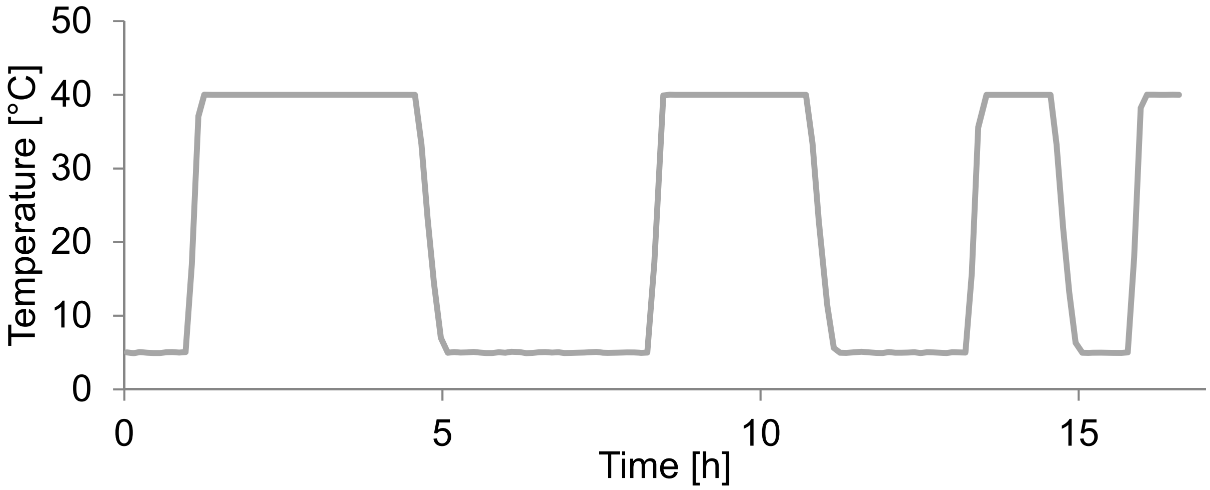
Factors tested:

- Max ambient T°
- Time at ambient T°
- Nr of cycles 2-8°C/ ambient T°
- Shaking
- Etc.

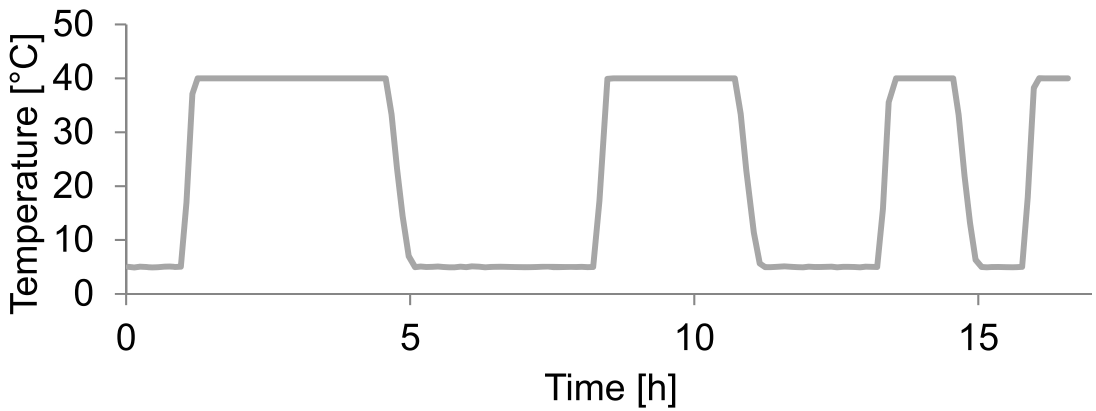
Exposure to high temperature (30-40°C) for long time (48h) cause liquid in the needle

More in detail:





Results:



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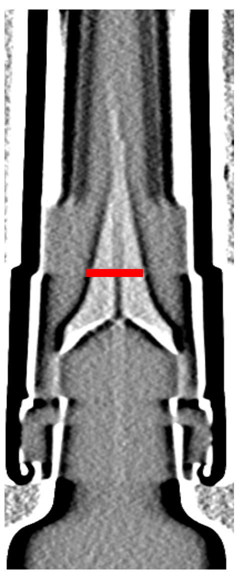

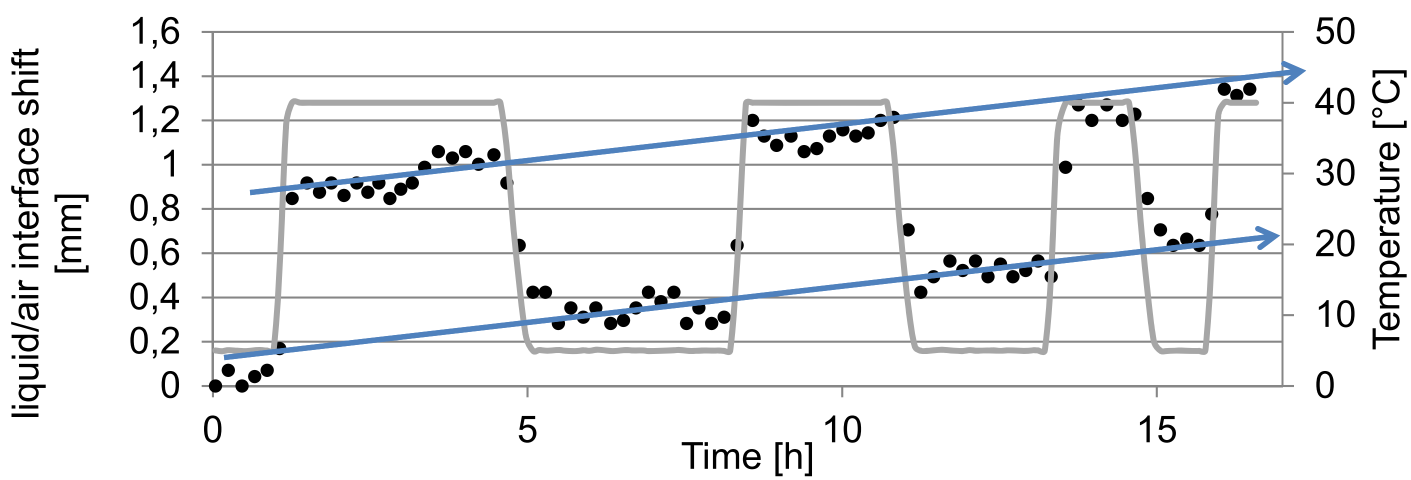

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Liquid enters the needle ← Study of the mechanism: factors and kinetics

↓

Solidification process ←
- Evaporation of the solvent through RNS elastomer
- Increase of DPS concentration and viscosity

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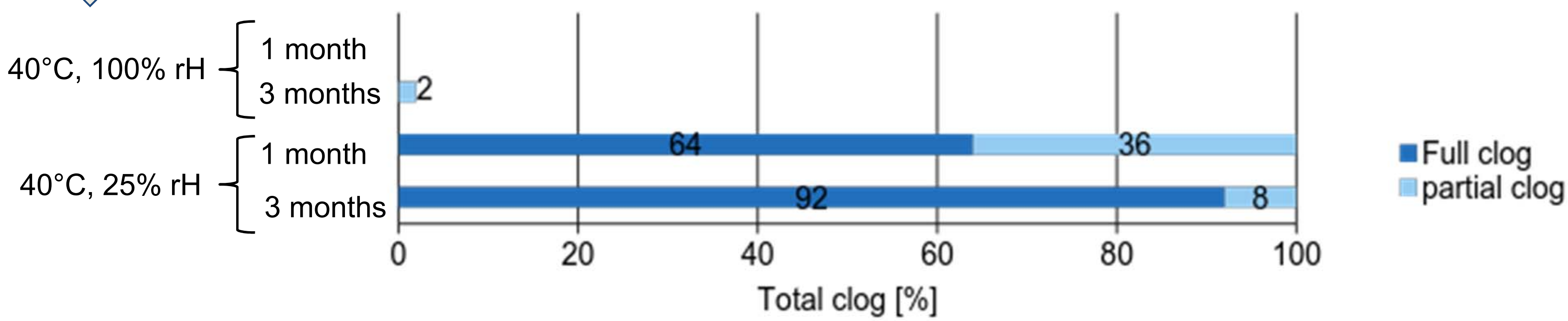
Liquid can not be correctly injected

Goal:
Understanding clogging mechanism for high conc DPS in PFS
Identify /investigation root causes

RNS elastomer might be water vapor permeable

Observation: prevention of water vapor transmission through RNS reduced needle clog rate:

Accelerated storage conditions



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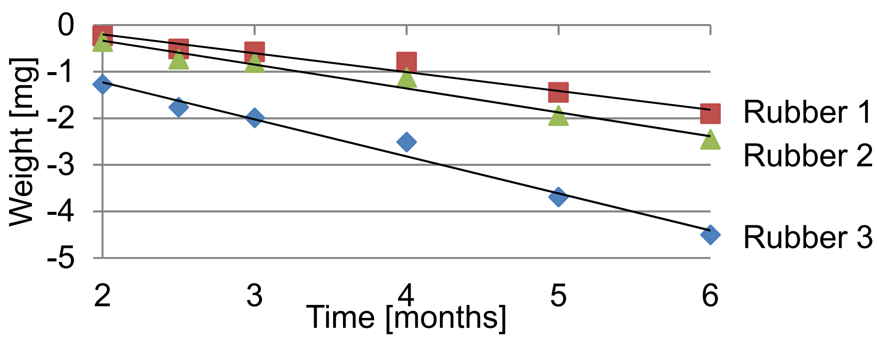
How much water vapor can pass through the RNS?

<u>No clear values from suppliers</u>

- **Gravimetric method**→ weight loss study
- **Measure the WVTR** → (water vapor transmission rate) through rubber sheet with same formulation as the RNS

Gravimetric method: results



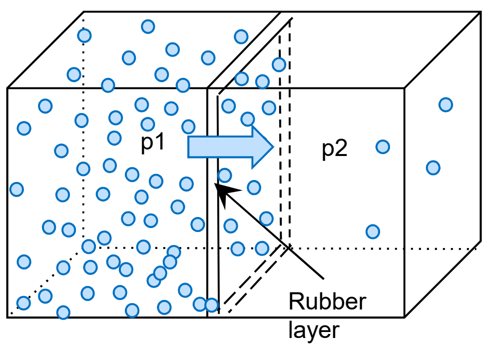
Weight change of single PFS during accelerated storage conditions: 40 °C, 25% rH

Different rubber formulations showed different weight loss

<u>The slope of the line is the WVTR</u>

Measurements of the water vapor transmission rate (WVTR)

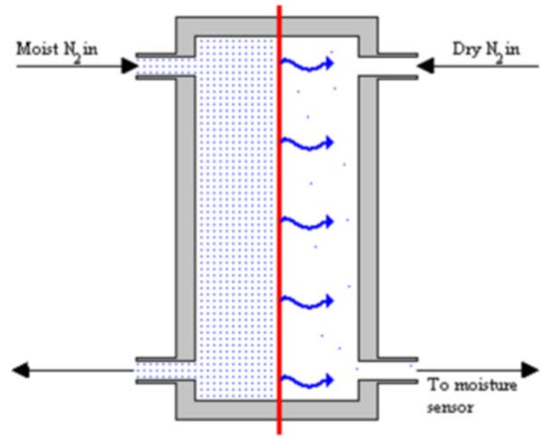
On rubber sheets with the same rubber formulation as the RNS



WVTR = K (p1 - p2) / l

K = coefficient of permeation
p = water vapor partial pressure
(ΔPP = p1 - p2)
l = layer thickness

Set up of the measurements:



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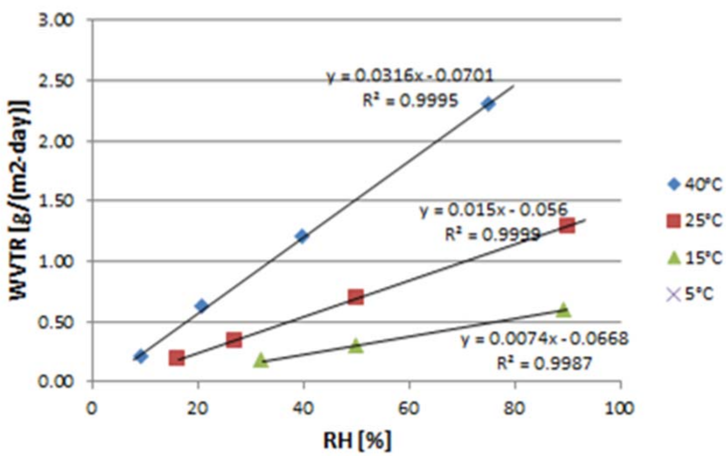
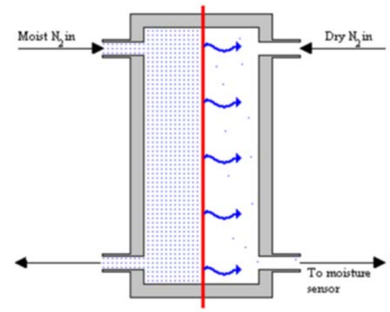
Advantages:
- low temperature
- faster method (systematic inv.)

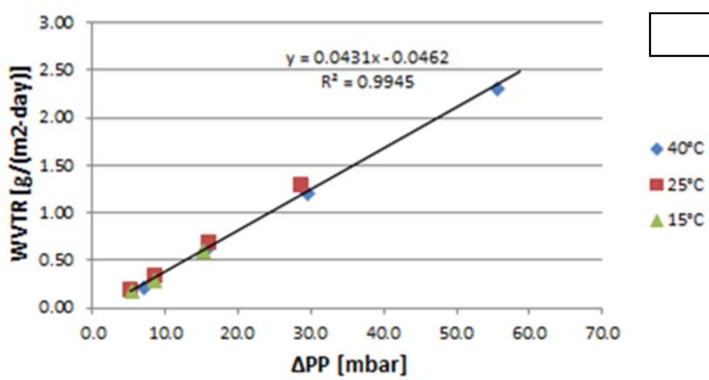
Results:



Rubber 1 sheet

The difference of RH on the two sides induces water vapor diffusion





Rubber 1 sheet

1) ***Difference of Partial Pressure (ΔPP) is the*** *driving force for vapor diffusion*

2) Interpolation:
We can calculate the WVTR at each T° knowing the ΔPP (T° and RH)

WVTR vs ΔPP: linear relation

Combining the two methods we can calculate the water loss at each storage conditions

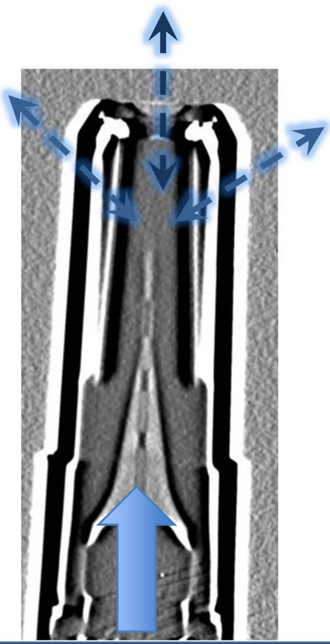
Ex: Needle Volume (27 G RW) ~ 700 µg

Theoretical time necessary to “empty” a needle (RNS 1): 2 months at 25 °C, dry conditions

Clogging rate after 3 M
at same conditions:
43% clogged

There must be a water-replacement mechanism preventing 100% full clogging

→ Water replacement from the syringe barrel?



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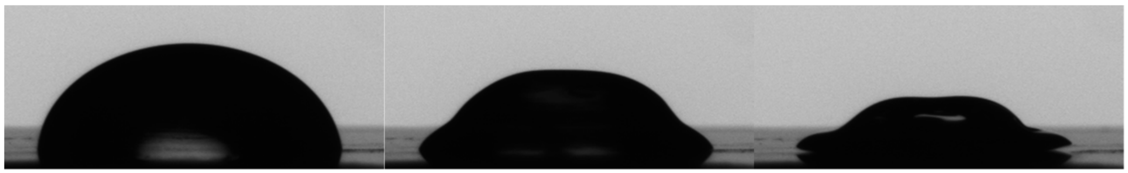
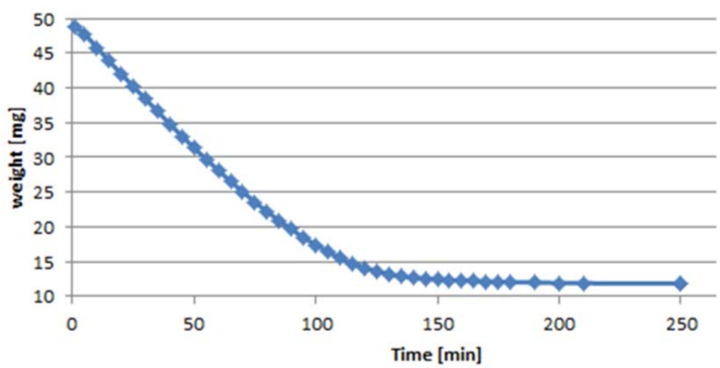
Increase of DPS concentration and viscosity:

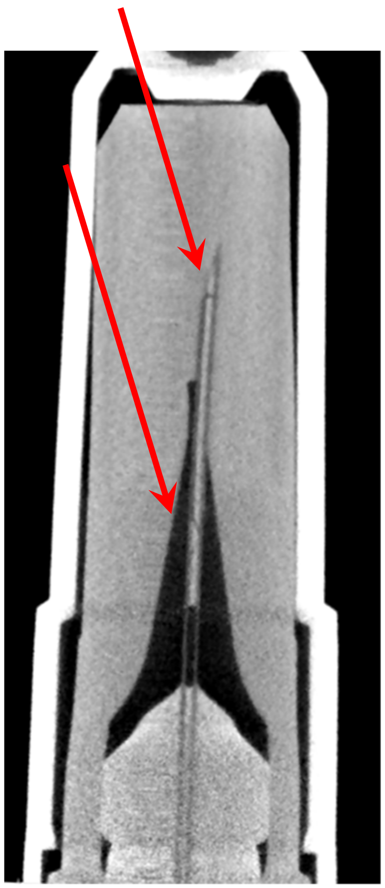


Drying of a high concenztration mAb drop (left drying at room conditions: 23 °C, 40% rH



Weight change of a high concentration mAb drop

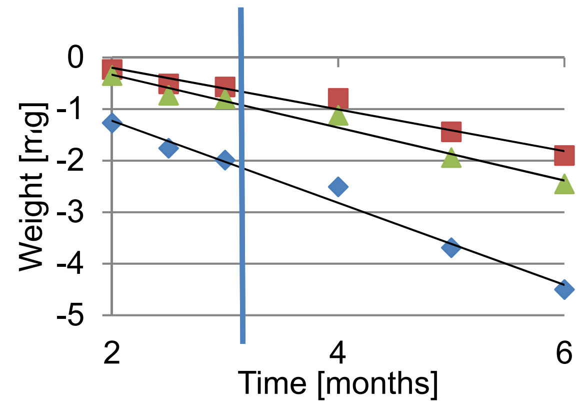
(left drying at room conditions: 23 °C, 40% rH)



Tomography: cracks in the solidified material inside the needle

Increase of DPS concentration and viscosity:

mAb+blue dye in a needle glass, left open at room T°



Weight change of three PFS/RNS configurations (storage at 40 °C, 25% rH)

- Segments shrink while drying
- While the segment closer to the needle tip is clogged, the remaining segments are still liquid (moving)

- Segments closer to the needle tip dry earlier and faster
- A solidified segment is sufficient to cause clogging
- Formation of a porous clog (water vapor can pass through)→ water evaporation continues
- Pressure resistant clog (no gas exchange at short time range)

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Summary and conclusion:

The presence of liquid in the needle is a prerequisite for needle clogging

- ✓ Mechanism of liquid entering the needle is clarified: ΔP causes liquid in the needle (ΔT, mech.P, atm P fluctuations)

Solvent evaporates through the needle shield

- ✓ The WVTR via different types of RNS was characterized
- ✓ The mechanism of WVT is clarified: linear dependency on the ΔPP

Clog formation

- ➢ importance of the correct storage conditions + shipping
- ➢ solvent evaporation is an important driving factor in the clogging phenomenon
- ➢ Water loss can be predicted at certain storage conditions (based on the ΔPP)
- ➢ solvent evaporation can be tuned by choosing the appropriate RNS rubber formulation and/or storage conditions

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Acknowledgements

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