DE MONTFORT UNIVERSITY LEICESTER

Leicester School of Pharmacy

Novel Impedance-based Methodologies to Determine the Drying Rate and the Vial Heat Transfer Coefficient during Freeze Drying

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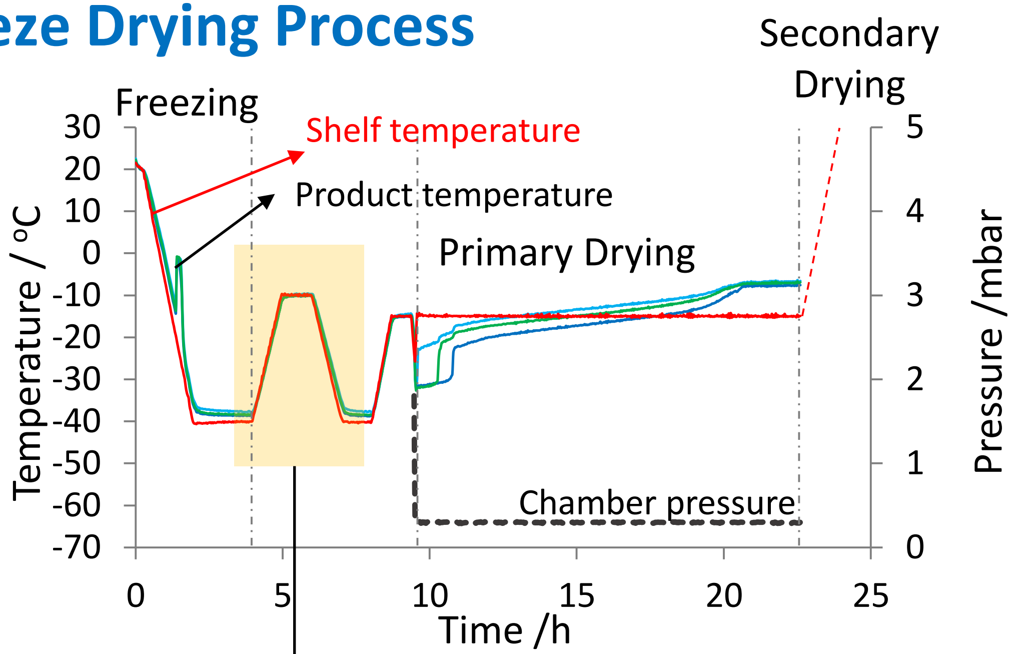
BIOPHARMACEUTICAL **QUALITY BY DESIGN**

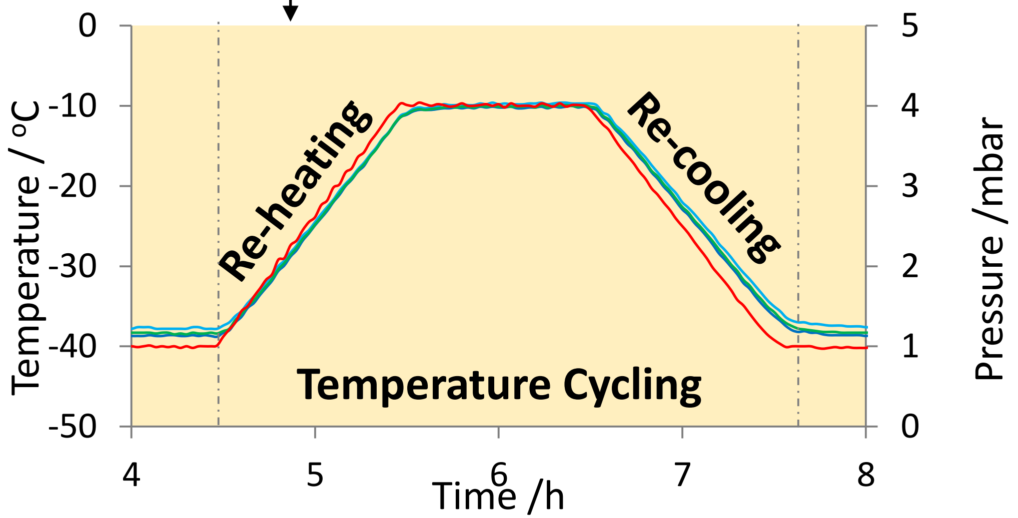
Outline

- The Freeze Drying Process
- Problem of Heterogeneity in Freeze Drying
- Mechanism of Coupled Heat and Mass Transfer
- Features of through vial impedance spectroscopy (TVIS)
- Use of Average Temperature from 3 Thermocouples to Calibrate the TVIS system: a justification
- Temperature Calibration of the TVIS system
- TVIS Application in Primary drying
  - Temperature prediction
  - Drying rate
  - Vial heat transfer coefficient (K_V)
- Acknowledgements

The Freeze Drying Process

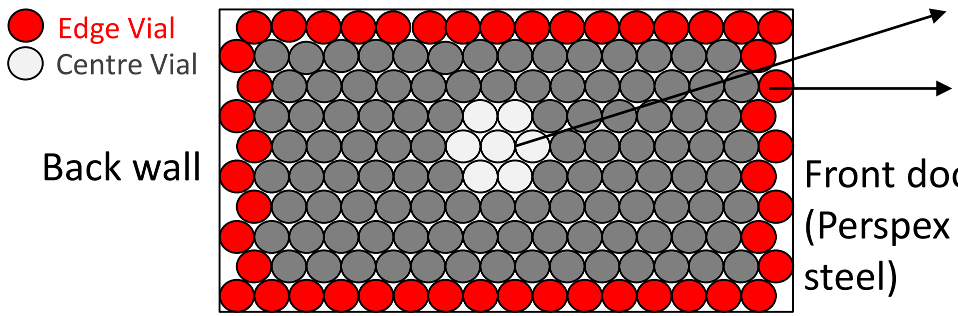
Virtis Advantage Plus Lab Freeze-Dryer





Problem of Heterogeneity in Freeze Drying

- Freeze drying is **heterogeneous**



- Freeze drying is an expensive: Primary Drying is longest!
- Two important parameters
  - **Drying rate**: most process monitoring devices provide a **batch measurement** of sublimation rate (e.g. MTM) or use **interruption** techniques e.g. Gravimetric
  - **Product temperature**: Single vial temperature sensors are **product invasive** and alter the heat and mass transfer process, e.g. Thermocouples!

Patel and Pikal (2009) Pharm Dev Tech. 14(6) 567–587

Mechanism of Coupled Heat and Mass Transfer

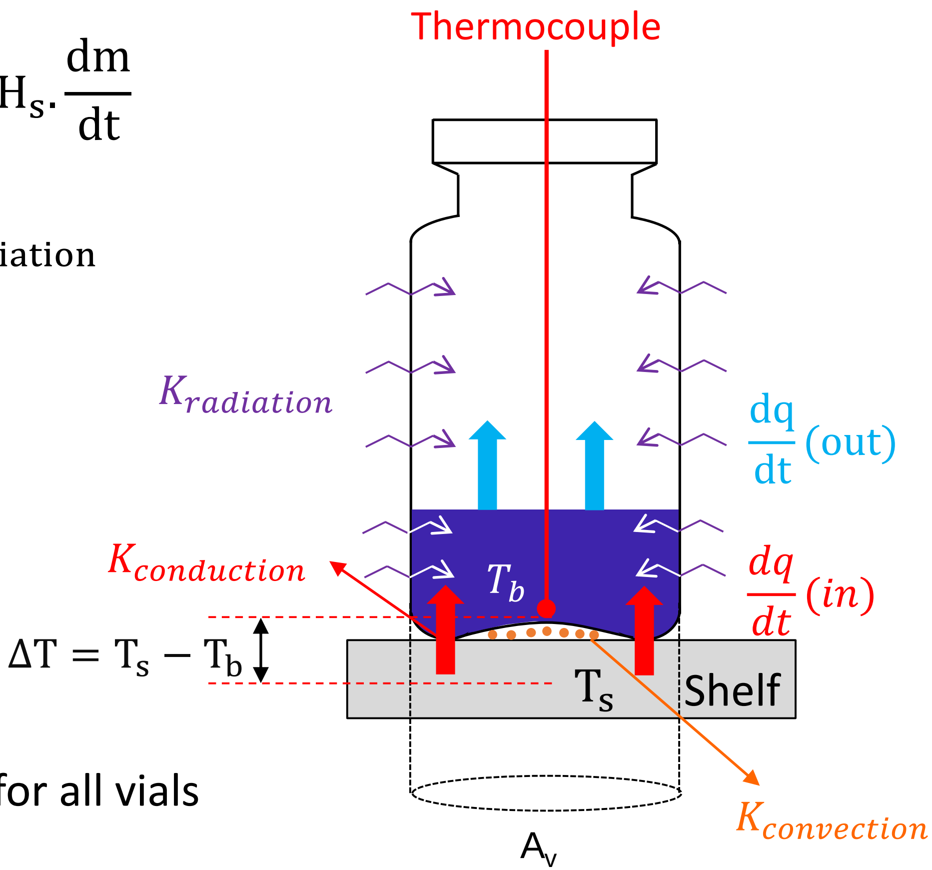
$$\frac{dq}{dt}(in) = A_v . K_v(T_s - T_b) \ \& \quad \frac{dq}{dt}(out) = H_s . \frac{dm}{dt}$$

$$K_V = K_{conduction} + K_{gas\ convection} + K_{radiation}$$

Under steady state

$$\frac{dq}{dt}(in) = A_v . K_v(T_s - T_b) = \frac{dq}{dt}(out) = H_s . \frac{dm}{dt}$$

$$\therefore K_v = \frac{H_s . \frac{dm}{dt}}{A_v(T_s - T_b)}$$



External area of cross section of the vial projected onto shelf

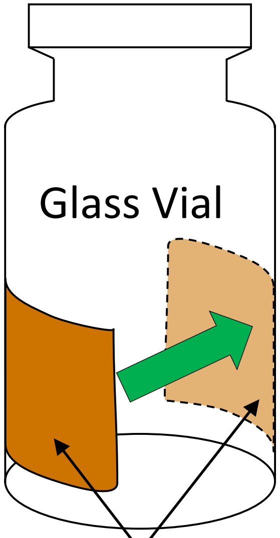
Assumption: Heat is transferred via the base for all vials

Accurate determination of dm/dt and product temperature is needed especially for edge vials

Pikal et al. (1984) J Pharm Sci. 73 (9) 1224-1237

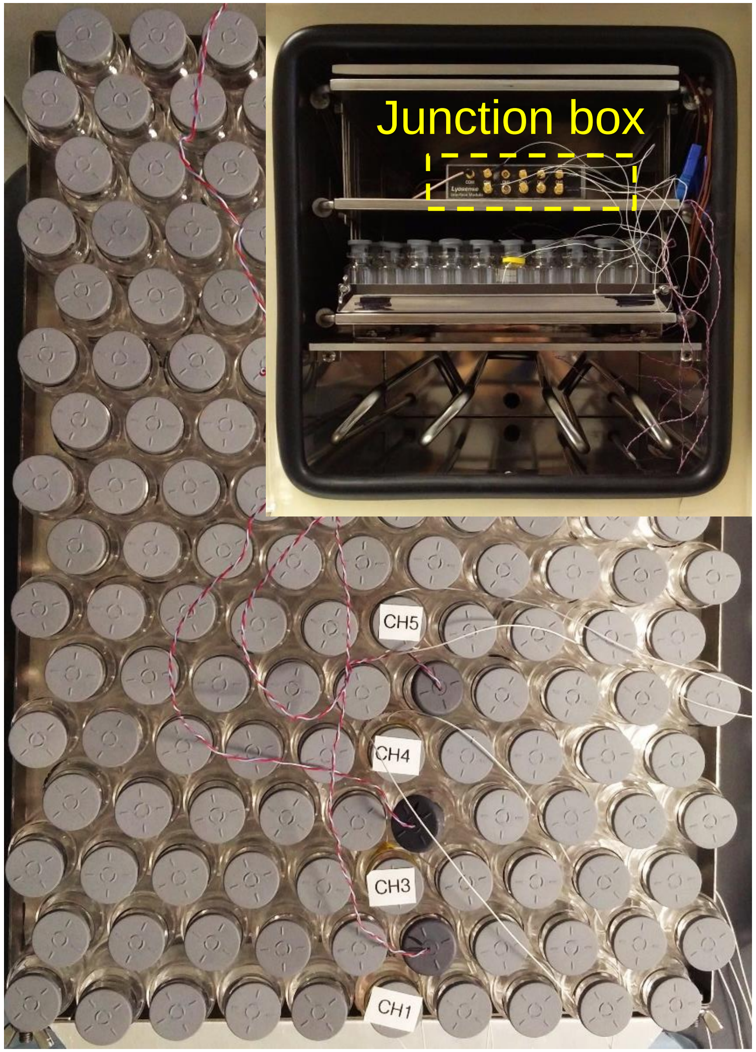
Through Vial Impedance Spectroscopy (TVIS)

- Impedance measurements across a vial using **copper electrodes** attached **externally** to the glass wall
- Hence "Through Vial Impedance Spectroscopy"

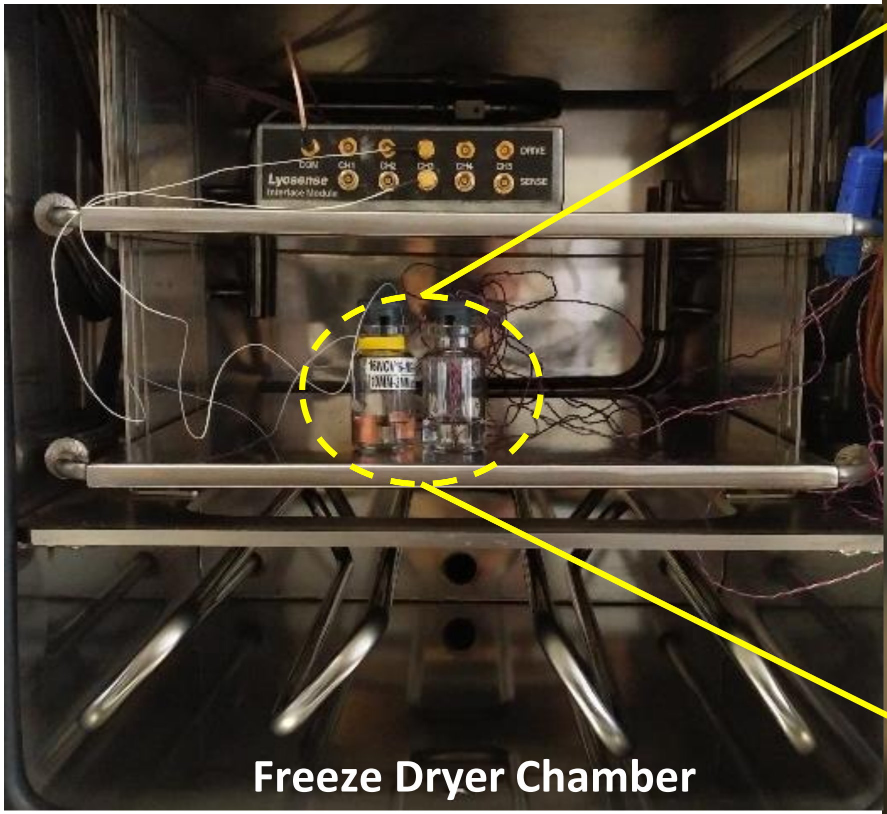


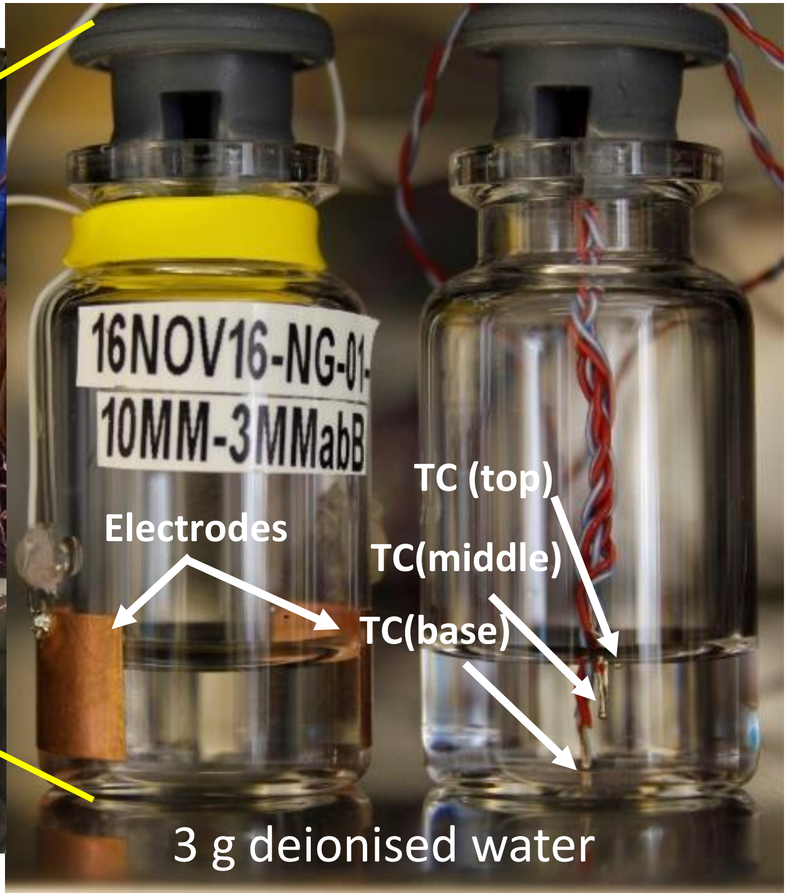
Features

- Single vial, "Non-product invasive"
- Both freezing and drying characterised in a single technique
- Un-perturbing to the packing of vials and stoppering still possible

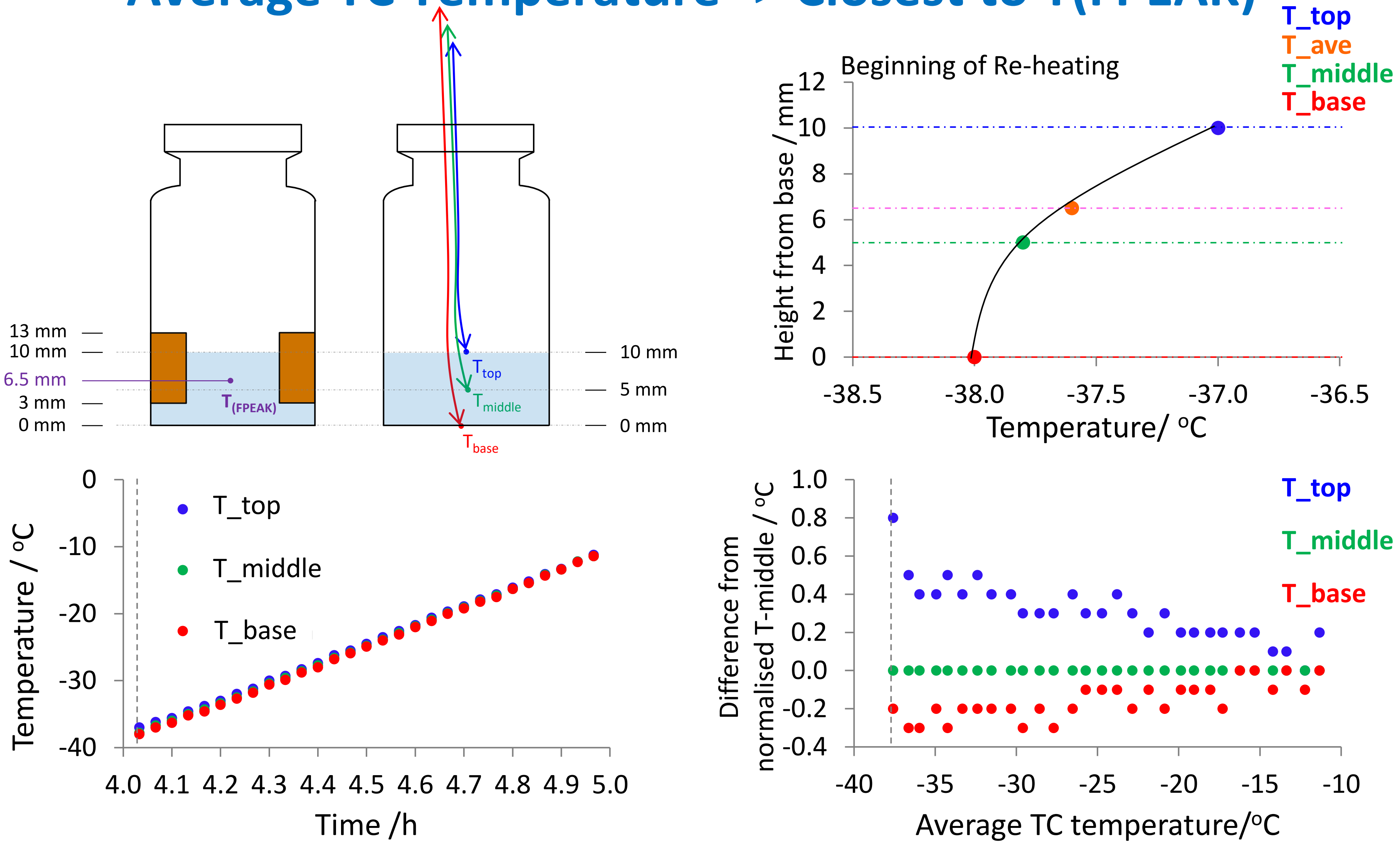


Use of Average Temperature from 3 Thermocouples to Calibrate the TVIS System: A Justification





Average TC Temperature -> Closest to T(FPEAK)



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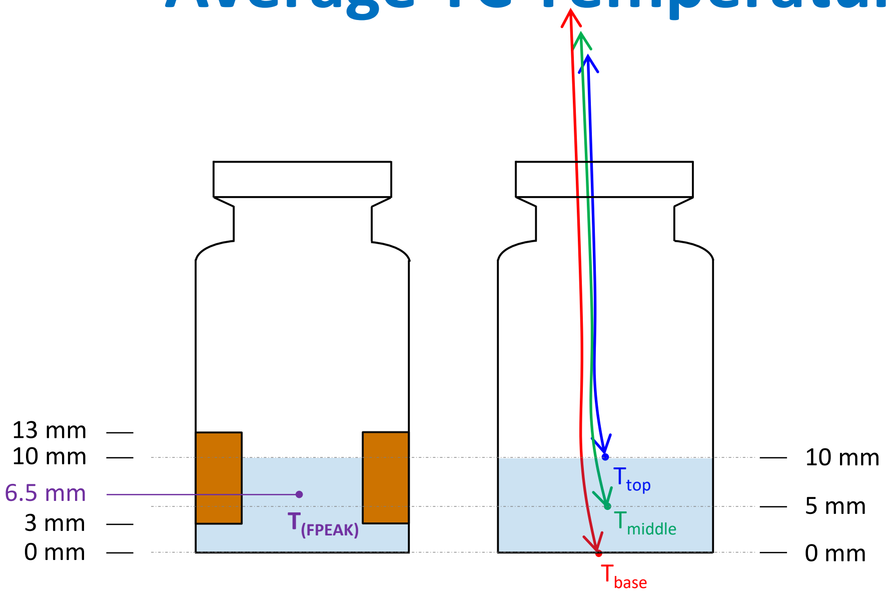

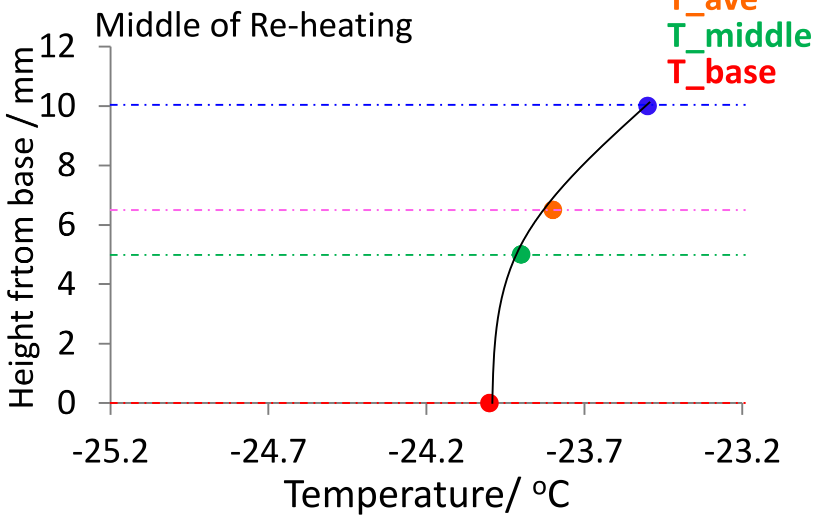

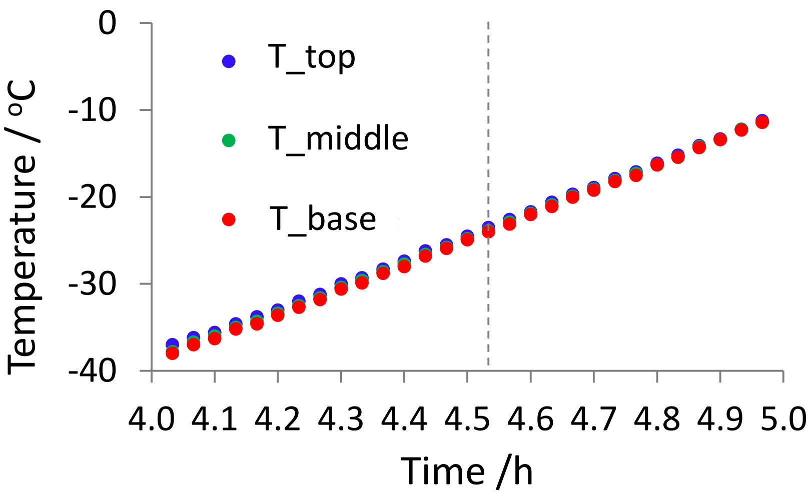

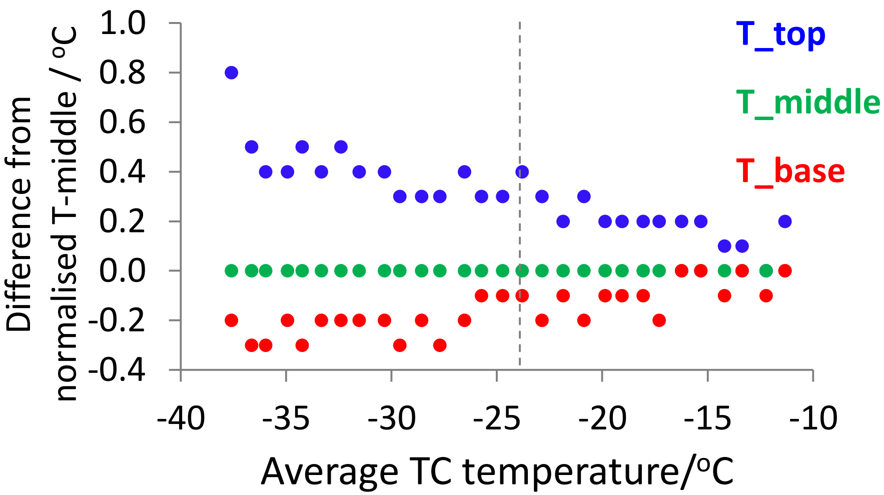

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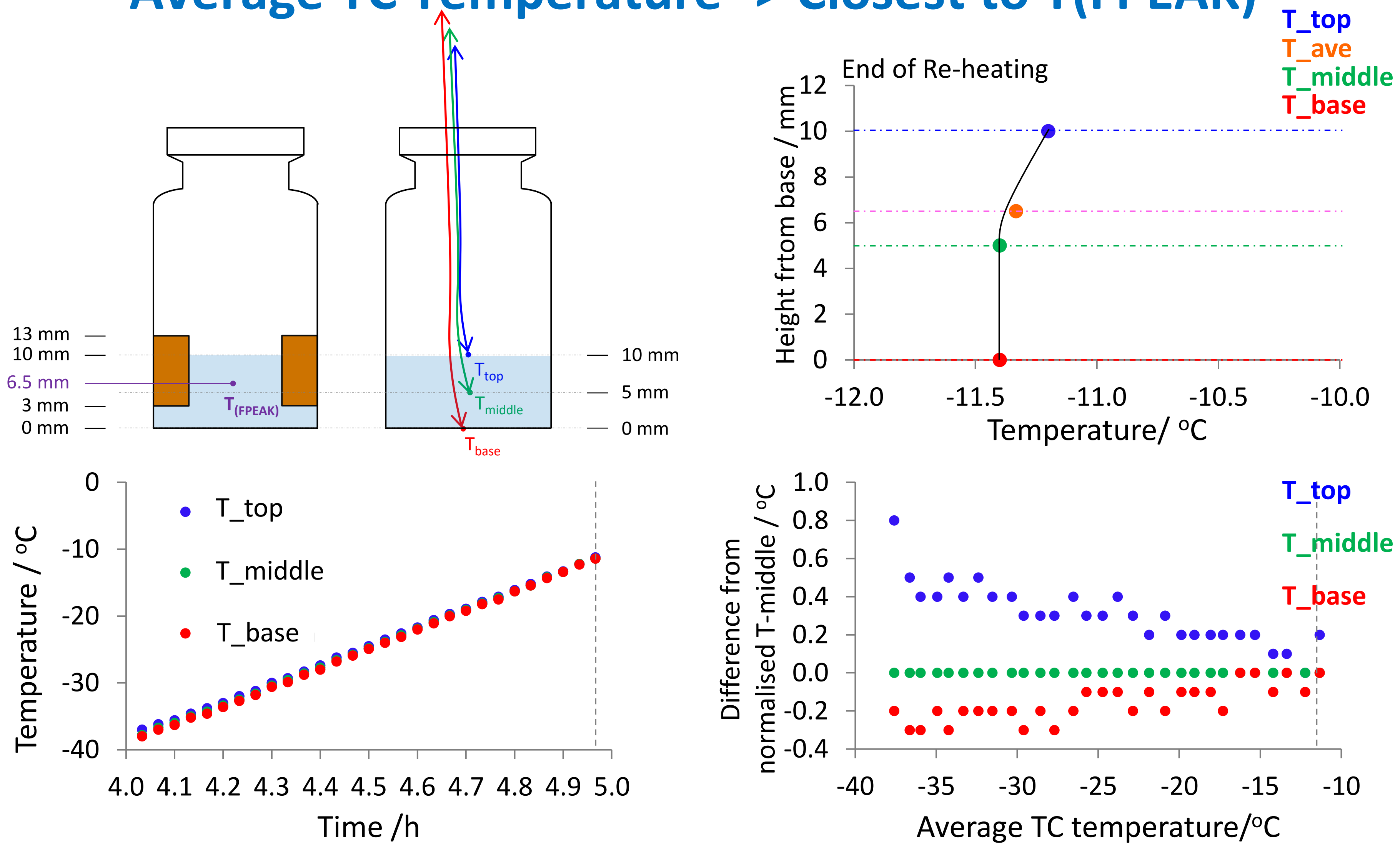
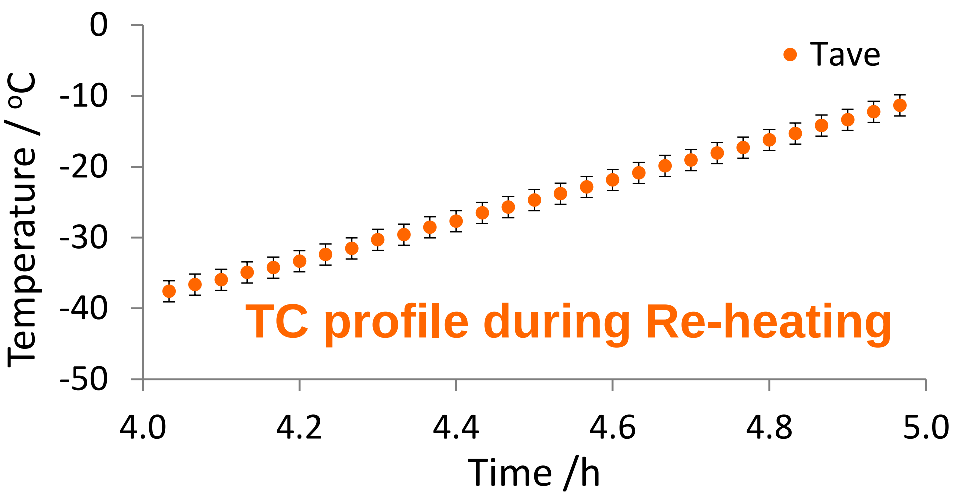
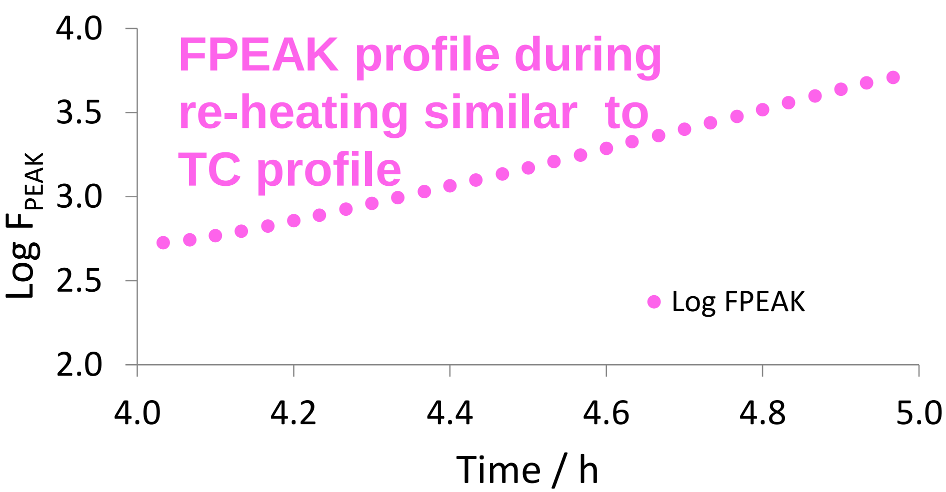
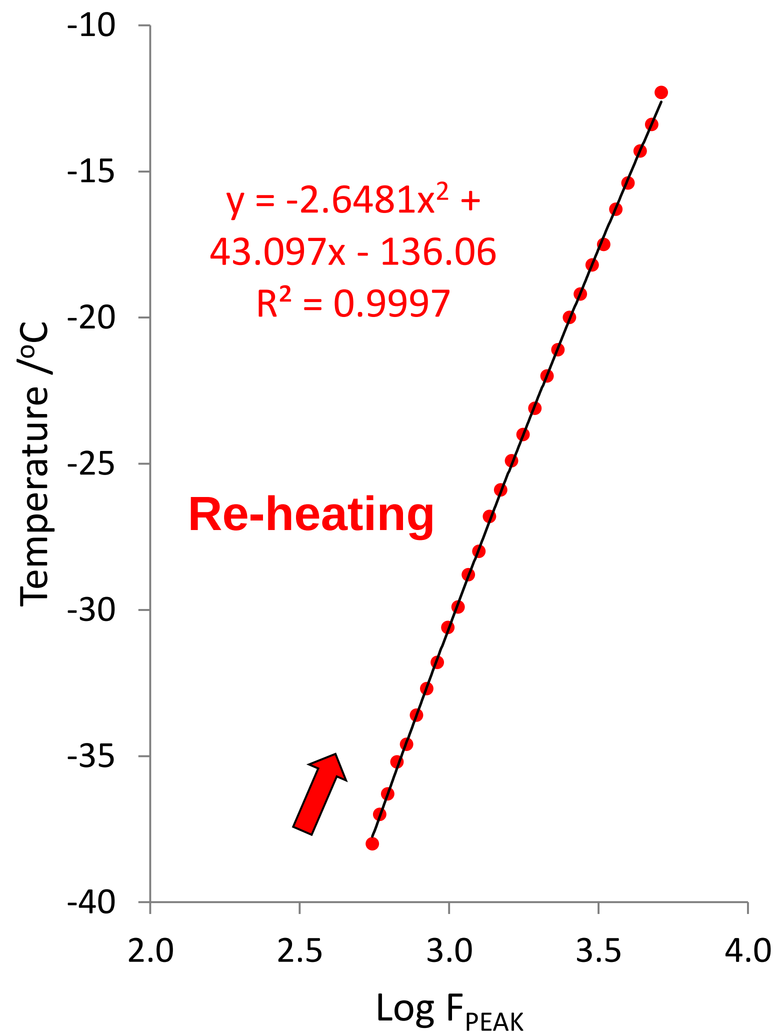


Temperature Calibration Plot



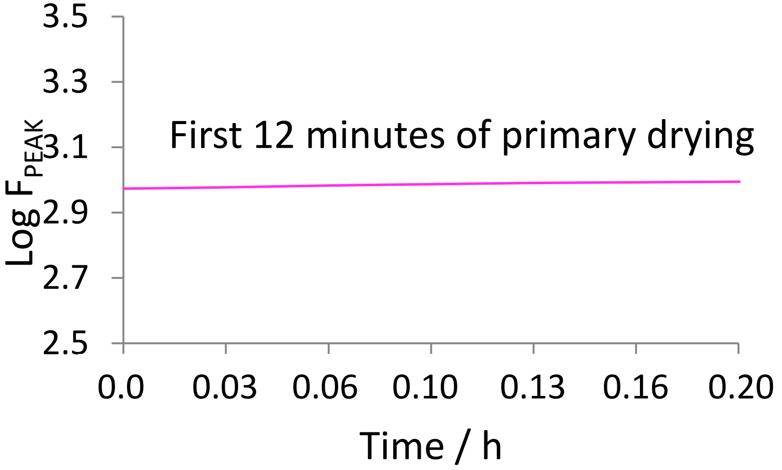


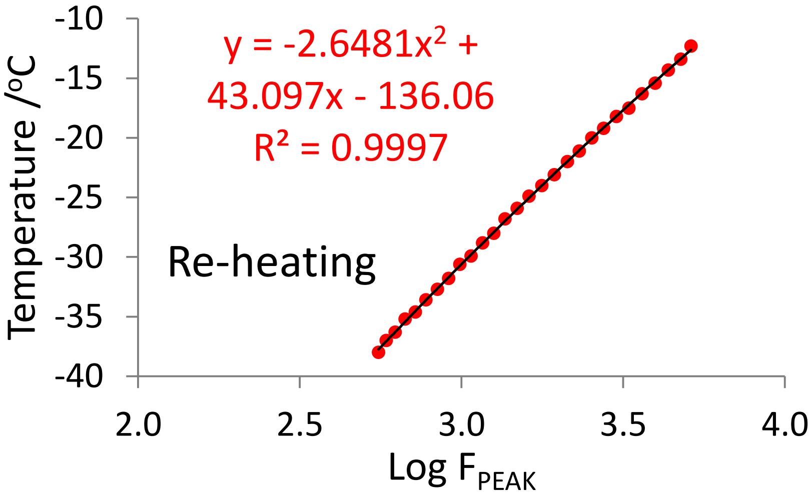


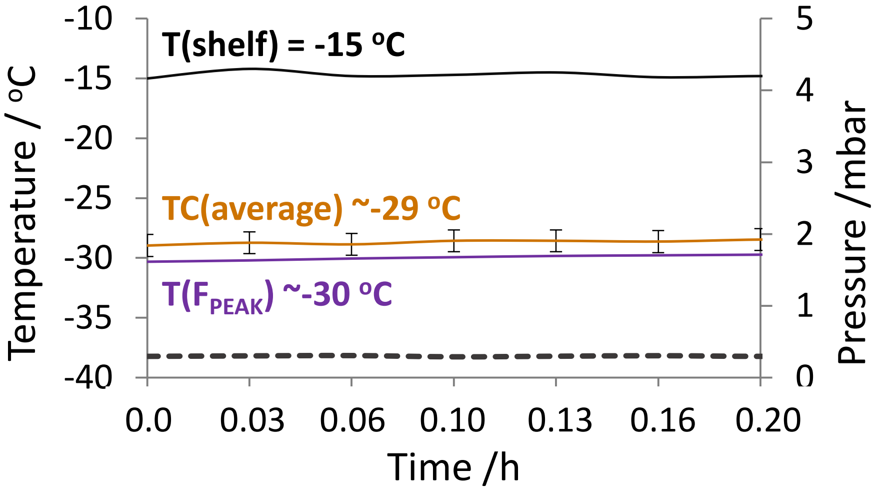
TVIS Application in Primary Drying

Temperature Prediction during Primary Drying

- Log FPEAK was recorded throughout the freeze drying process
- The calibration equation obtained during Re-heating and Log FPEAK values during primary drying were used to predict T(FPEAK) during primary drying
- Good agreement between TC (average) and T(FPEAK) over the first 10 minutes

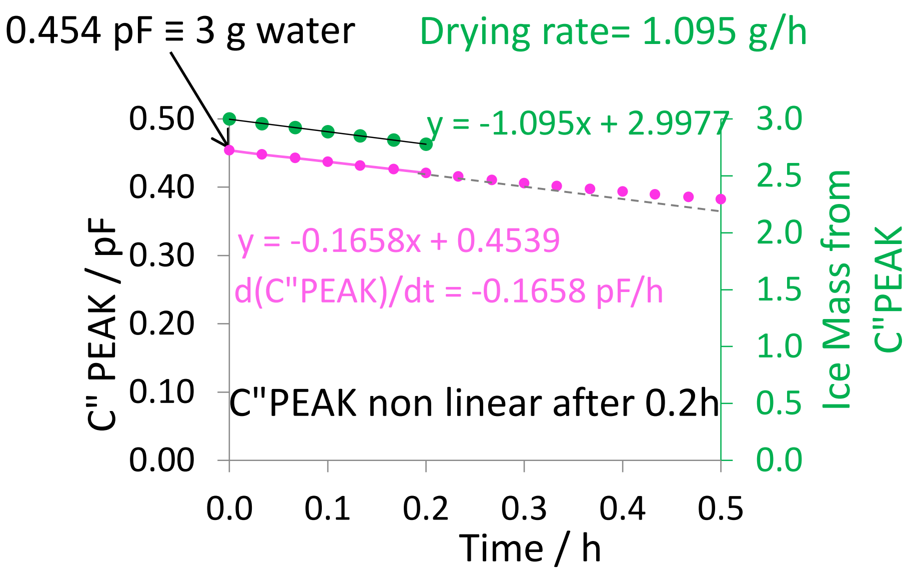




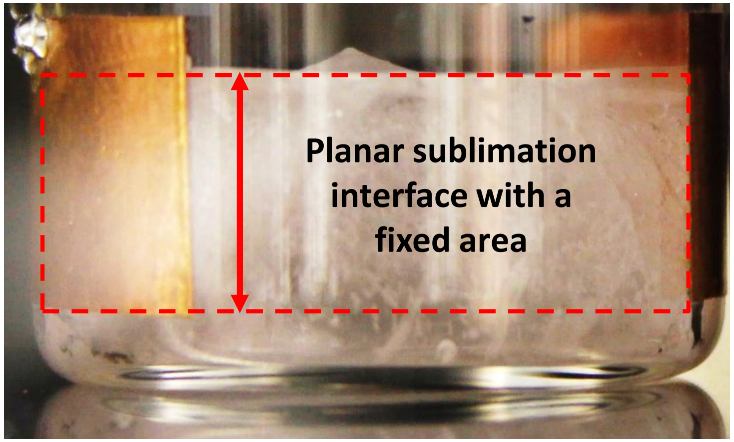


Drying Rate Prediction

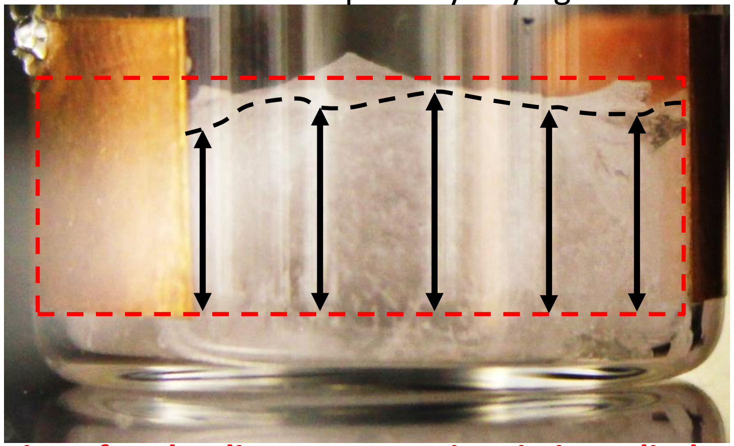
Drying rates are based on the assumption of a planar sublimation front



0 h of primary Drying



0.2 h of primary Drying



Shape of the sublimation front became non-planar after 0.2 h (12 min) and therefore, C"PEAK cannot be assumed to be proportional to ice cylinder height

C"PEAK at 0h = 0.454 pF

C"PEAK at 0.2 h = 0.421 pF

% decrease ~7% within the first 12 minutes

Undulating interface leading to uncertainty in ice cylinder height

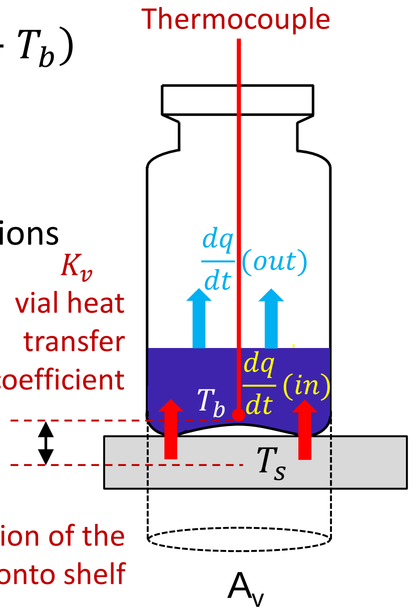
Estimation of Vial Heat Transfer Coefficient

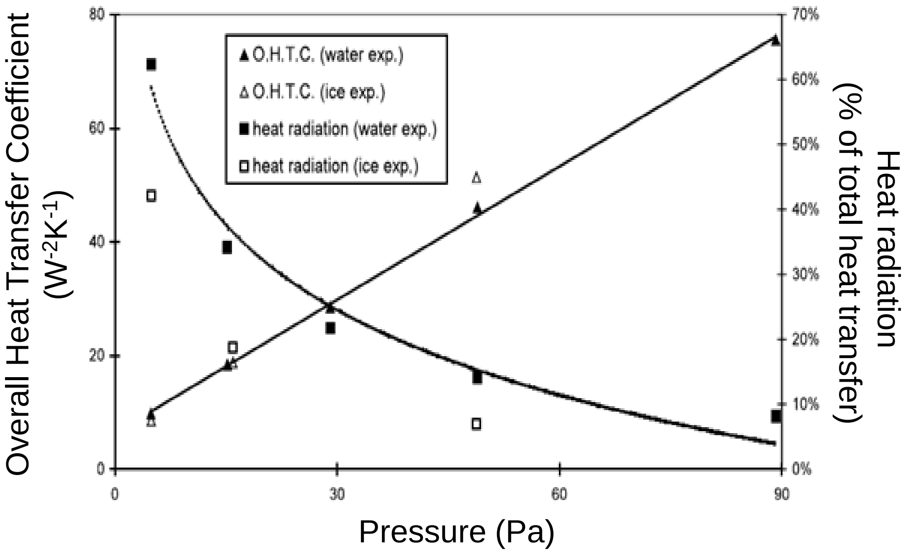
$$\frac{dq}{dt}(in) = A_v.K_v(T_s - T_b)$$

$$\frac{dq}{dt}(out) = H_s.\frac{dm}{dt}$$

Under steady state conditions

$$\therefore K_v = \frac{H_s.\frac{dm}{dt}}{A_v(T_s - T_b)}$$





Brülls and Rasmuson (2002) Int. J. Pharm. 246, 1-16. Heat transfer in vial lyophilization

H_s	$4301\ Jg^{-1}$
Dm/dt	$1.095gh^{-1}$ (from TVIS)
A_v	$0.024\ m$ i.e. $\frac{\pi(0.024)^2}{4}$) $= 0.0045m^2$) for 10 mL tubing Vial
T_s	-15^oC or 258 K
T_b	-30^oC or 243 K from T(FPEAK)
K_v	**$127.5\ Js^{-1}K^{-1}m^{-2}$ [@ 40 Pa, 40 µBar]**

Conclusion

- Freeze Drying is heterogeneous
- Existing technologies in the market have limitations
- TVIS
  - single vial technique
  - non-product invasive
  - drying and product temperature of individual vials can be determined in a single experiment across the shelf
  - Time lapse photography along with TVIS measurement showed the drying rate and Kv should be determined within the first 12 minutes that corresponds to ~7% ice sublimation
  - Kv was ~127 $\mathrm{Js^{-1}K^{-1}m^{-2}}$, i.e. 4-8 times higher than the values found in literature.

Acknowledgements, Recent Projects & Collaborators

- De Montfort University
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- Sanofi : Tim McCoy

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bluefrog design

NIBSC Confidence in Biological Medicines

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Thank You