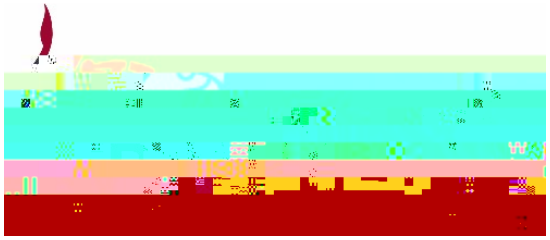


Through Vial Impedance Spectroscopy (TVIS)

A new PAT for freeze-drying cycle development

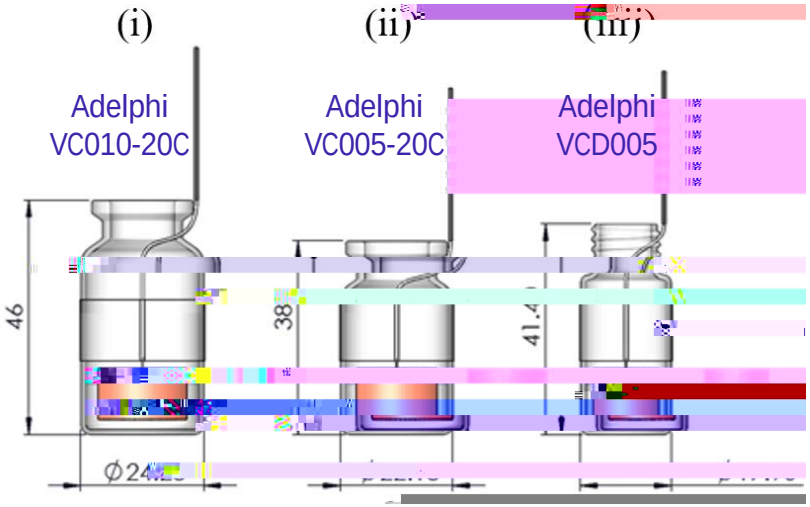
Smi

Outline

- Introduction
  - o

Through Vial I

TVIS Measurement System



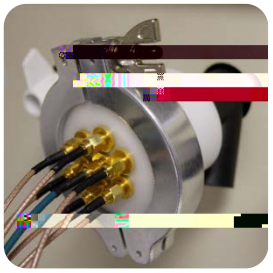
- The designs of various vials that have been modified with copper foil electrodes (10 mm in height and 3 mm from the base of each container

i. 20 mm crimp-neck vial with 10 ml nominal capacity
ii. 20 mm crimp-neck vial with 5 ml nominal capacity
iii. screw-neck vial with 5 ml nominal capacity

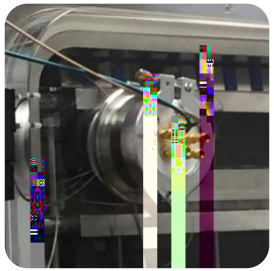
- The different styles of a bespoke pass-through for TVIS systems

A. Connected via the manifold hose on the outside of the dryer
B. Connected via the port on top left side of the door on the dryer
C. Connected to a port on the top of the drying chamber

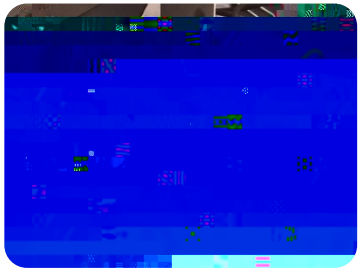
A



B



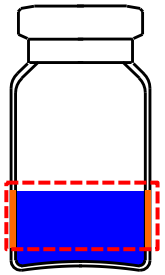
C

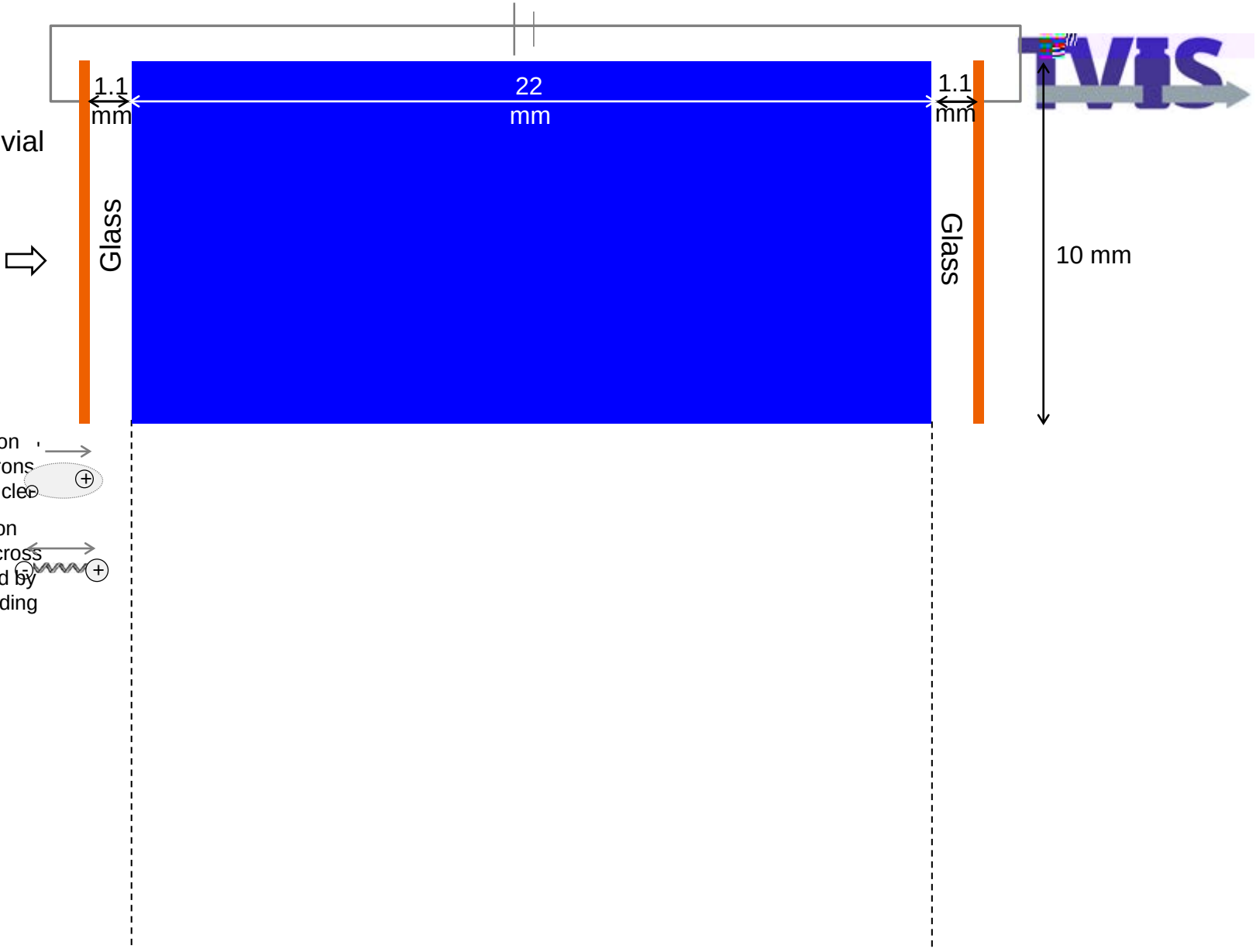


Through Vial Impedance Spectroscopy (TVIS)

Dielectric Loss Mechanisms

Measurement vial





Electronic polarization
distortion of electrons
relative to the nuclei

Atomic polarization
distortion of nuclei across
a heteroatom bond by
stretching and bending

' R P L Q D Q W D W 7 ! ºC) . D S S U R [î

Gener onrmig <0003>ationr L-C / Tc -0.023 Tw -16.709.671())Tj aDC D593 0Tw 6.66 -2.162())Tj -C

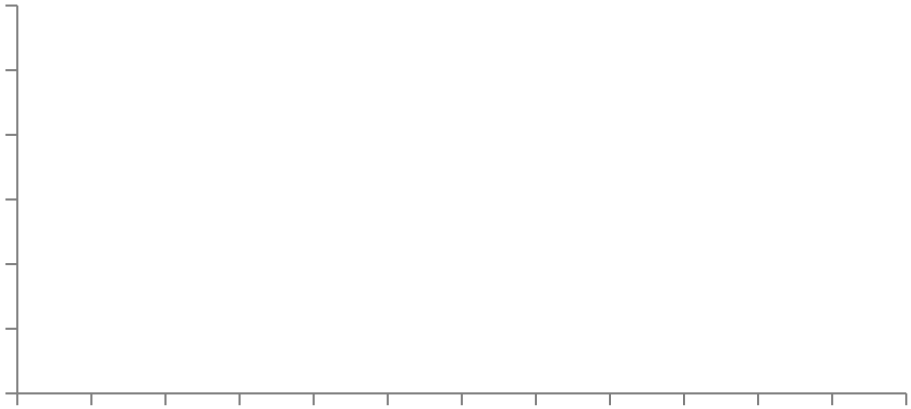
Through Vial Impedance Spectroscopy

Frozen Water and Dielectric Relaxation of Ice

I. : The polarization of the water dipole in liquid water at 20 , with a dielectric loss peak frequency of ~ 18 GHz

II. : The Maxwell-Wagner (MW) polarization of the glass wall of the TVIS vial at 20 with a dielectric loss peak frequency of 17.8 kHz

III. : The dielectric polarization of ice at 20 , with a dielectric loss peak frequencies of 2.57 kHz



Through Vial

Through Vial

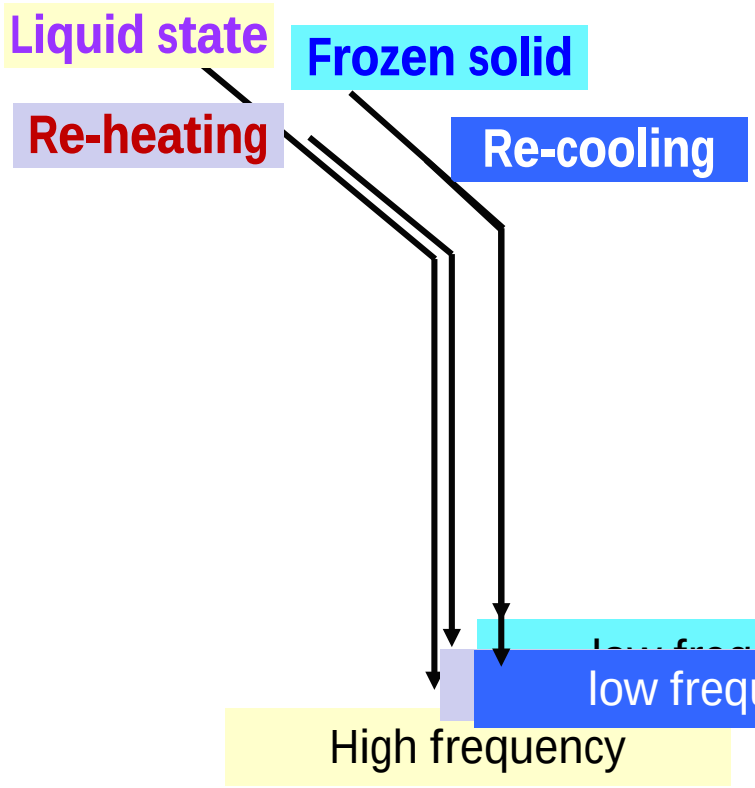
Through Vial

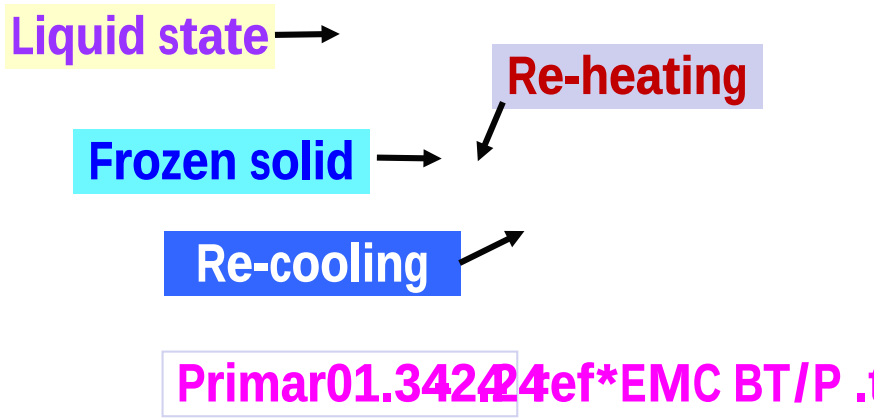
Through Vial

Imaginary Part of Capacitance

Real Part of Capacitance

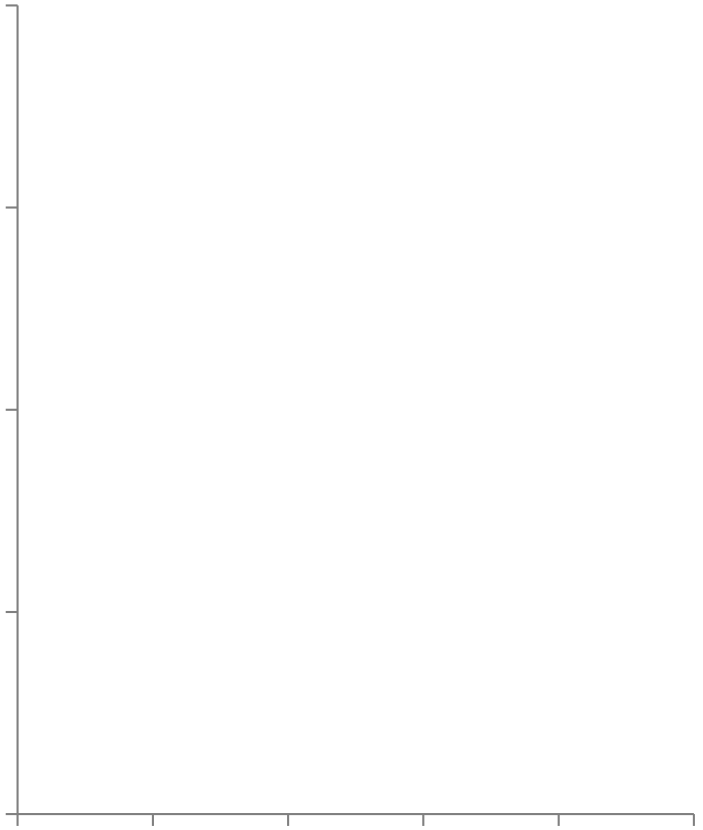
Annealing = Re-heating and Re-cooling





Dielectric loss spectrum

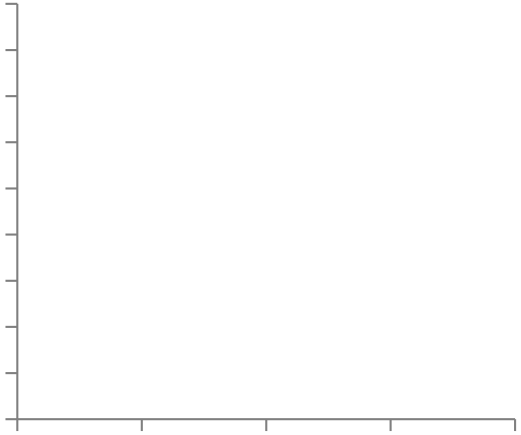
- *Data analysing software (LyoView ™) identifies the peak frequency ((É ¾ º Ä and peak amplitude (%Ó É ¾ º)Ä in the imaginary part of the capacitance spectrum*



Through Vial Impedance Spectroscopy (TVIS)

Temperature calibration & Temperature prediction

Temperature Calibration



Through

T

Through Vial Impedance Spectroscopy (TVIS)

Heat Transfer Coefficient Determination

Heat Transfer Coefficient (- é)Determination

Parameters	TVIS
Drying rate	

Heat Transfer Coefficient (-

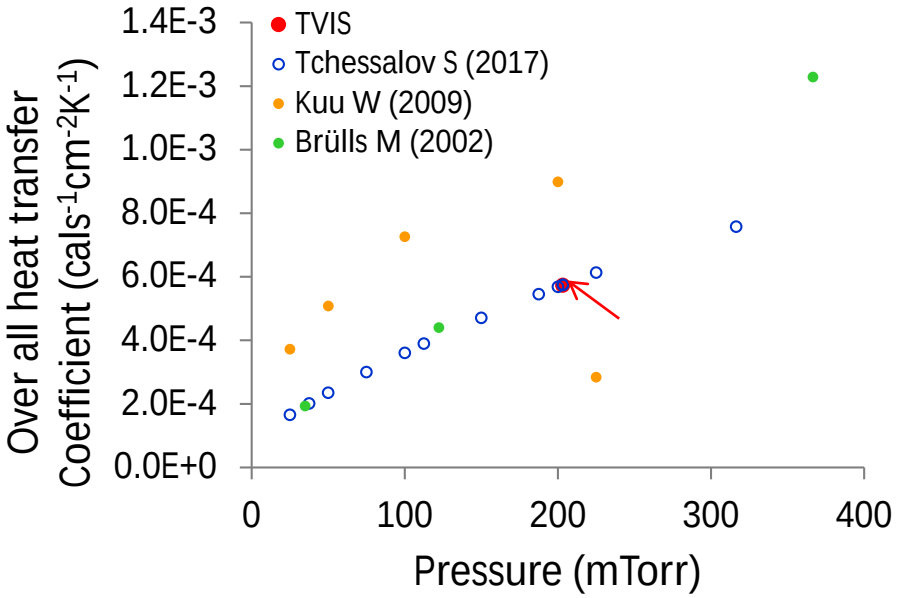
Heat Transfer Coefficient (- é) Determination

$$- é = \frac{\cdot \frac{¿ I}{¿ P}}{\#ø(6æ F 6\tilde{} O)}$$

$$- é(270\ P \succ) N = \frac{¿}{}$$

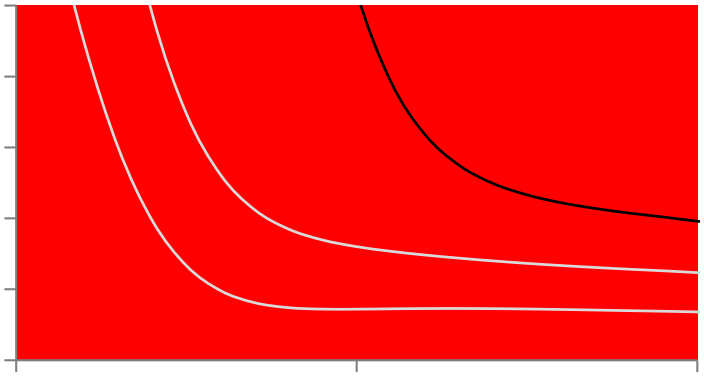
. is the latent heat of sublimation of ice (2844 J $\tilde{g}^{-1}$ or 679.7 cal $\tilde{g}^{-1}$) and $\#ø$ is external cross-sectional area of the base of the TVIS vial (4.62 cm^2)

Heat Transfer Coefficient (- é)Determination

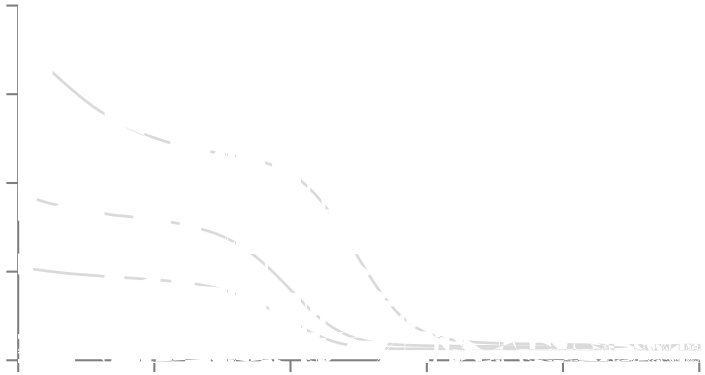


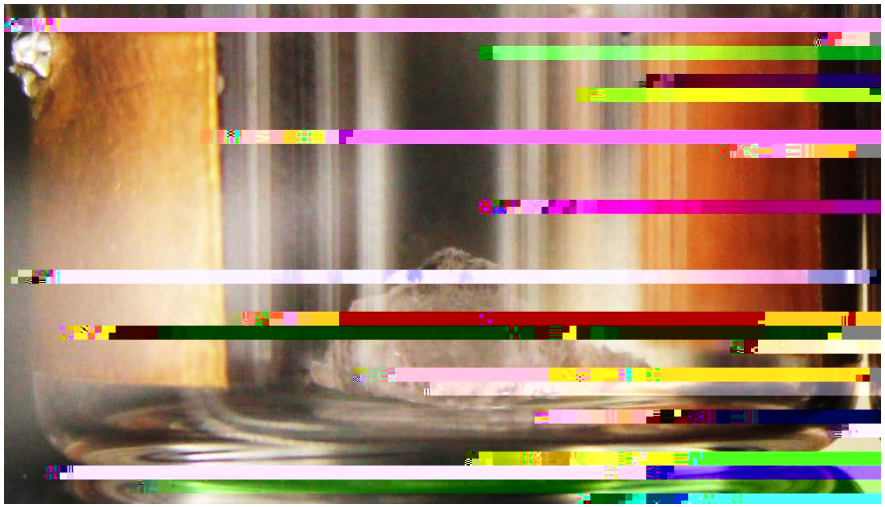
Through Vial Impedance Spectroscopy (TVIS)

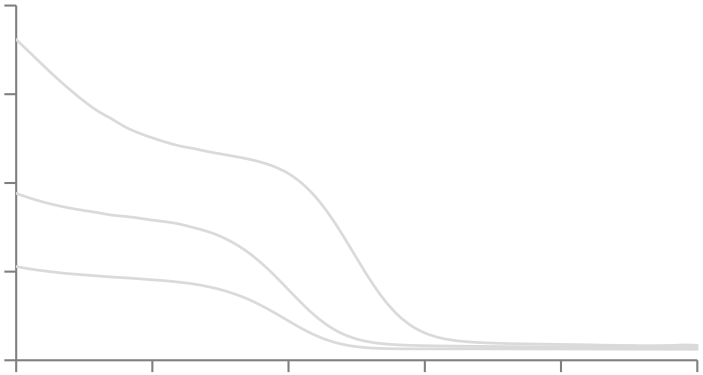
End-point Determination

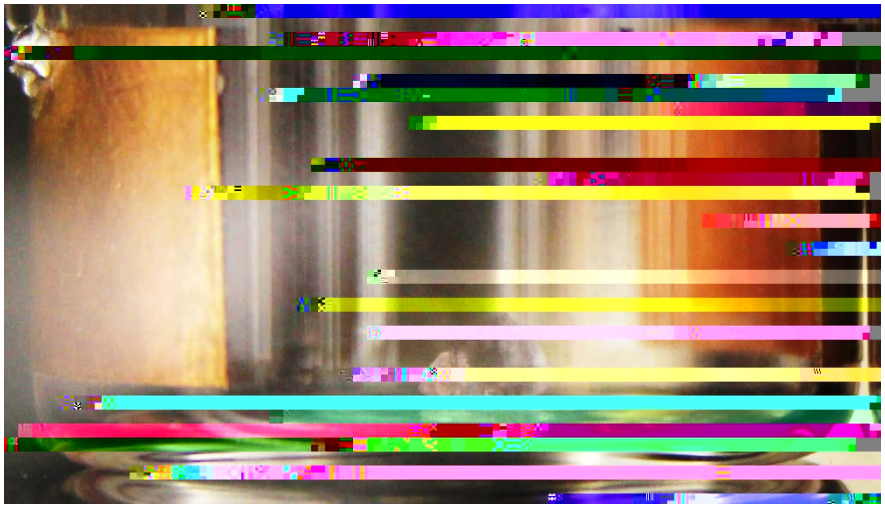


Through Vial Impedance Spectroscopy









T

T

- End point determine by high frequency (i.e. 100 kHz for ic1.3 (er.0.5 1)(e)0.5.2 9e

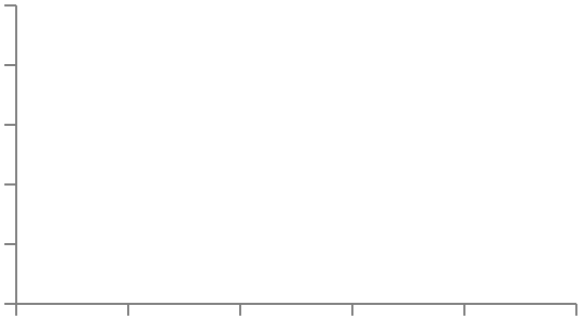
Through Vial Impedance Spectroscopy (TVIS)

Product Resistance Determination

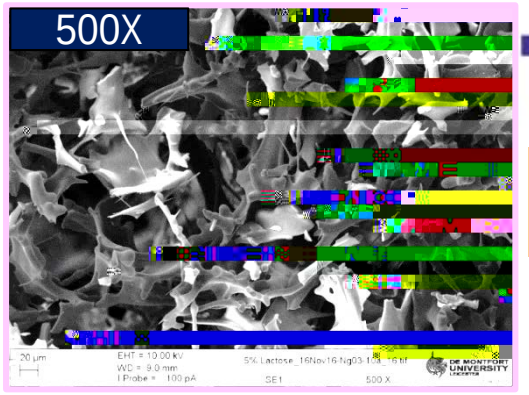
Product Resistance (R_p) Determination

4

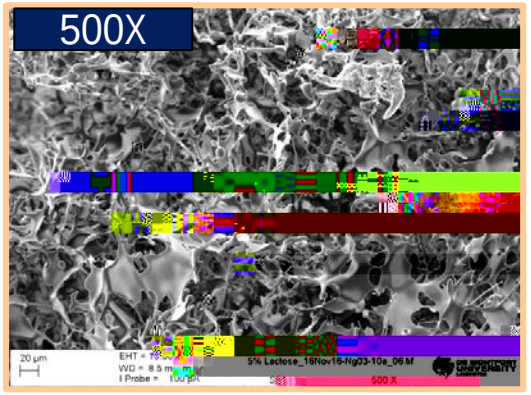
Product Resistance (R_P) Determination



3 mm



Top layer
Fine pores



Middle layer
Micro-collapse

500X

Bottom layer
Full collapse

Through Vial Impedance Spectroscopy (TVIS)

Collapse Phenomena

5% Sucrose +0.55% NaCl

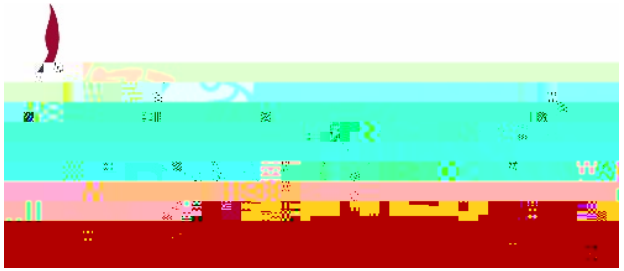
Summary results of sugar- salts solutions

Parameters	Unit	S-1	S-2	S-3
Component				
Sucrose	%w/v	5	5	5
Sodium chloride	%w/v	-	0.26	0.55
€ñ **(DSC)**	°C	**-33.7**	**-38.0**	-41.8
Temperature stabilization period		III to IV	III to IV	III to IV
(Before ramping shelf temperature)	h	23.3 - 23.6	23.3 - 23.6	23.1 - 23.6
€(r | q m w	°C	-36.0 to -35.6	**-37.0**	**-38.3 to -37.7**
Surrogate drying rate (Š †q m w¤Š**)**š	pF/h	0.0380	0.0644	0.0864
Structural state		Non-collapse	micro-collapse?	Micro-collapse
		VII to VIII	VII to VIII	VII to VIII
Temperature stabilization period	h	26.0 - 26.8	26.0 – 26.4	26.0 -26.2
(After shelf temperature constant)	°C	-26.4 to -25.6	-30.1 to -30.0	-32.8 to -32.7
Surrogate drying rate (Š †q m w¤Š**)**š	pF/h	0.2243	0.1227	0.1569
Structural State*		Micro-collapse	Collapse	Collapse

Through Vial Impedance Spectroscopy

Acknowledgements, Recent Projects & Collaborators

- De Montfort University, School of Pharmacy
  - Evgeny Polygalov: co-inventor of TVIS instrument
  - Yowwares Jeeraruangrattana. PhD student
  - Bhaskar Pandya. PhD student
  - Irina Ermolina. Senior Lecturer



GEA Pharma Systems

SANOFI

Government Support for industry

LyoDEA
Lyophilization process analytics
By dielectric analysis

BIOSTART
Biopharmaceutical Stability at
Room Temperature

AtlasBio
Analytical Technologies for the
Stabilization of Biopharmaceuticals