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Z-FDM
Micro-Sample Impedance Spectroscopy for Lyo-Formulation Development

Geoff Smith, De Montfort University, Leicester, UK

Content

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1. Overview of the experimental set up
2. Applications
   - Freezing (ice nucleation, growth and solidification end point)
   - Annealing (rates of change of the ice mass)
   - Glass transition determination

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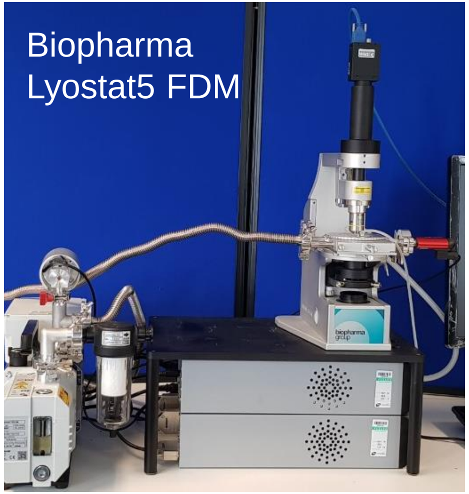
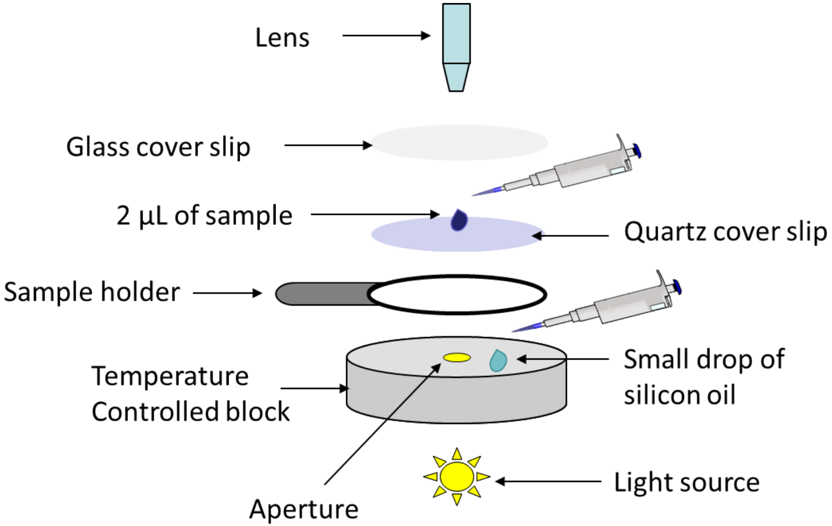
Freeze-drying microscopy (FDM)

Real-time observation of the behavior of formulations during freeze-drying

Typically used to study the critical collapse temperature (Tc), and its relationship with

- The glass transitions (T_G) of amorphous components, and/or
- The melting of crystalline components (T_{EU})





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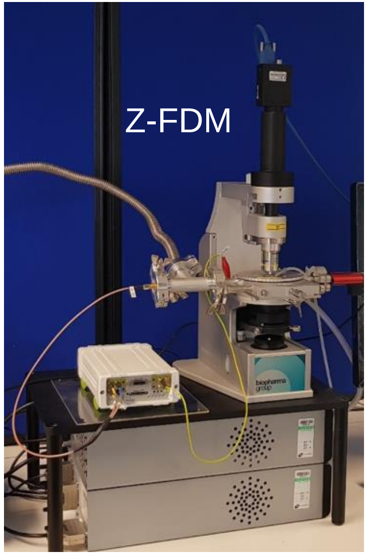
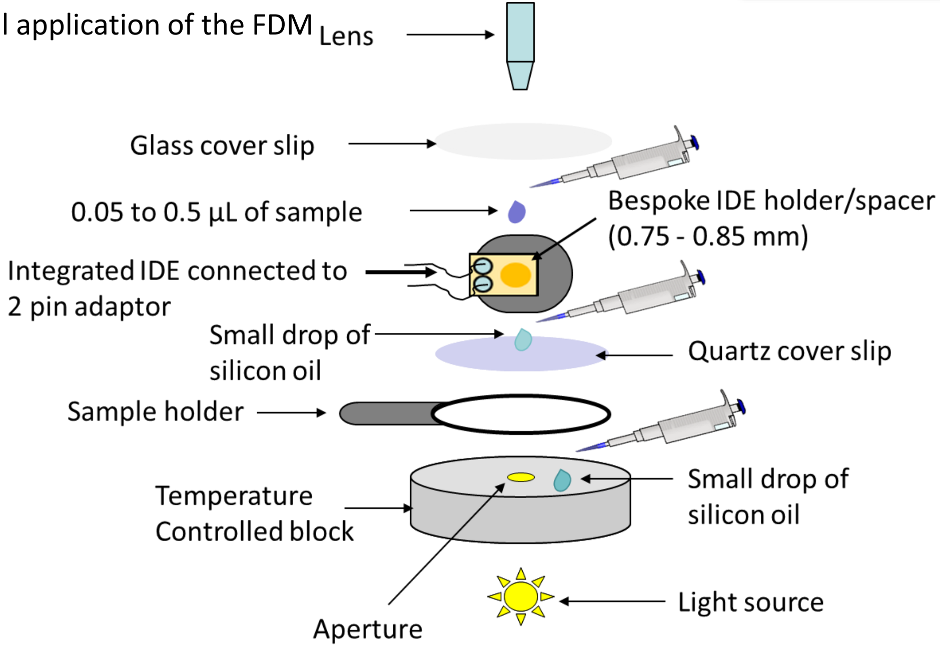
Impedance enabled FDM

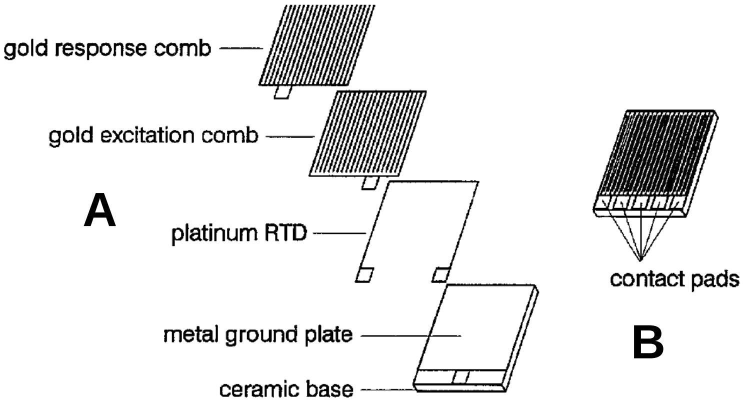
- ✓ Impedance analyzer connected to the FDM with bespoke adapters
- ✓ FDM stage remains intact, and IDE sit above the quartz cell
- ✓ Gold IDE does not affect the optical application of the FDM





Interdigitated electrodes (IDEs)

- IDEs have been used in past for the prediction of lyophile collapse temperature



A: Showing individual components of a single surface, co-planer, interdigitated-comb sensor and **B:** the complete sensor

RESEARCH ARTICLE

Prediction of Lyophile Collapse Temperature by Dielectric Analysis

KENNETH R. MORRIS[a], SEAN A. EVANS[b], ALAN P. MACKENZIE[c], DONALD SCHEULE[d], and NICHOLAS G. LORDI[e]

[a]Pharmaceutics R & D, Bristol-Myers Products, Hillside, NJ, [b]College of Pharmacy, Rutgers University, Busch Campus, Piscataway, NJ, and Pharmaceutics R & D, Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ, [c]University of Washington, Seattle, WA, and Lyophilos, Mercer Island, WA, [d]Physics Department, Case Western Reserve University, Cleveland, OH, and [e]College of Pharmacy, Rutgers University, Busch Campus, Piscataway, NJ

ABSTRACT: A new method for predicting lyophile collapse temperatures based upon dielectric analysis (DEA) of frozen two component systems is presented. The method, called the take off frequency model (TOF), relies both on the inherent ability of DEA to detect molecular motion and on the abrupt change in viscosity experienced by a frozen sample undergoing a glass-liquid transition. Collapse temperatures for binary glass forming systems (an antibiotic, sucrose, trehalose, or sorbitol, with water) were in good agreement with the values reported in the literature. DEA was easily able to detect glass transitions poorly defined by differential scanning calorimetry (DSC). Conservative lyophilization cycles for simple systems can be quickly determined on the basis of the TOF model.

Introduction

Dielectric analysis (DEA) has been used extensively in polymer science for determining the characteristics of polymer films (1). There is also a considerable history of DEA in the study of molecular properties including those of biological molecules (2–6). With the advent of commercially available instruments (see Experimental), some preliminary pharmaceutical applications have been explored in our lab. The current work summarizes efforts to characterize representative frozen aqueous systems intended for lyophilization for the purpose of determining the highest allowable temperature for primary drying without collapse.

Pikal (7) has shown that there is a correlation between collapse temperature (Tc) and the glass transition temperature (Tg′) of glass forming systems. There are, however, difficulties in the determination of Tg′ by the common methods such as differential scanning calorimetry (DSC), conductivity, etc. DSC may require relatively high concentrations in systems with very low energy transitions and direct current or single frequency resistivity measurements depend on ionic content and do not easily distinguish first order from higher order transitions. It has also been documented that the Tg′ may precede the observed Tc by varying intervals up to several degrees C (7). It was thought that DEA might provide a more sensitive and accurate measure of Tg′ for reasons described below. As with most techniques, we have come to view DEA as complementary to classical thermal techniques for the complete characterization of such transitions. This report will present the basis of our "model" for predicting the Tc based on DEA results. This is a new application of the technique and the development of our model may provide an approach that will prove useful in the study of other pharmaceutical processes and systems.

Background

Basically, DEA involves the construction of a capacitor in which the sample to be examined is the dielectric material between the capacitor plates. A sinusoidal voltage of fixed amplitude and known frequency is impressed across the capacitor and the resulting current is followed with time. Changes in the phase of the current relative to that of the applied voltage are then used to calculate the dielectric constant (ϵ). Since ϵ is ultimately a function of frequency and temperature, it is not a constant and is simply referred to as permittivity or relative permittivity. This concept may be described mathematically in terms of the force that the dielectric material experiences in the capacitor. For a static field Maxwell's relationship (cgs system) (8) for a non polar dielectric is

$$\vec{D} = \epsilon_r \vec{E} \quad (1)$$

where D is the displacement force, E is the electric field inside the capacitor ($D = E$ in vacuo), and ϵ_r is the

Received September 15, 1993. Accepted for publication May 18, 1994.
This work was presented in part on 5/14/92 in Newark, DE at the Spring Thermal Analysis Symposium & Exhibition on Applications in the Food, Pharmaceutical and Cosmetic Industries sponsored by the Thermal Analysis Forum of Delaware Valley and as a poster at the Eastern Regional AAPS Meeting on 6/2/92 in New Brunswick, NJ.
Author to whom correspondence should be addressed: Dr. Sean A. Evans, ImmuLogic Pharmaceutical Corp., 610 Lincoln Street, Waltham, MA, 02154.

Mackenzie, A. P., Evans, S. A. and Morris,. Prediction of Lyophile Collapse Temperature by Dielectric Temperature by Dielectric Analysis Prediction of Lyophile Collapse Temperature by Dielectric Analysis, *PDA J Pharm Sci and Tech* **1994**, *48* 318-329.

Interdigitated electrodes (gold on glass)

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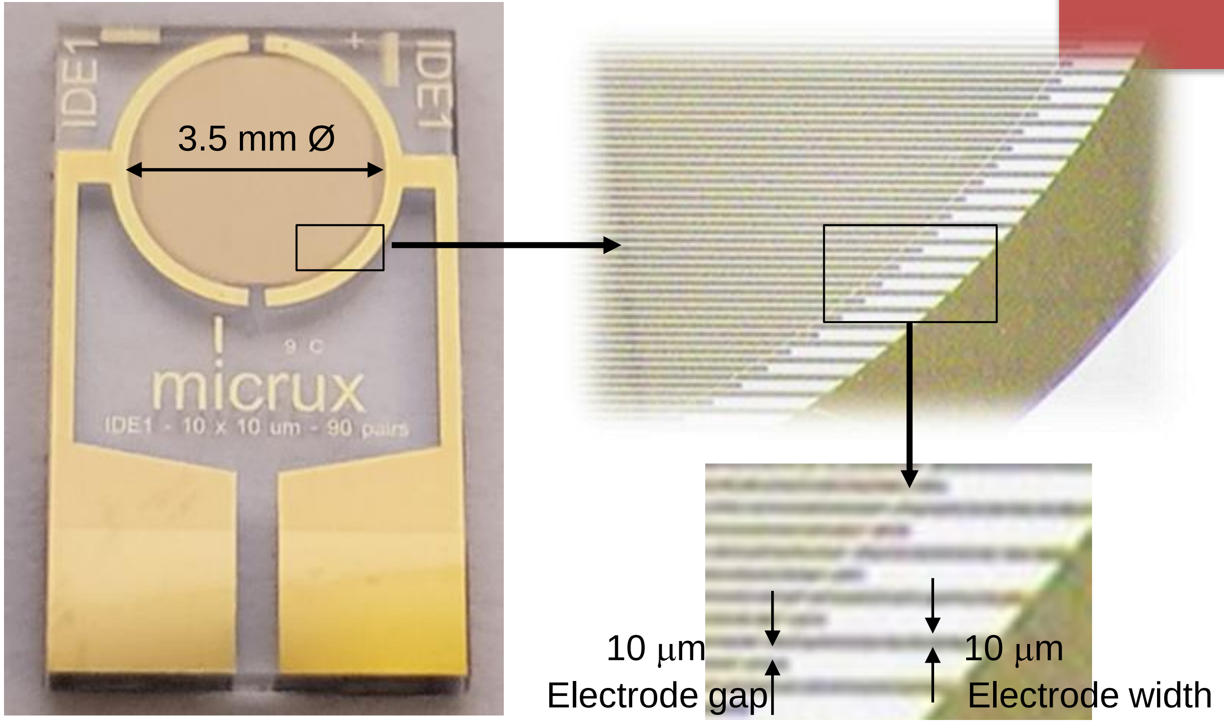

Commercial IDE – Micrux™

Dimension:
10 x 6 x 0.75 mm

Interdigitated electrodes (gold on glass)

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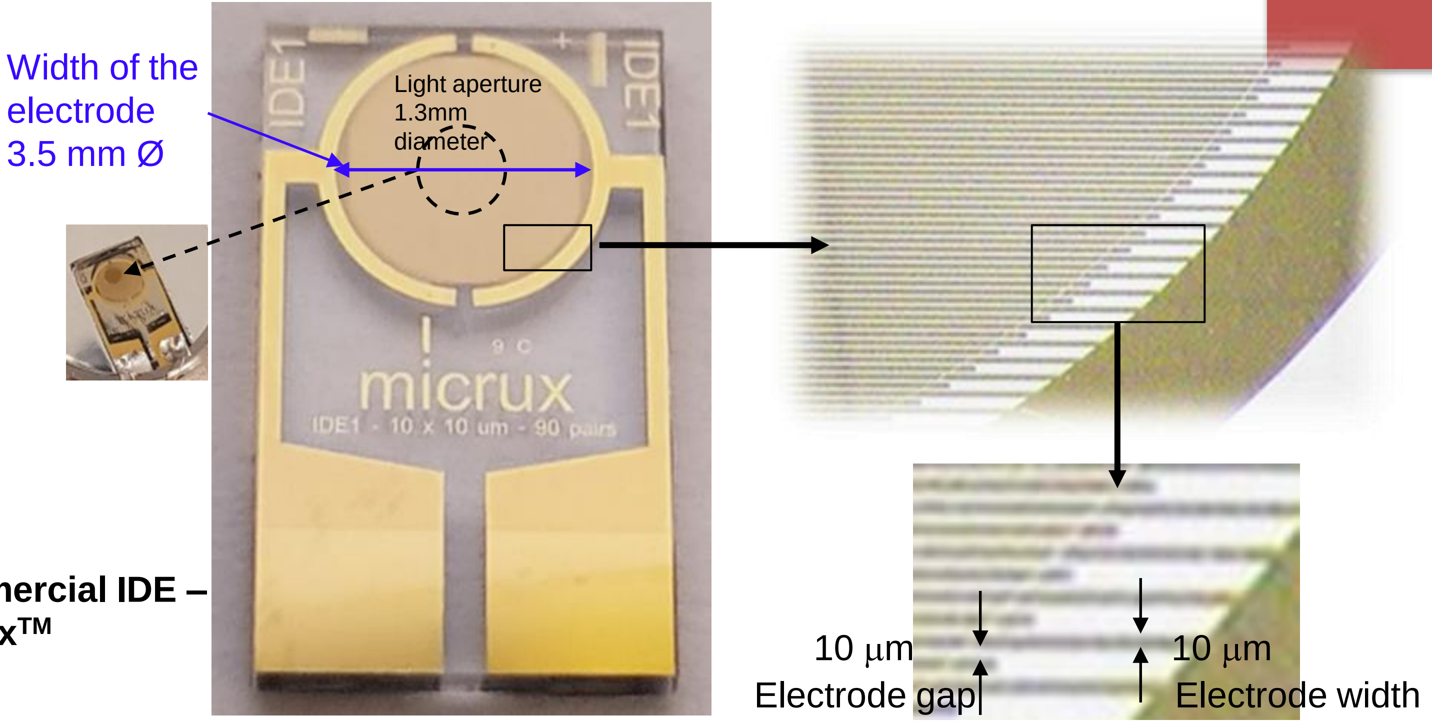

Commercial IDE – Micrux™

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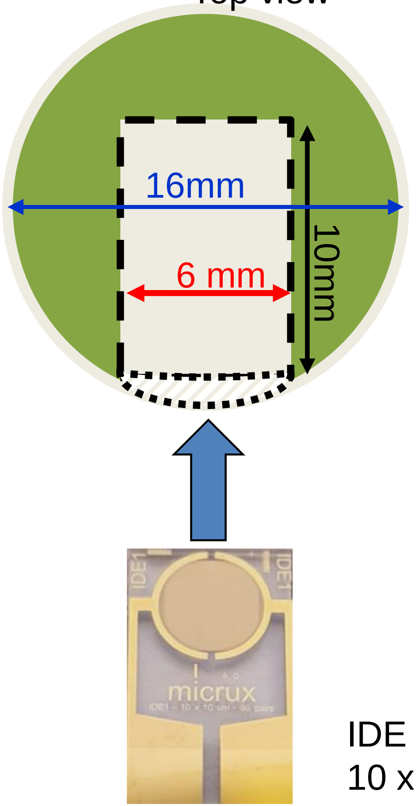
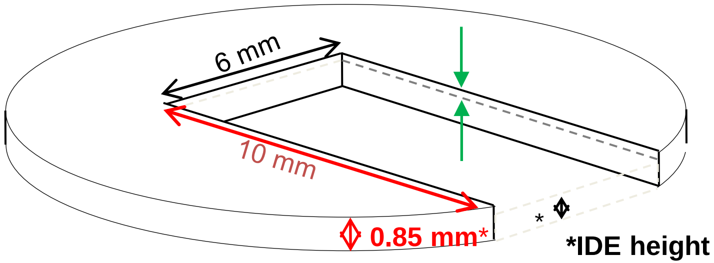
Design of IDE holder



IDE dimensions:
10 x 6 x 0.75 mm



* different height of IDE adaptors used for initial assessment:

- 0.85 mm
- 0.90 mm
- 0.95 mm
- 1.00 mm

IDE is lower than the adapter and sample height derived between difference between then IDE adaptor size

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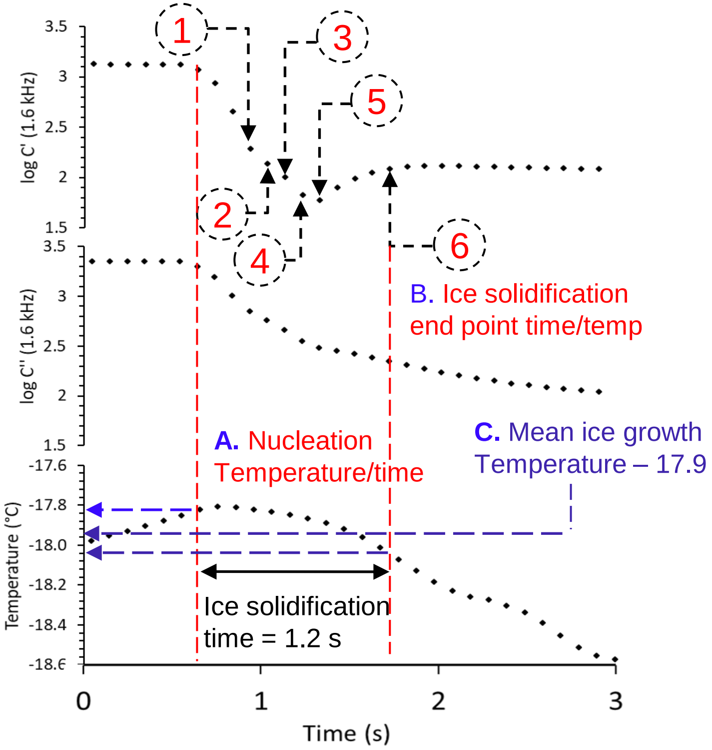
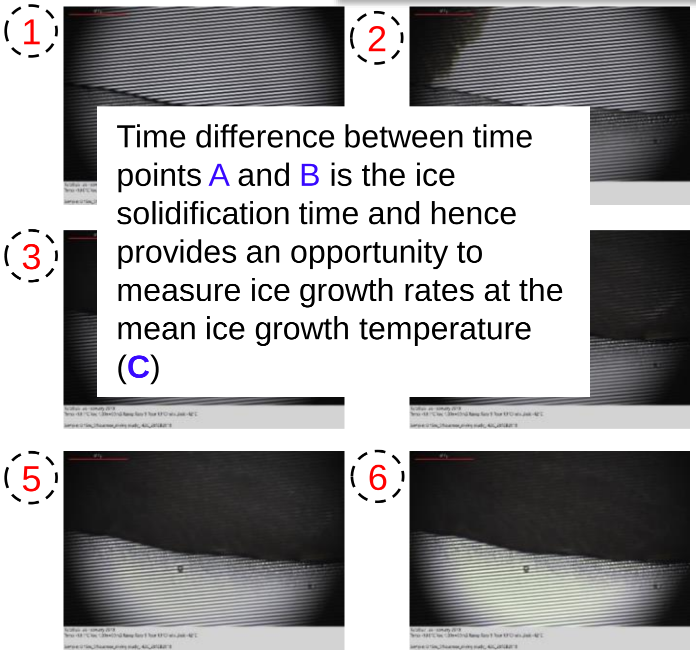
Z-FDM – Applications in freezing (nucleation temperature, ice growth rates, solidification end point)

Observations on Sample size

Case study of 5% w/v Sucrose solution

Nucleation of 0.5µL of 5% Sucrose





Time difference between time points A and B is the ice solidification time and hence provides an opportunity to measure ice growth rates at the mean ice growth temperature (C)

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Ice growth rates

- 1 mL of 5% w/w sucrose has 0.95 g water
- Assumption: unfrozen fraction comprises 80:20 ratio of sucrose to water
- It follows that 0.0125 g (0.05 x 20/80) is bound and produces 0.9375 g ice

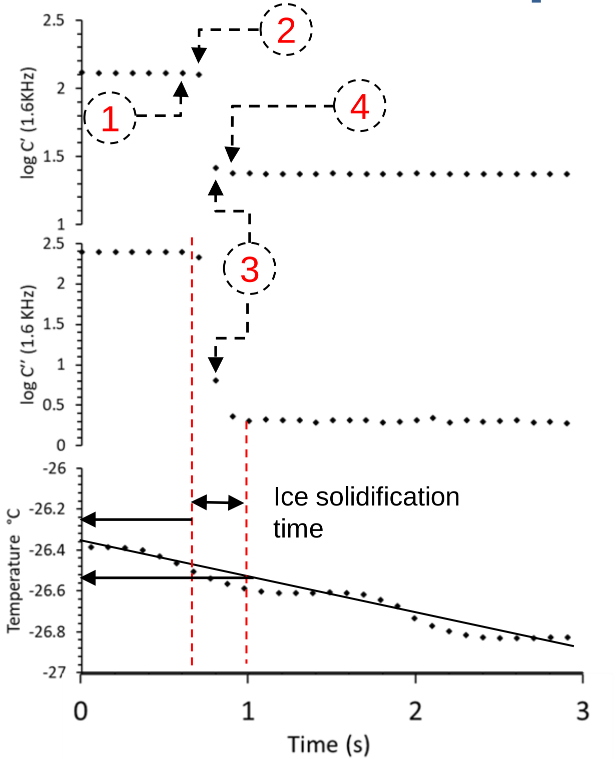
Estimated from:

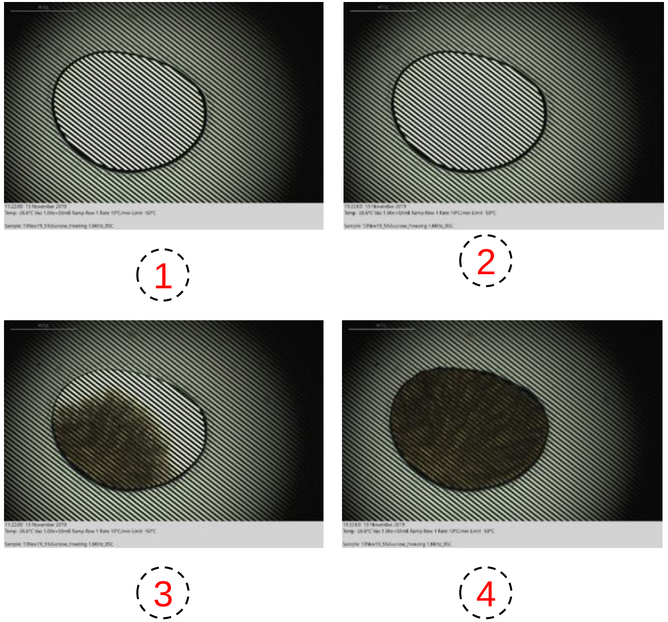
Larger sample : 0.5 µL of 5% sucrose (produces 4.688E-04 g ice)

- Ice formation time = 1.2 s (12 data points – more accurate)
- Ice growth rate: 4.688E-04 / 1.2 = 0.39 mg/s

Relevance : ice crystal size?

Nucleation of **0.05µL** of 5% Sucrose





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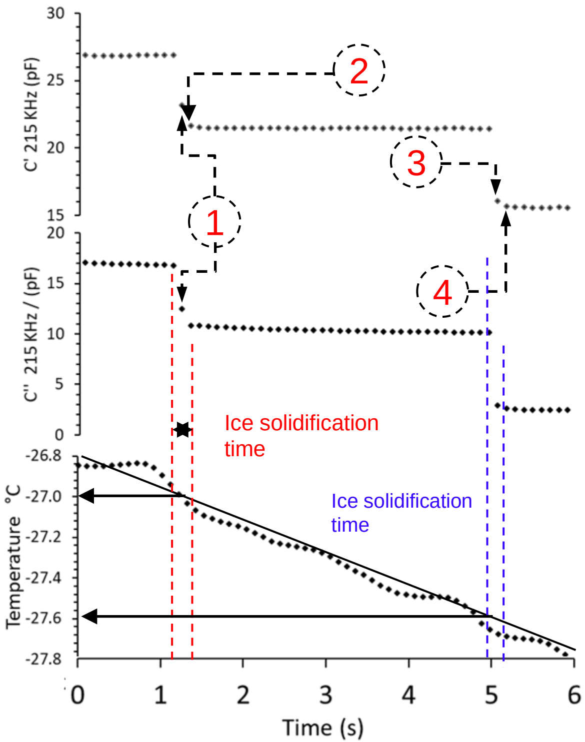
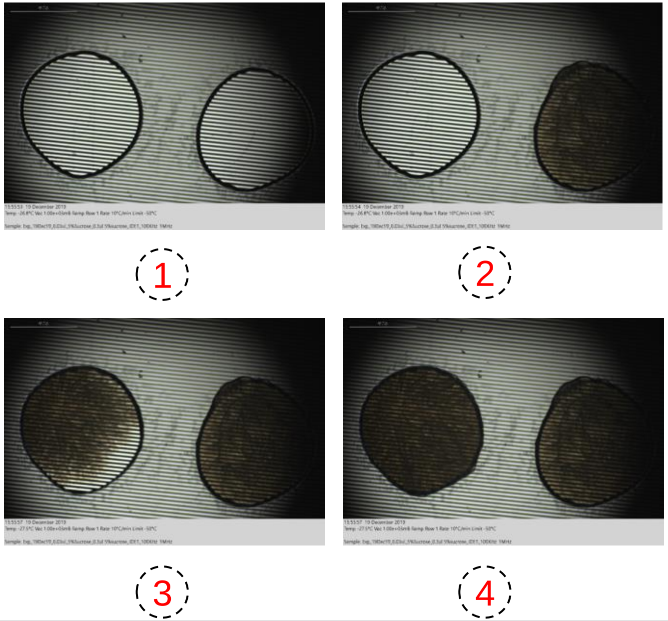
Nucleation of 2 x **0.03µL** of 5% Sucrose





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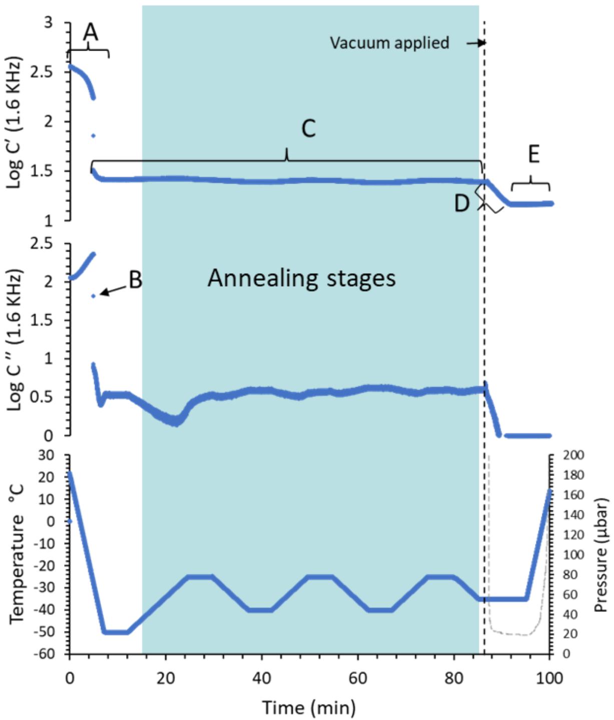
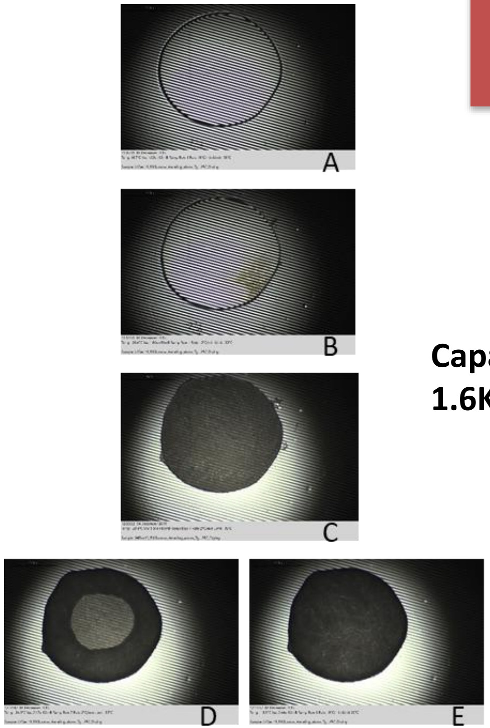
Z-FDM – Applications in freezing (Annealing)

Case study of 5% w/v Sucrose solution

Full process of **0.05µL** of 5% Sucrose





Capacitance data measured at 1.6KHz

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Annealing of 5% w/v Sucrose solution

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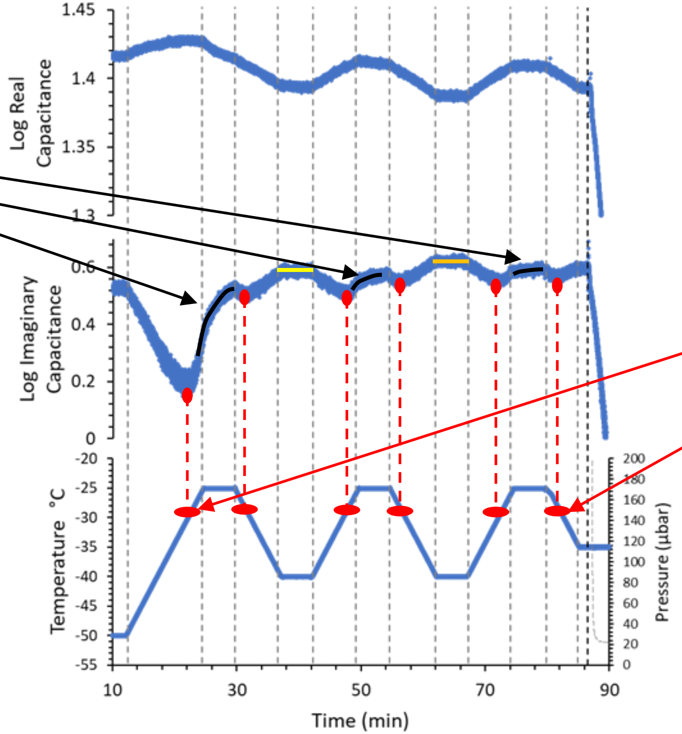
Structural changes on re-heating decrease with each annealing



Excursions in temperature just above the glass transition

Capacitance data measured at 1.6KHz

0.05 µL 5%sucrose

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Glass transition detection with TVIS

Case study of 5% w/v Sucrose solution

Structural Modification studied by TVIS

5% Sucrose solution

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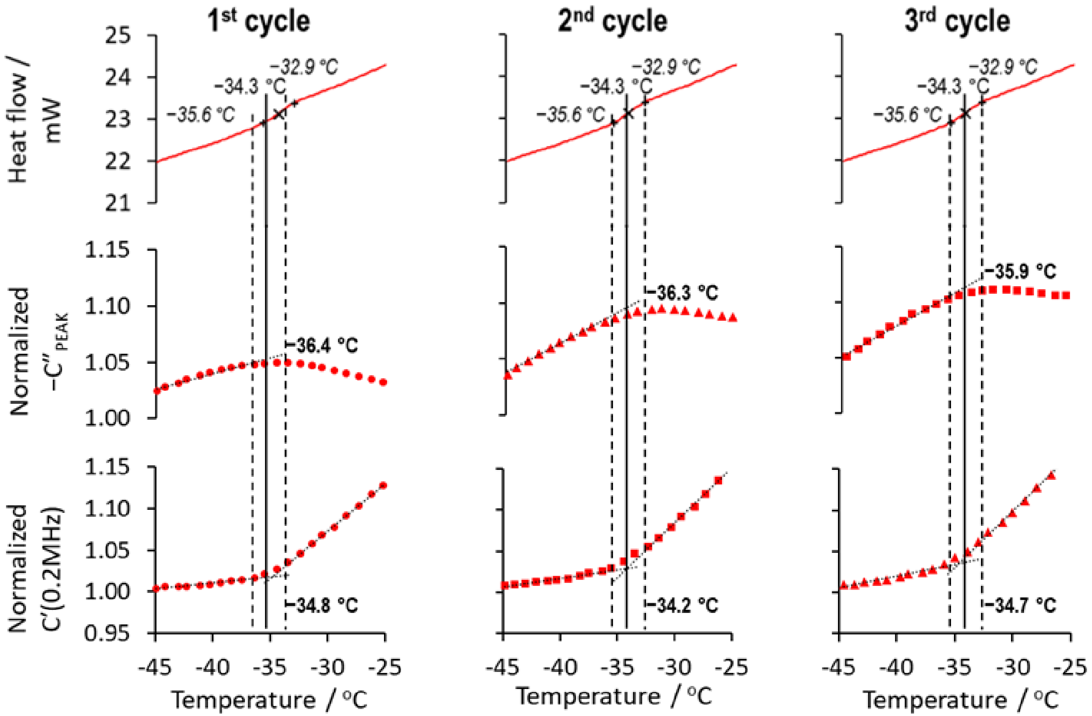
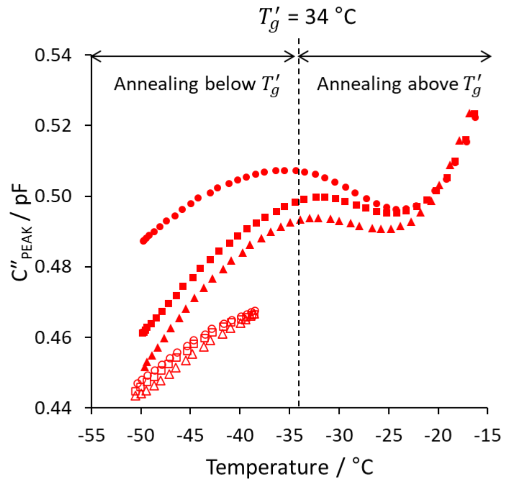
DSC Thermogram





Closed symbols demonstrated the data when the sample was heated above its glass transition of freeze concentration (T_g' = -34°C) whereas the product which annealed below transformation points of -35 °C were represented by *open symbols*. Circle, square and triangle are 1st, 2nd and 3rd re-heating accordingly

Structural Modification studied by TVIS

5% Sucrose solution

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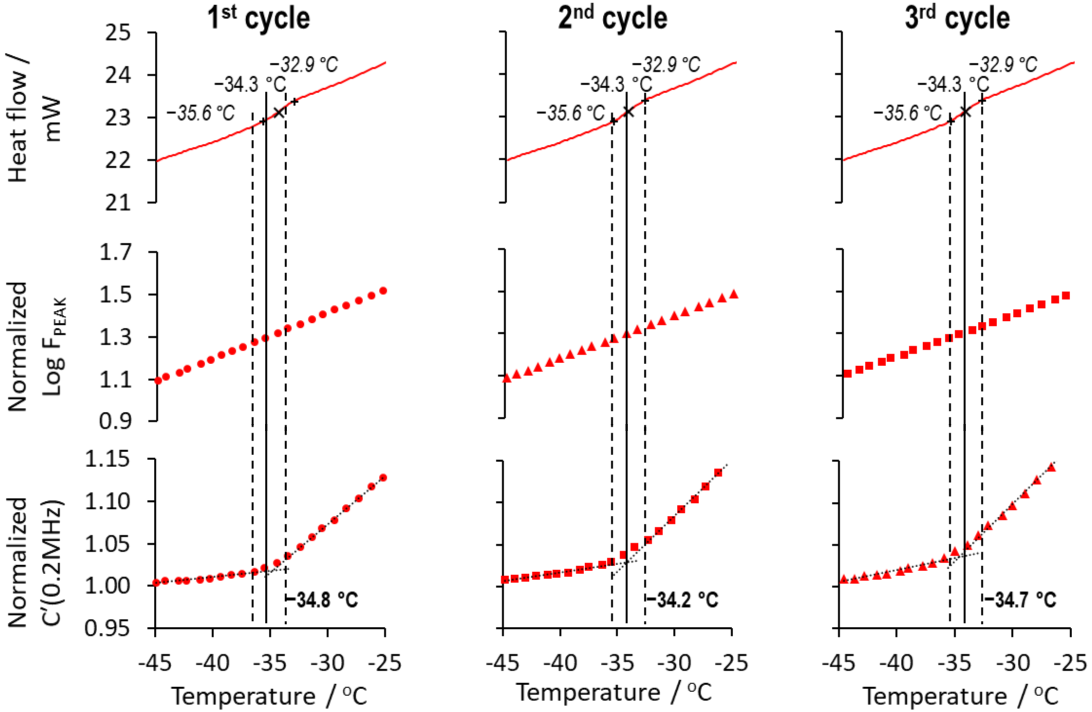
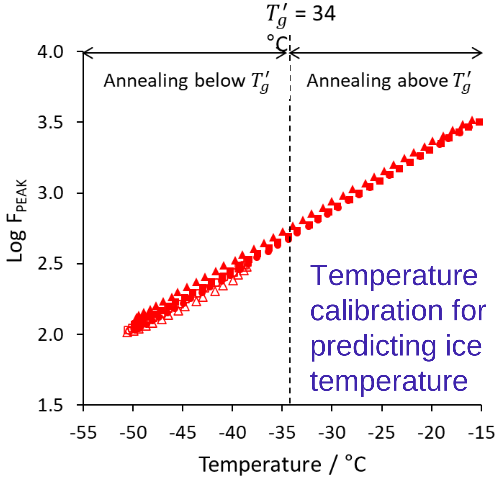
DSC Thermogram





Temperature calibration for predicting ice temperature

Closed symbols demonstrated the data when the sample was heated above its glass transition of freeze concentration (T_g' = -34°C) whereas the product which annealed below transformation points of -35 °C were represented by *open symbols*. Circle, square and triangle are 1st, 2nd and 3rd re-heating accordingly

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Glass transition detection with Broadband Dielectric Spectrometer

Case study of 5% w/v Sucrose solution

Spectroscopy System (sub Hz to 10 MHz)

Spectroscopy System (sub Hz to 10 MHz)

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Spectroscopy System: BDS (Sub Hz to 10 MHz)

Inter-digitated electrode

Commercial state of the art broad-band dielectric spectrometer (BDS) from Novocontrol GmbH (mHz to 10 MHz)

BDS sample cell arrangement

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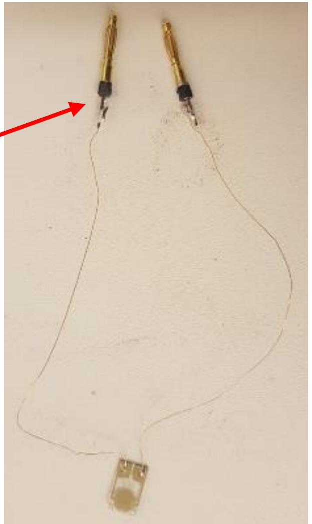
Interdigitated Electrode

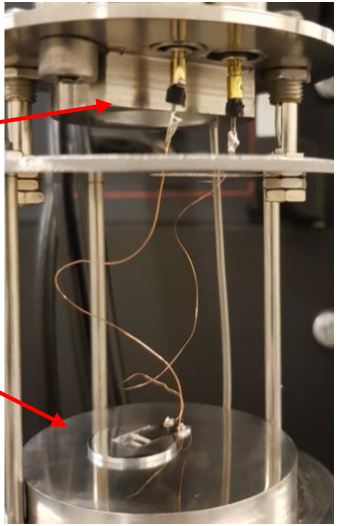
IDE connected to banana plug with copper wire



IDE cell for BDS

Banana plug connected to the BDS cell

IDE holder on BDS cell and used as a sample spacer/ IDE holder



IDE arrangement on BDS stage

BDS sample cell arrangement

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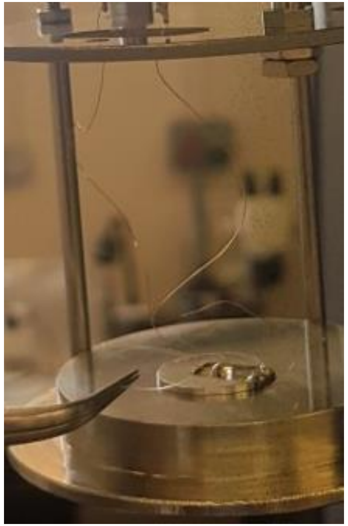
Place IDE inside the holder

Add 2 µL of 5%w/v Sucrose



Place coverslip

Sample ready for analysis

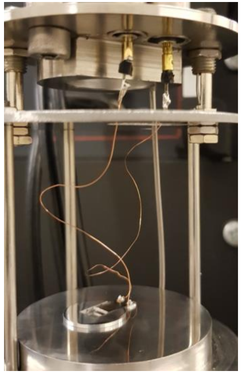
Spectroscopy System (sub Hz to 10 MHz)

IDE

Cover slip

Adapter -spacer

Placed on a cradle



NB: IDE filled with 2 μL volume

5% w/v Sucrose solution re-heating profile compared with DSC thermogram

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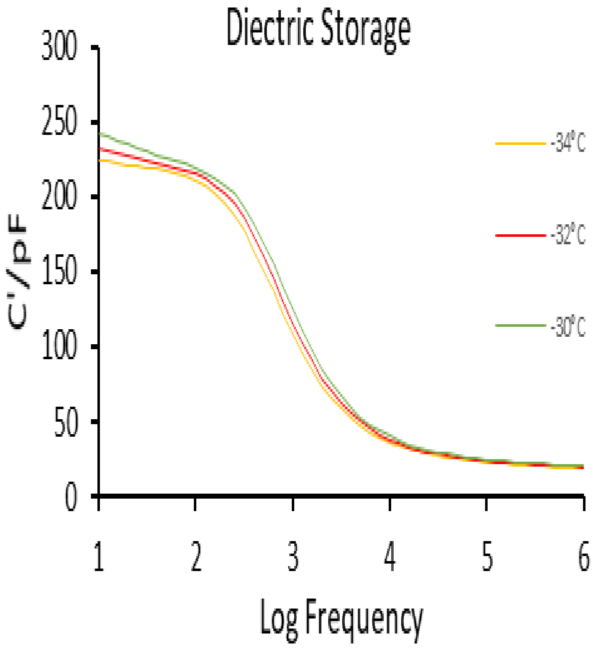
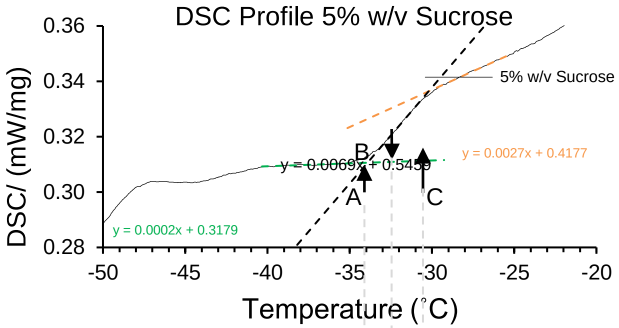
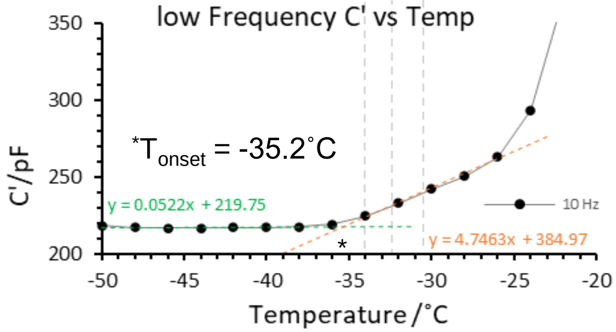


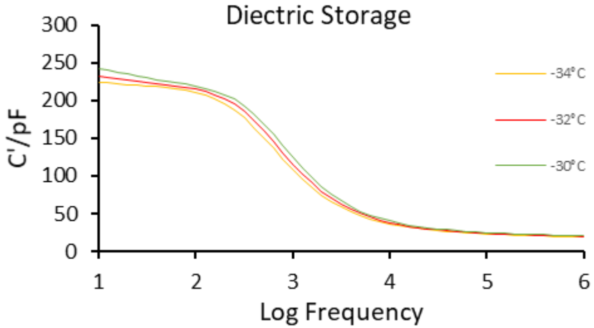


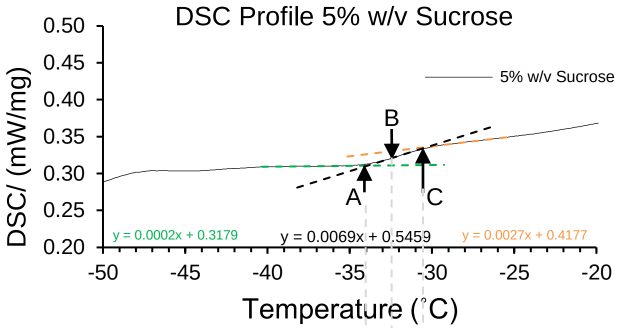


A - onset -34.0˚C
B - mid point -32.3˚C
C - end point -30.5˚C

10 Hz

5% w/v Sucrose solution re-heating profile compared with DSC thermogram





A - onset -34.0˚C
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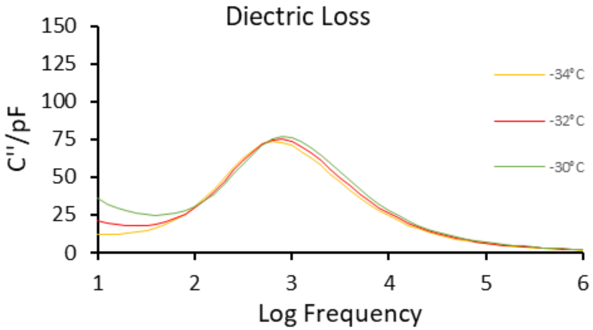

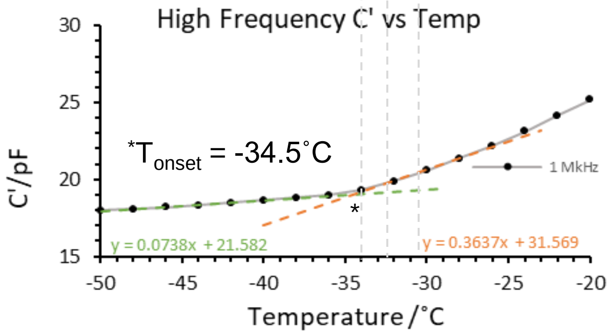

1 MHz

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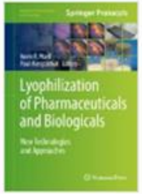
Further Reading



Lyophilization of Pharmaceuticals and Biologicals pp 241-290 | Cite as

Through Vial Impedance Spectroscopy (TVIS): A Novel Approach to Process Understanding for Freeze-Drying Cycle Development

Authors Authors and affiliations

Geoff Smith, Evgeny Polygalov

- Introduction to TVIS theory
- Description of the measurement principles
- Dielectric loss and relaxations mechanisms (liquid and frozen states)

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Further Reading

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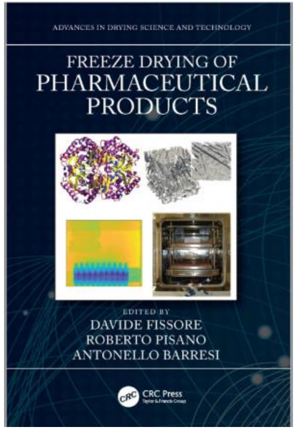


Freeze Drying of Pharmaceutical Products

1st Edition

Davide Fissore, Roberto Pisano, Antonello Barresi

Hardback
£118.00

CRC Press
November 13, 2019 **Forthcoming**
Reference - 214 Pages - 4 Color & 66 B/W Illustrations
ISBN 9780367076801 - CAT# K405807
Series: Advances in Drying Science and Technology

Chapter 5 Through Vial Impedance Spectroscopy (TVIS) A New Method for Determining the Ice Nucleation Temperature and the Solidification End point

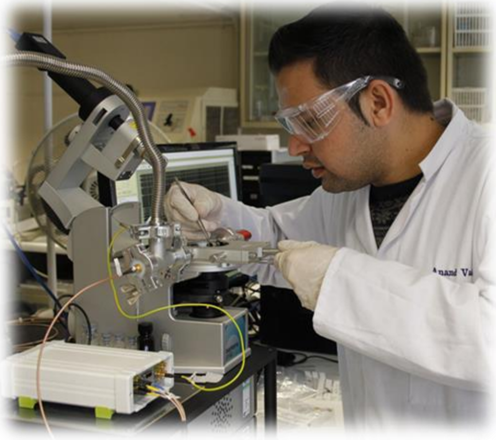
Acknowledgements

Innovate UK for Funding for Z-FDM development (FastLyo Project 133425)

In collaboration with ….

bps biopharma process systems

Oncolytika



Anand Vadesa (PhD 2018)
Funded by UKRI – EPSRC

UKRI Engineering and Physical Sciences Research Council

UCL

Acknowledgements, Recent Projects & Collaborators

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- De Montfort University, School of Pharmacy
  - Anand Vadesa. PhD student
  - Neill Horley. Senior Lecturer
  - Glen McCann: Lecturer
- University College London
  - Prof. Paul Dalby
- Biopharma Process Systems
  - Kevin Ward

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TVIS Through Vial Impedance Spectroscopy

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Government Support for industry

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Lyophilization process analytics
By dielectric analysis

BIOSTART
Biopharmaceutical Stability at Room Temperature

AtlasBio
Analytical Technologies for the Stabilization of Biopharmaceuticals