# The Application of Through Vial Impedance Spectroscopy (TVIS) for Optimization Freeze-Drying Process

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**"Non-invasive, real time lyophilisation process monitoring would increase process understanding and accelerate development of stabilized biopharmaceutical formulations at room temperature."**

## TVIS Technology

In-line monitoring system for the freeze drying process consisting of:

- Freeze-drying vial with external electrodes
- Pass through for cabling
- External Impedance spectrometer.

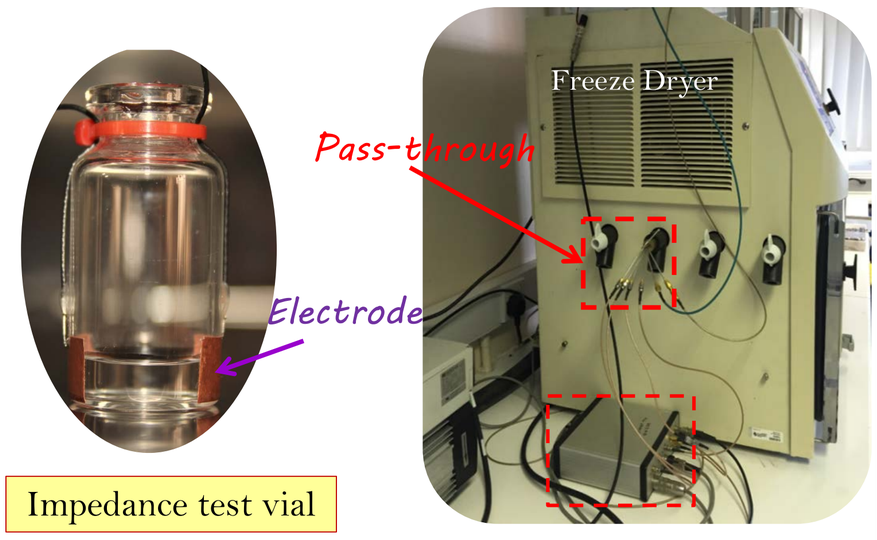
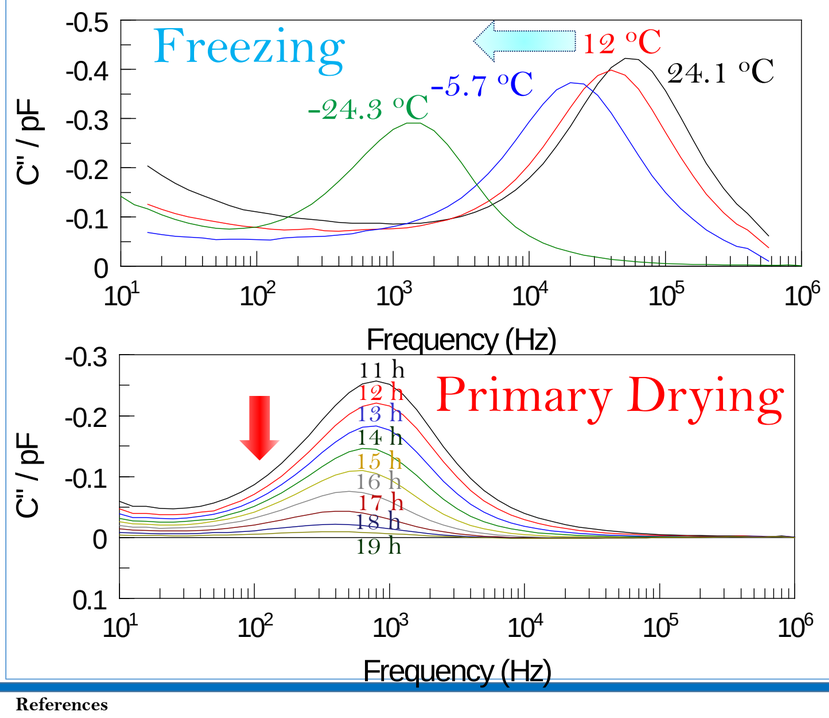



Figure 1. TVIS Technology

## TVIS Technology Principle

Process analytical technology based on impedance spectroscopy

- Electrical impedance determines the ability of materials to conduct electricity under an applied voltage .
- Impedance is a function of dielectric and conductive properties and therefore the physical state of vial and its contents.
- Principal parameter effecting measured impedance is resistance/conductivity of sample within the vial.
- Changes in electrical parameters mirror the condition of the sample throughout the lyophilisation process.
- The capacitance spectrum is related to *the resistance/ conductivity and capacitance of the vial contents.*
- Data viewing software (LyoView ™) identifies the peak frequency ($F_{PEAK}$) and the peak amplitude ($C''_{PEAK}$) in the imaginary part of the capacitance spectrum
- $F_{PEAK}$ can be used to monitor phase behaviour (ice formation, glass transitions) and product temperature
- $C''_{PEAK}$ can be used to monitor the amount of ice remaining during primary drying, from which the drying rate and the end point may be determined.



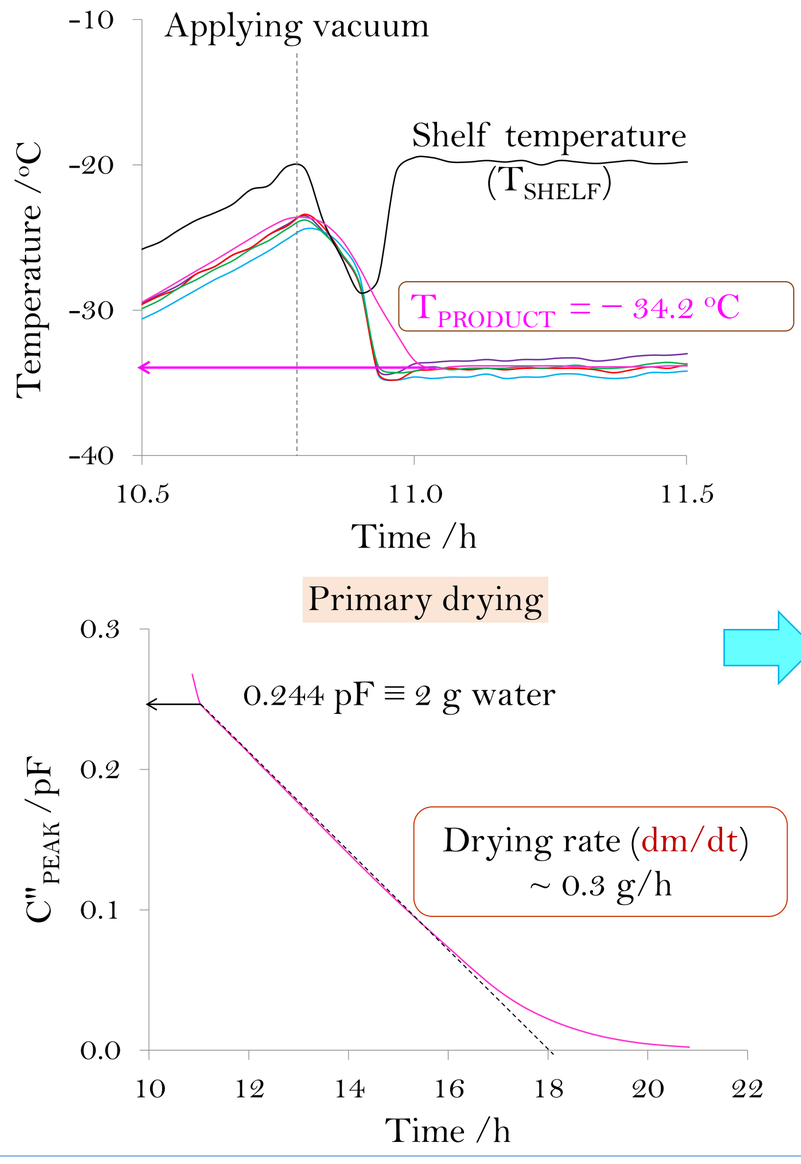

## TVIS Advantage

1. Non-invasive, real time full cycle lyophilisation monitoring including :
   - Cooling rate, Freezing and Annealing
   - Primary and Secondary Drying end point
2. Optimization of the primary drying process by:
   - Heat Transfer Coefficient ($K_V$) Determination
   - Dried Product Resistance ($R_P$) Determination
3. Can be applied in standard freeze dryers
4. Integrated, bench top, single vial, TVIS enabled analytical freeze dryer

# TVIS APPLICATIONS

## Heat Transfer Coefficient ($K_V$) Determination

- The product temperature ($T_{PRODUCT}$) derived by ***TVIS*** is one of the parameters needed for $K_V$ determination
- Sublimation rate or drying rate (dm/dt) is estimated by ***TVIS***




$K_V$ determination

$T_{PRODUCT}$ and dm/dt from ***TVIS***

$$K_V = \frac{\frac{dm}{dt} \times 2844\, J \cdot g^{-1}}{0.00045 m^2 (T_{SHELF} - T_{PRODUCT})}$$

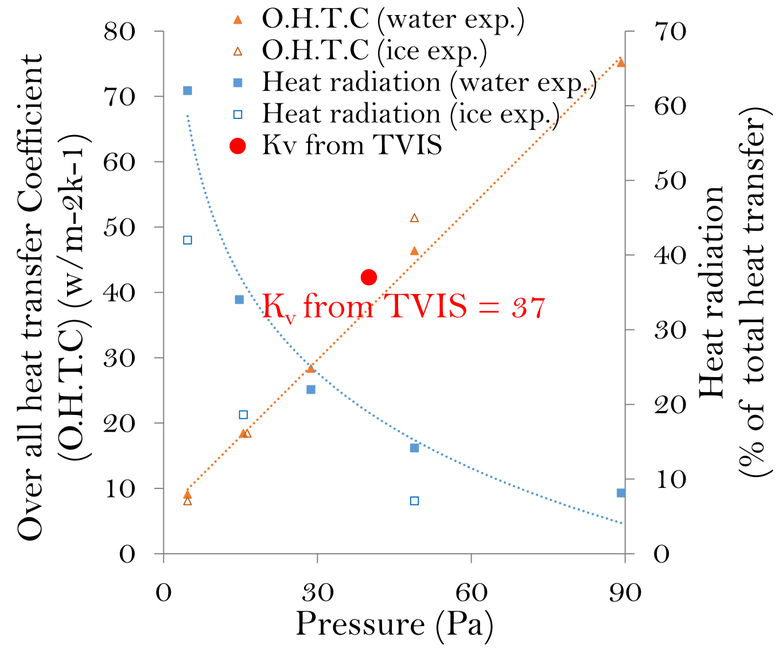
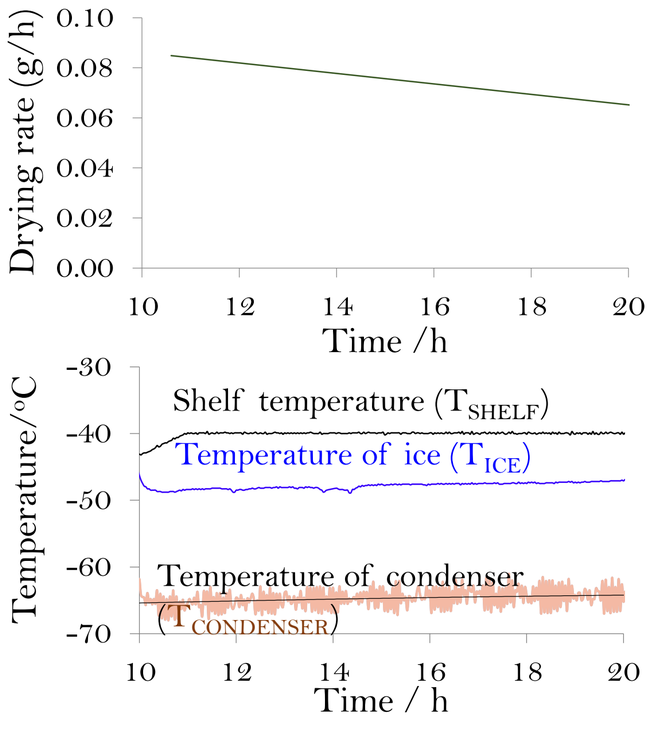



Figure 2. $K_V$ values for 10 mL tubing vials (Brülls et al. 2002)

## Dried Product Resistance ($R_P$) Determination

- $C''_{PEAK}$ from ***TVIS*** is proportional to the amount of ice; therefore it is estimated for drying rate (dm/dt)
- Partial pressure of ice ($P_{ICE}$) and condenser ($P_{CONDENSER}$) calculated from temperature of ice ($T_{ICE}$) and condenser ($T_{CONDENSER}$) by using Clausius- Clapeyron derived equation




*Clausius- Clapeyron derived equation*

$$\ln(P) = \left(\frac{-6144.96}{T_{ICE\ or\ CONDENSER}}\right) + 24.02$$

$R_P$ determination

dm/dt from ***TVIS***

$$Rp = \left(\frac{P_{ICE} - P_{CONDENSER}}{\frac{dm}{dt}}\right) \cdot 3.8\, cm^2$$

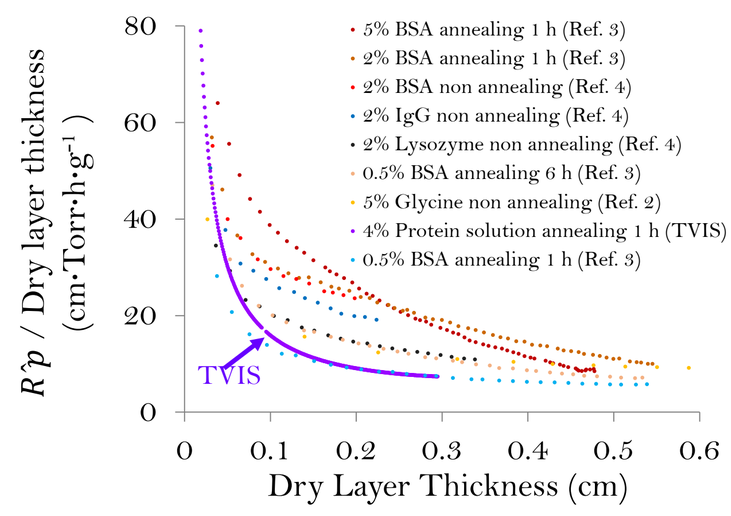



Figure 3. The ratio of Rp and dry thickness as the function of dry thickness

**References**

1. BRÜLLS, M. and RASMUSON, A. (2002) Heat transfer in vial lyophilization. International Journal of Pharmaceutics, 246 (1–2), pp. 1-16.
2. GIESELER, H., KRAMER, T. and PIKAL, M.J. (2007) Use of manometric temperature measurement (MTM) and SMART™ freeze dryer technology for development of an optimized freeze-drying cycle. Journal of Pharmaceutical Sciences, 96 (12), pp. 3402-3418.
3. JOHNSON, R.E. et al. (2010) Use of manometric temperature measurements (MTM) to characterize the freeze-drying behavior of amorphous protein formulations. Journal of Pharmaceutical Sciences, 99 (6), pp. 2863-2873.
4. LEWIS, L.M. (2010) Characterizing the Freeze–Drying Behavior of Model Protein Formulations. Aaps Pharmscitech, 11 (4), pp. 1580-1590.
5. SMITH, G., POLYGALOV, E. and PAGE, T. (2011) Electrical Monitoring of a Lyophilization Process. GB2480299 (A)
6. TANG, X.C., NAIL, S.L. and PIKAL, M.J. (2005) Freeze-drying process design by manometric temperature measurement: design of a smart freeze-dryer. Pharmaceutical Research, 22 (4), pp. 685-700.