FACULTY OF PHARMACEUTICAL SCIENCES

LABORATORY OF PHARMACEUTICAL PROCESS ANALYTICAL TECHNOLOGY

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PRACTICAL IMPLEMENTATION OF DYNAMIC PRIMARY DRYING SETTINGS IN A CONTINUOUS FREEZE-DRYING PROCESS

INTRODUCTION

- **Continuous** freeze-drying = 1) **Spin freezing** vials with N_2-gas (→ thin product layer) + 2) Perpetual **vacuum chamber** with **radiation** as energy supply method (→ more uniform)
- **Mechanistic** model of the continuous drying step[1] → most **optimal** dynamic dryer **settings:** chamber pressure (P_C) & radiator temperature (T_{rad}).
- Continuous processing → unit doses processed one by one → enables **individualised** process **settings** per vial → **reducing** effects of **uncontrolled factors** → uniform quality

AIM: Supercooling = **uncontrolled** factor → vial-to-vial dry product resistance (R_p) **variability** ➔ **adjust** dynamic dryer **settings** per unit dose based on **supercooling** temperature (T_{SC})

SPINFREEZING

Material & methods:

- Spinfrozen at 2000 RPM with 50 l/min nitrogen gas of -30±3 °C
- 3,9 ml solution (5 % mannitol) in 10R Schott vial
- Experimental groups: scratched vial wall (**Scored**) vs (**Regular**)
- Vial Temperature (T_{Vial}) with **Infrared** (IR) **thermometer**
- T_{SC} = temperature just before nucleation (1A at Graph 1)

Results:

- **Nucleation** → Appearance of **clear white ice** (Figure 1: 1A vs 1B)
  → Simultaneous **rise in** T_{vial} towards 0 °C (Graph 1)
- **Wide range** of T_{SC} were observed (i.e. between -4 °C and -12 °C)

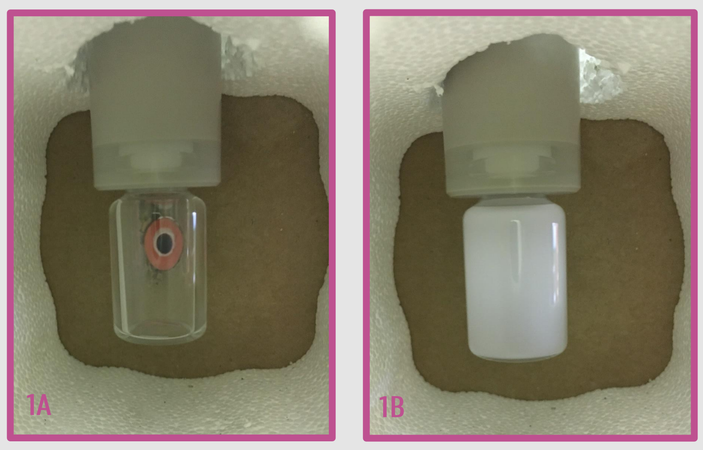
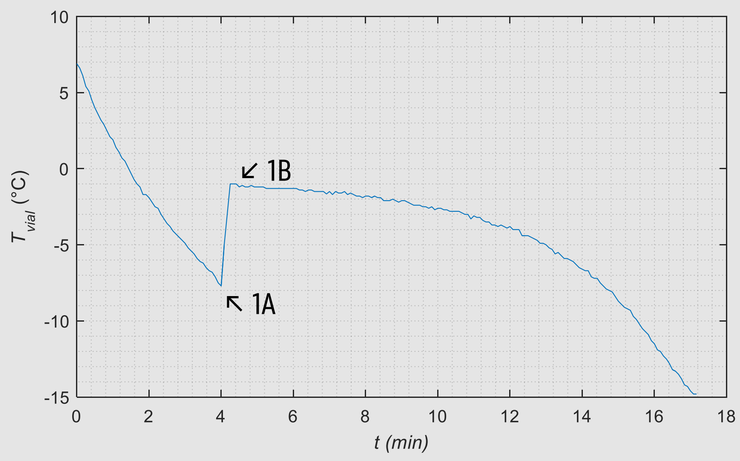
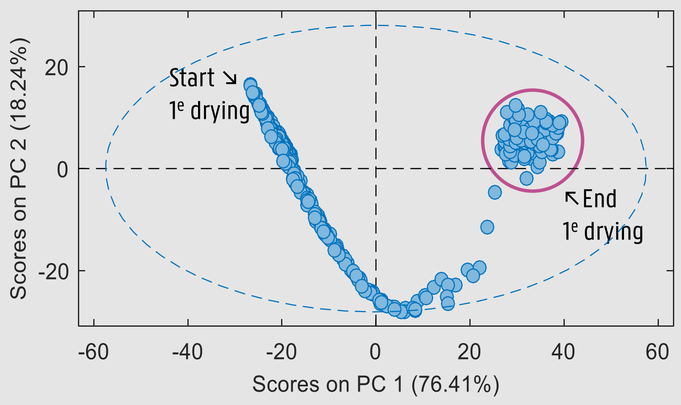


Figure 1: Spinned vial just before (1A) and right after (1B) nucleation



Graph 1: Observed vial temperature with infrared thermometer during spinfreezing

PRIMARY DRYING



Graph 2: Scores plot from PCA analysis: primary drying end point

Material & methods:

- 15 vials with a T_{SC}: -4 to -12 °C **dried** by **radiation** (18W) at 55 Pa (Figure 2)
- Every 20 s **NIR spectra** → Savitzky-Golay smooting and SNV preprocessing
- Principal component analysis (**PCA**) → primary drying **end point** (Graph 2)
- 1e Derivative → **peak shifts** at 5250 & 7074 cm^{-1} → **product temp** (T_p)

(1) $P_i = e^{\frac{-6140,4}{T_p}+28.916}$ (2) $R_p = \frac{(P_i - P_c) \times A}{\dot{m}_{sub}}$ (3) $R_p = R_{p0} + \frac{A_{Rp} \times l}{1 + B_{Rp} \times l}$

- Average **sublimation rate** ($\dot{m}_{sub}$) = filling volume / 1e drying time (by NIR)
- R_p estimated using (1) and (2) and plotted against **dry layer thickness** (l)
- Parameters in (3) fitted → A_{Rp} & B_{Rp} linearly **regressed** to the observed T_{SC}

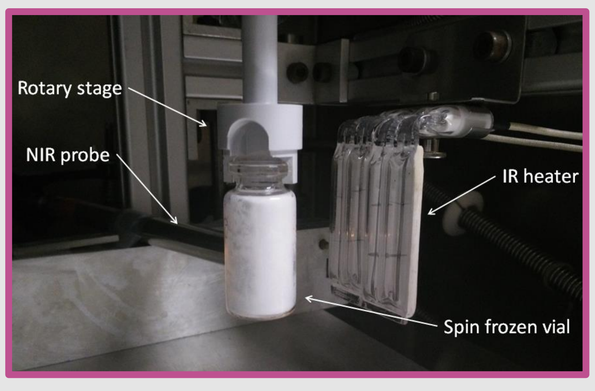
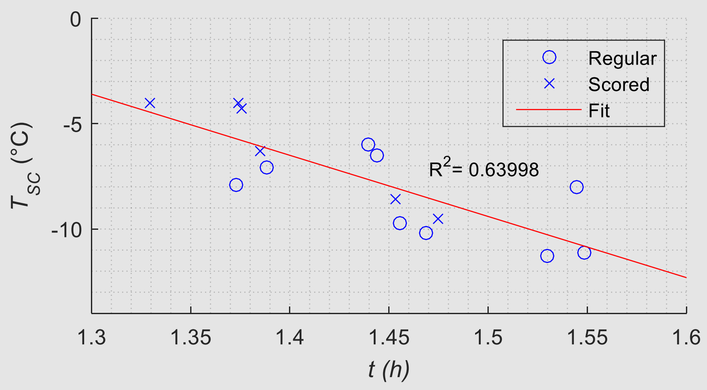


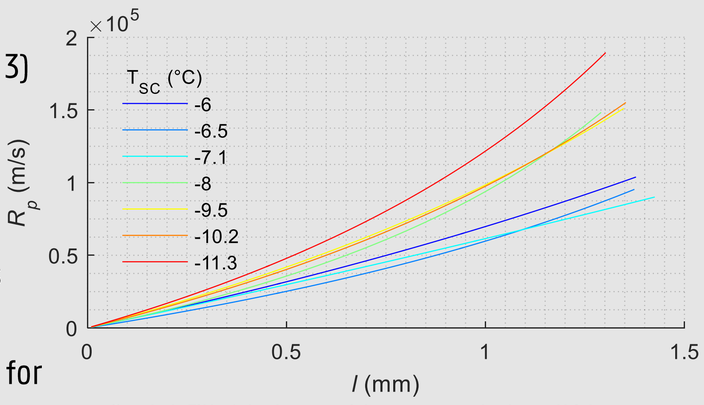
Figure 2: Radiation primary drying stage with NIR probe

Results:

- Linear **relation** between T_{SC} and **1e drying time** with R² of 0.64 (Graph 3)
  → similar observation by Searles in regular frozen vials[2]
- For 7 out of 15 vials the T_p **prediction** (RMSE: 4°C): reasonably feasible
  → R_p calculated and plotted against l (Graph 4)
- Linear **relation** between A_{Rp} and T_{SC} observed with R² of 0.76
  → similar observation by Rambhatla with controlled nucleation[3]
- **Unclear** regression of B_{Rp} to T_{SC} with R² of 0.31
- T_p dominant in R_p calculation ➔ **error** on T_p prediction to **big** for reasonable R_p predictions



Graph 3: Observed T_{SC} versus primary drying time by NIR



Graph 4: Fitted dry layer resistance versus dry layer thickness

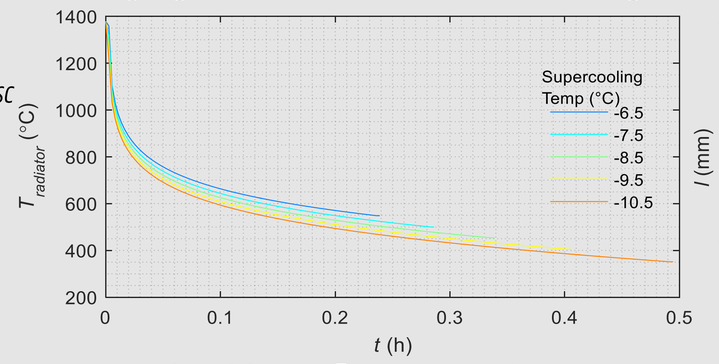
DYNAMIC SETTINGS

Material & methods: A full integrated **Labview** 2015SP1 **application** was developed containing (Figure 3):

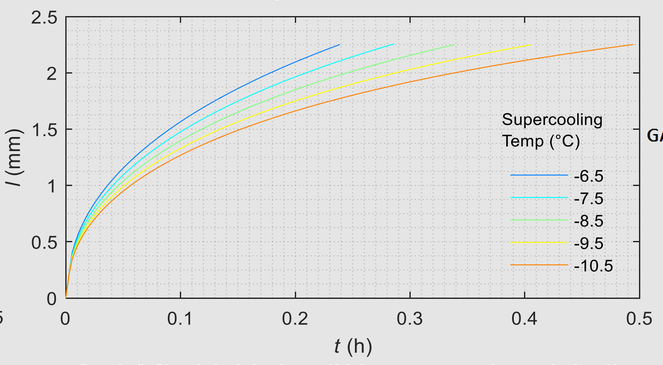
- Primary drying **mechanistic model** developed in Matlab R2015b[1] → prediction of most **optimal** dryer **settings** (P_C & T_{rad})
- **Capturing** all model **input variables**: formulation properties (i.e. R_{p0}, A_{Rp} & B_{Rp}); vial dimension, freeze dryer configuration, filling volume …
- **Data acquisition** from the **Pirani** vacuum gauge and **Actuator drivers**: **Gas dosing valve** and NIR radiator by the **Power source**

Results:

- A_{Rp} & B_{Rp} **predicted** for several T_{SC}
- **Safe** T_p of -10 °C assumed
- Labview → most optimal drying trajectories (graph 5 and 6)
- **considerable** difference in 1e drying time → **unrealistic** A_{Rp}



Graph 5: Simulated T_{rad} versus primary drying time



Graph 6: Simulated dry layer thickness versus primary drying time

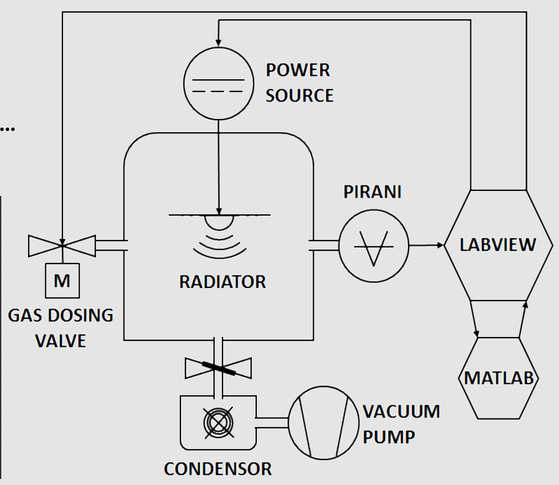


Figure 3: Piping and instrumentation diagram of primary drying set-up; M: motor actuated

CONCLUSION

- **Supercooling temperature** (T_{SC}) effect upon the **primary drying** of spinfrozen vials observed; similar to reports by literature[2,3]
- **NIR** spectra → Primary drying **end point** detection by PCA; T_p **prediction** by peak shift of the 5250 & 7074 cm^{-1} waterbands
- R_p calculations **overestimated** due to the inaccuracy of the product temperature (T_p) predictions → unrealistic A_{Rp} parameters
- Full integrated controlled drying system developed, capable of **individualised** optimal drying **settings** to compensate for **uncontrolled factors**: i.e. supercooling temperature ➔ more uniform batch quality

1: Van Bockstal (2017). J. Pharm. Sci. (106) 71-82;
2: Searles (2001). J. Pharm. Sci, (90) 872–887;
3: Rambhatla (2004). AAPS PharmSciTech, (5) 1-9;

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