Hands-on:

Development of a cycle based on data derived from the formulation

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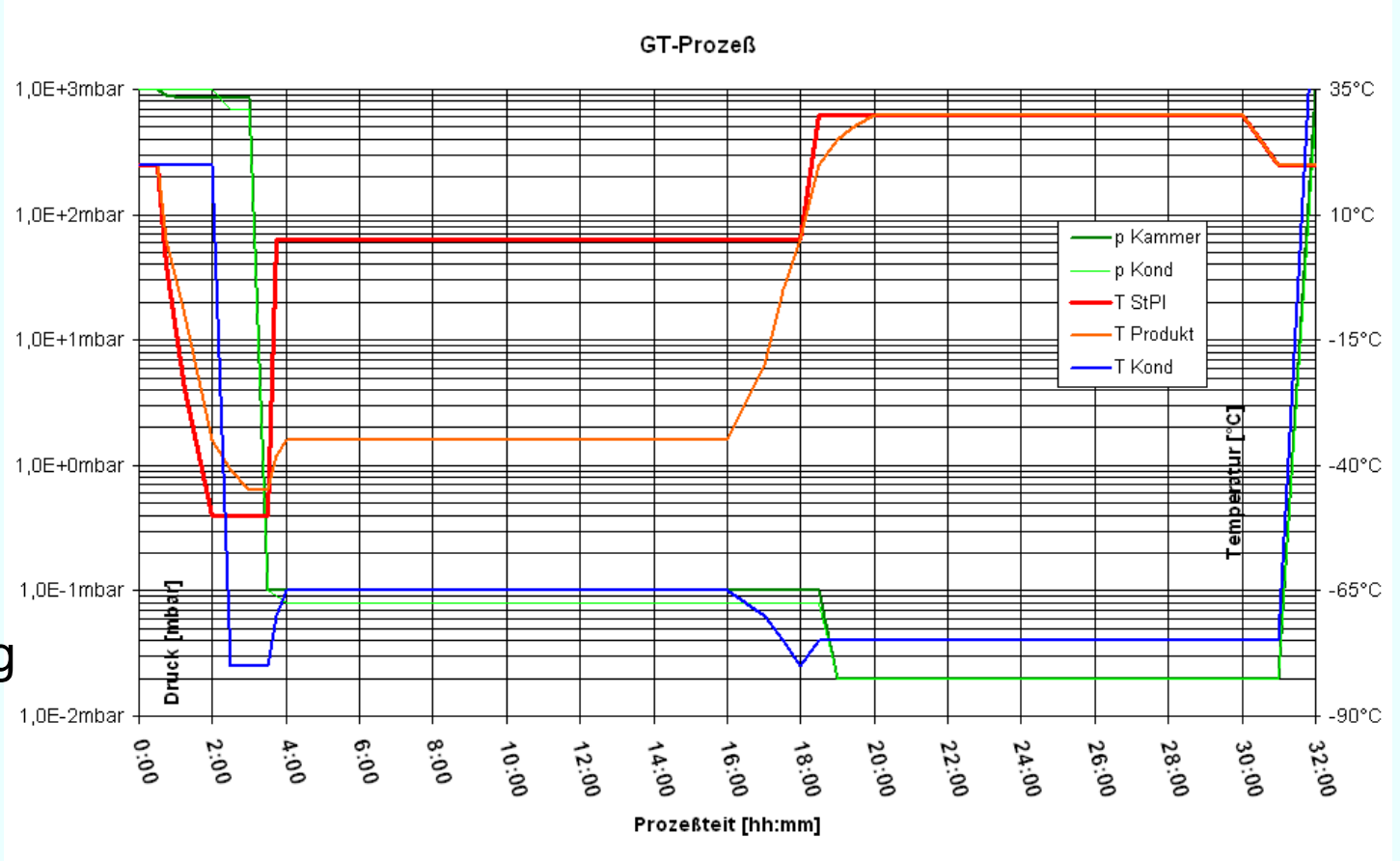
Volunteer for PDA

Freeze Drying Cycle

- Freezing
- Evacuation with condenser cooling
- Sublimation
- Desorption
- Defrosting (during unloading, Start of Turn-Around)

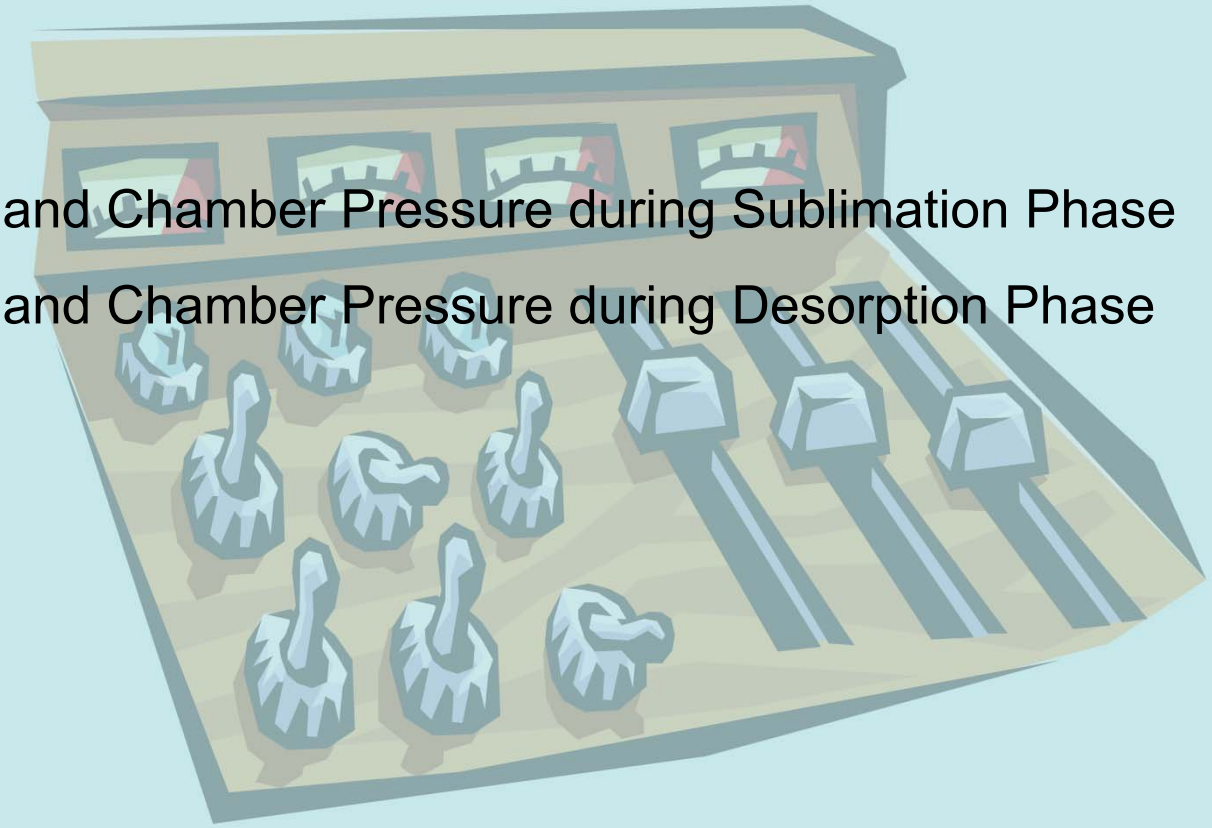


Critical Process Aspects

Nucleation (Freezing)	• **Pore Size** *(Cooling Rate, Nucleating Temperature)* • **Structure of Solid** *(Cooling Rate, Temperature – Time Profil)*
Sublimation (Primary Drying)	• **Critical temperature during sublimation** *(Sublimation Rate, Vapor pressure)* • **Complete removal of ice**
Desorption (Secondary Drying)	• **Residual Moisture** *(Desorption Rate, Gas Moisture, Temperature)*

Parameters for a Freeze Drying Recipe

- Freezing Rate
- Shelf Temperature and Chamber Pressure during Sublimation Phase
- Shelf Temperature and Chamber Pressure during Desorption Phase
- Step duration
- Ramping Rates



Parameters determined previously by formular developers

- Vial Design / Stopper Design
  - Standard Vial design according to ISO 8362-1
  - Standard Stopper design: EU/US, fitting with Vial neck
- Product composition / filling volume
  - 1,8ml required: Vial type 2R selected (Layer: 12mm)
  - 5m-% of solid content
  - Load per batch: 63kg
  - Evaporation Rate for ice free product: <0,000’5h^{-1}

Parameters determined previously by formular developers

- Sorption Isotherm shows a good relation between moisture and desorption between +25...35°C (p = 50µbar)
- Temperature for long-term storage
  - <40°C
- Required residual moisture for long-term storage
  - below 2%
  - Desorption Rate for target moisture: <0,000’05h^{-1}

Machine Parameters

- Cooling Rate at loaded shelfs: 1,5K/min
- Heating Rate at loaded shelfs: 2,0K/min
- Chamber Volume: 6.600l

Parameters for a Freeze Drying Recipe [1]

Freezing Phase

Selected ramp rate	1,5	K/min
Minimum temperature	-40	°C
Hold time	02:00	hh:mm

How could forced nucleation be implemented?

Sublimation phase

Sublimation pressure	200…400	[µbar]
Heating Rate	2	K/min
Shelf temperature	-10	°C
Step duration	24:00	hh:min

Detection of critical temperature

- Temperature resistance measurement at different ramping speeds

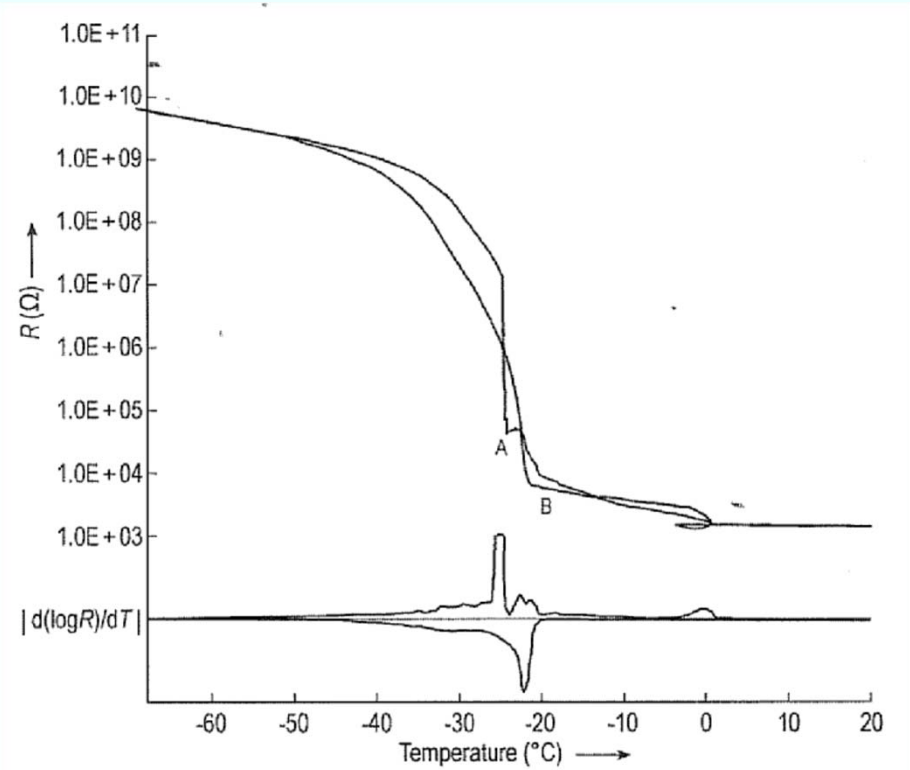


Fig. 1.22.2a. Typical electrical resistance plot of 1% NaCl solution with 1 °C/min cooling: event A at–24.5 °C during cooling, event B at 21.8 °C during warming

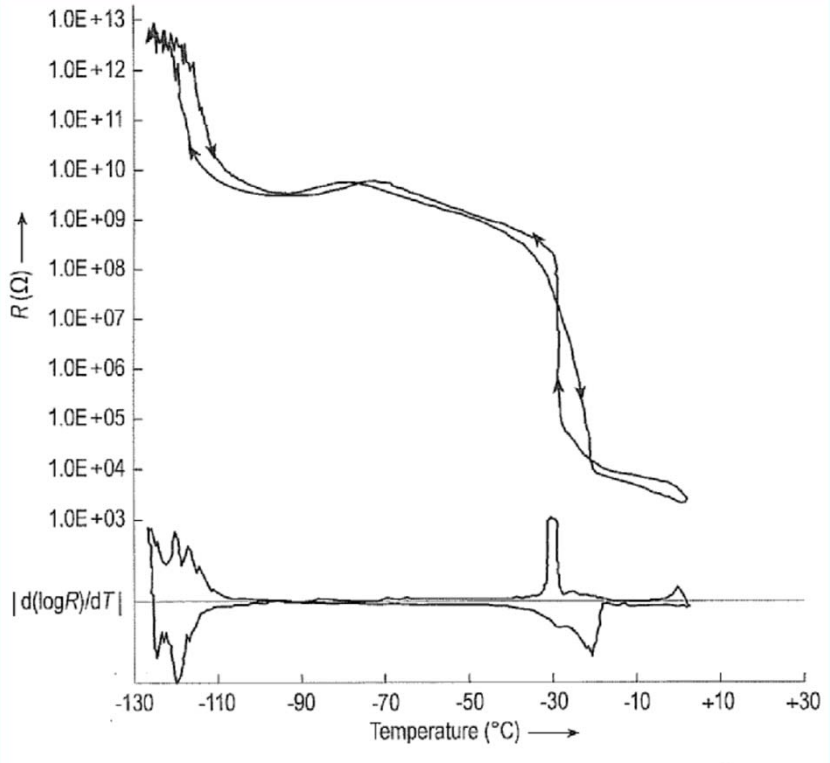
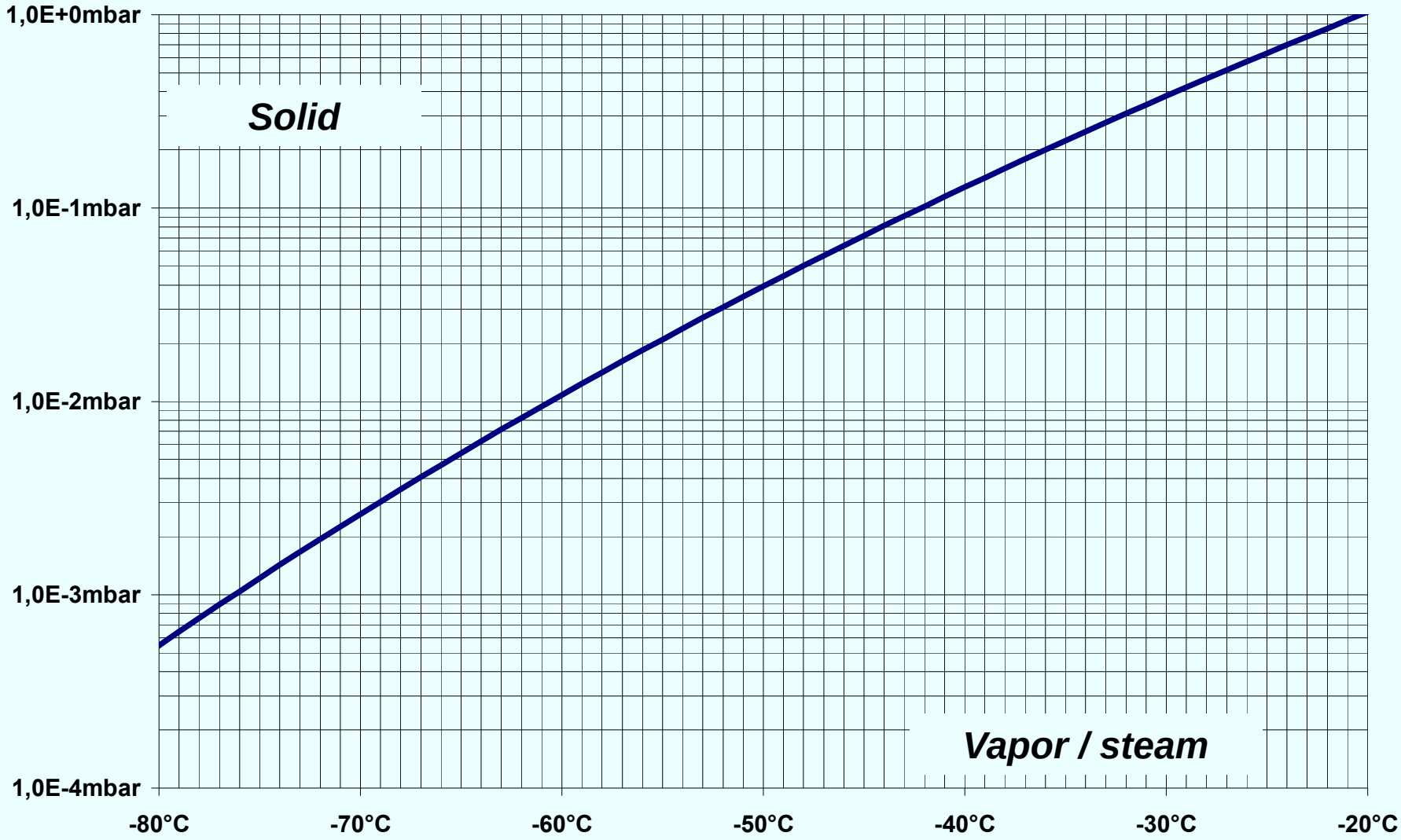


Fig. 1.22.1a. Electrical resistance as a function of temperature of 1% NaCl solution. Cooling rate 3 °C/min, warming rate 3 °C/min and the first derivative d(log*R*)/d*T* measured down to –120 °C


1,0E+0mbar
1,0E-1mbar
1,0E-2mbar
1,0E-3mbar
1,0E-4mbar
Solid
Vapor / steam
-80°C
-70°C
-60°C
-50°C
-40°C
-30°C
-20°C

Parameters for a Freeze Drying Recipe [2]

End of sublimation phase

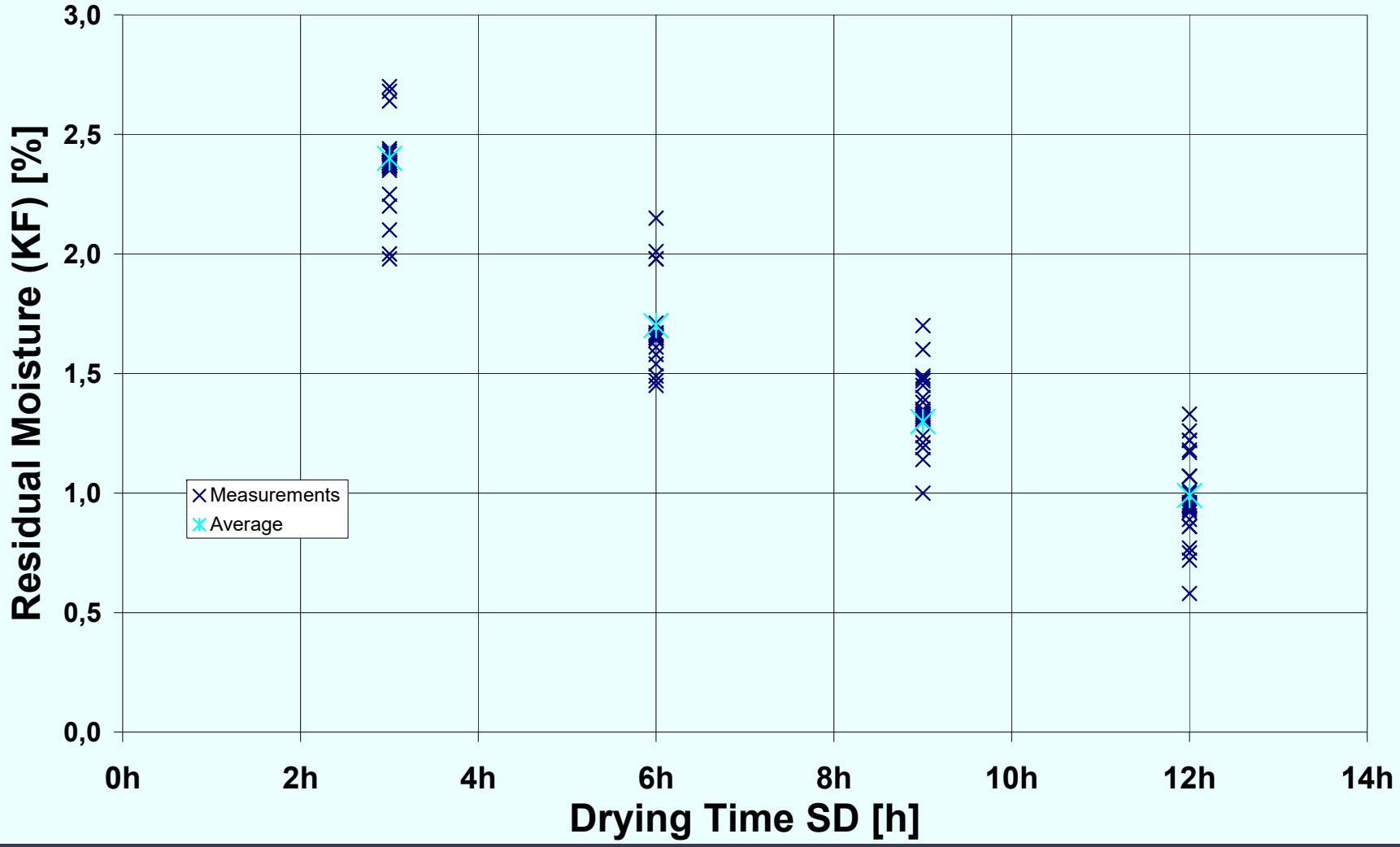
Pressure Rise for safe endpoint detection	**0,08047**	**[µbar/s]**

Desorption phase

Heating Rate	**2**	**K/min**
Shelf Temperature	35	°C
Desorption Pressure	50	[µbar]
Step duration	09:00	hh:min

PAT Quest: What could be done for a dynamic desorption control?

Residual Moisture (KF) decrease during SD



R&D Equipment

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Thank you for your attention!

Questions?