

4th International Conference on Lyophilization and Freeze Drying

THE INFLUENCE OF CRUCIBLE MATERIAL ON THE THERMAL PROPERTIES OF BINARY SOLUTIONS DURING DSC ANALYSIS AND ITS COMPARISON TO FREEZE-DRYING MICROSCOPY RESULTS

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INTRODUCTION

- Lyophilization (freeze-drying)



Advantageous method in reducing water content of heat sensitive products, such as pharmaceuticals, foods and biologicals

- The energy consumption



Relatively high compared to others, making it as a high cost drying process



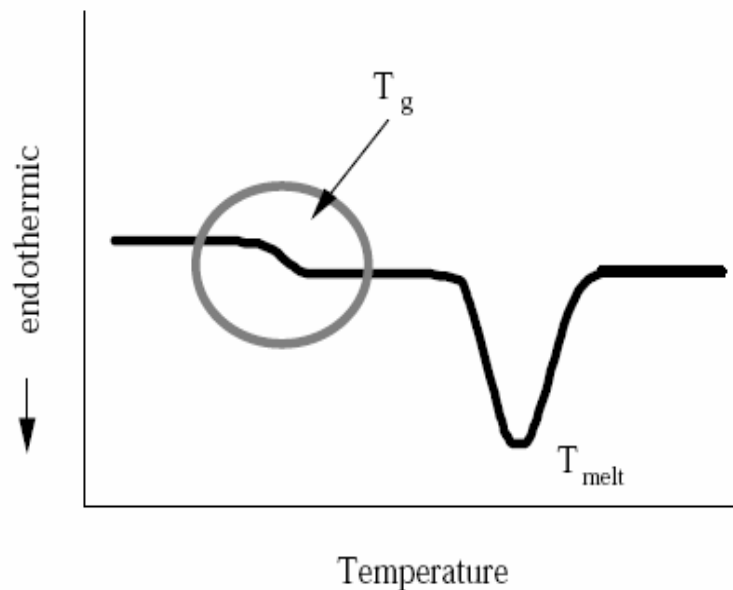
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INTRODUCTION

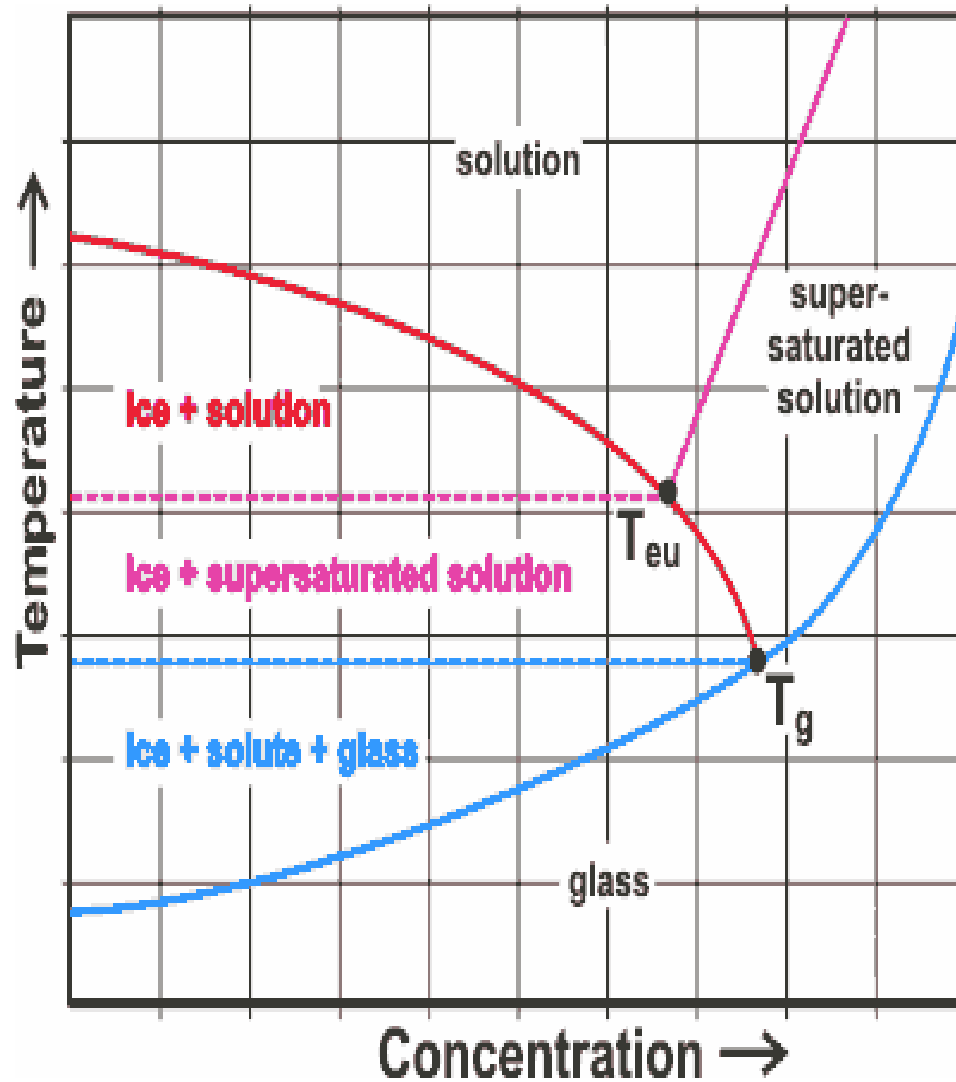
- Low-temperature thermal analysis



- To identify the critical values for freezing and primary drying as well as the characteristics that contribute to the behavior of a product during processing;

- To decrease the time and energy consumption;
- To optimize the drying conditions while maintaining the most possible high quality of the product;

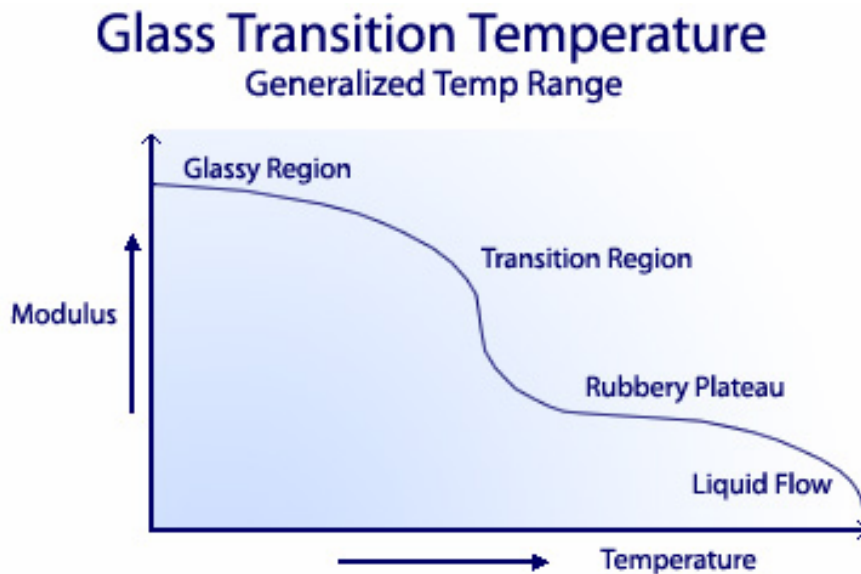
INTRODUCTION



- Crystallization temperature (T_{cryst});
- Glass transition temperature (T_g);
- Eutectic melting temperature (T_{eut});
- Recrystallization temperature (T_{recryst});
- Incipient melting (T_{im});
- Collapse temperature (T_c);
- Melting temperature (T_m);

INTRODUCTION

- $T_g' \sim 1-2 \text{ }^\circ\text{C } T_c$ (Pikal et al., 1990);
- Differential Scanning Calorimetry (DSC): has been used as a mean of assessing physicochemical (endothermic and exothermic) behavior during freezing and warming;



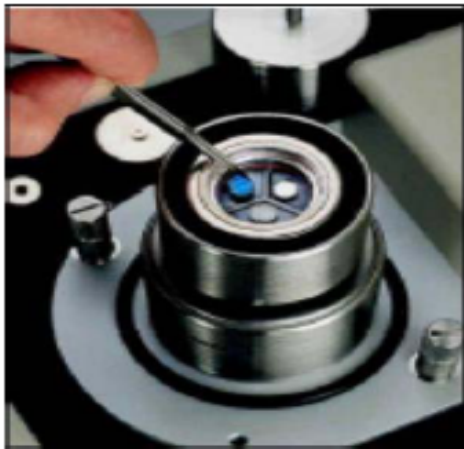
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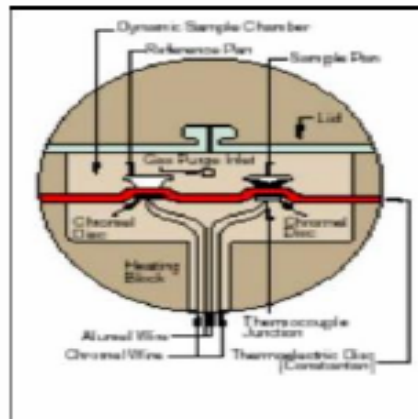
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INTRODUCTION

- During DSC analysis, aqueous formulations are commonly put into an aluminum crucible;
- Lyophilized formulations are most often manufactured in a type I glass container. The freezing behavior (ice nucleation and crystal growth) is then like to differ, given rises to differences in drying rates and product texture.



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OBJECTIVES

- To investigate the influence of different crucible materials on the results of DSC thermal analysis of three distinct solutions. In addition, the T_c and T_{eut} of these solutions were measured by freeze-drying microscopy and systematically compared to the T_g' and T_{eut} measured by DSC in order to confirm (or not) in complex media the similarity of values observed in binary aqueous solutions.

MATERIALS AND METHODS

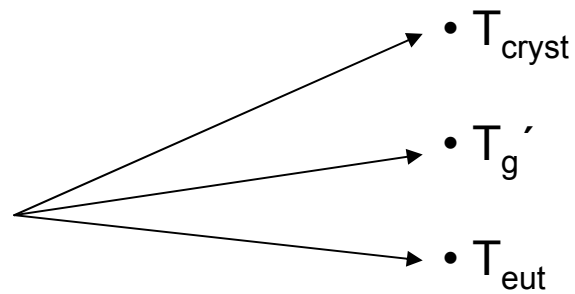
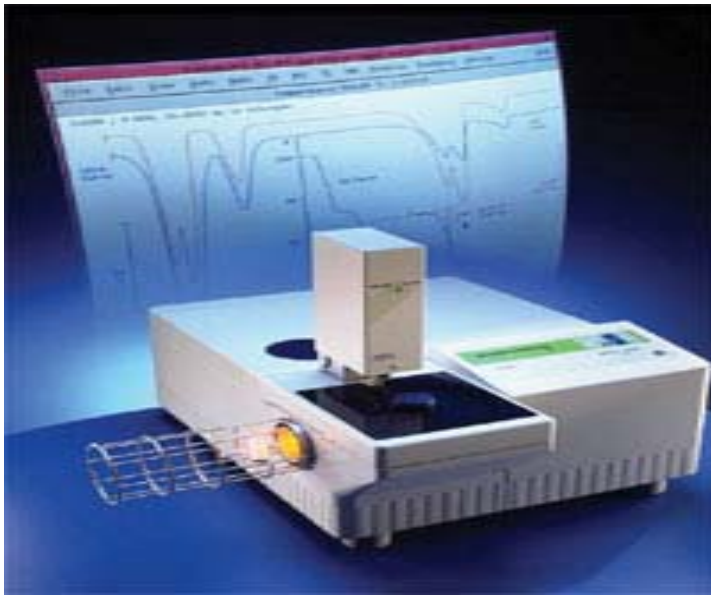
- 5% trehalose solution (w/w);
- 0.1 % of collagen solution type I from calf skin in 0.1 N acetic acid (w/v)
- NaCl solution 0.9 % (w/w);
- Crucible materials (DSC pans): 40 μ l aluminum standard crucible, 40 μ l quartz crucible, 40 μ l type I glass crucible.

Table 1. Thermal conductivity of materials

Crucible material	Thermal conductivity ($\text{w m}^{-1} \text{ }^{\circ}\text{C}^{-1}$)
Aluminum	237
Type I Glass (borosilicate)	1.14
Quartz	1.4

MATERIALS AND METHODS

- Differential Scanning Calorimetry
 - DSC Mettler-822;
 - Temperature calibration: distilled water (T_m : 0°C ; $\Delta H = 335 \text{ J g}^{-1}$);
 - 40 μl solution;
 - Cooling: 25 to -50°C ($-5^\circ\text{C min}^{-1}$);
 - Heating: -50 to 25°C (5°C min^{-1}).



MATERIALS AND METHODS

- *Freeze-Drying Microscopy*
 - Lyostat 2 (FDCS 196);
 - 0.9 % NaCl aqueous solution (temperature calibration) T_{eut} : -21.1°C ;
 - Cooling: 25°C to -50°C ($-5^{\circ}\text{C min}^{-1}$);
 - Heating: -50 to 25°C ($2^{\circ}\text{C min}^{-1}$);
 - Pressure: 100 mTorr.



RESULTS

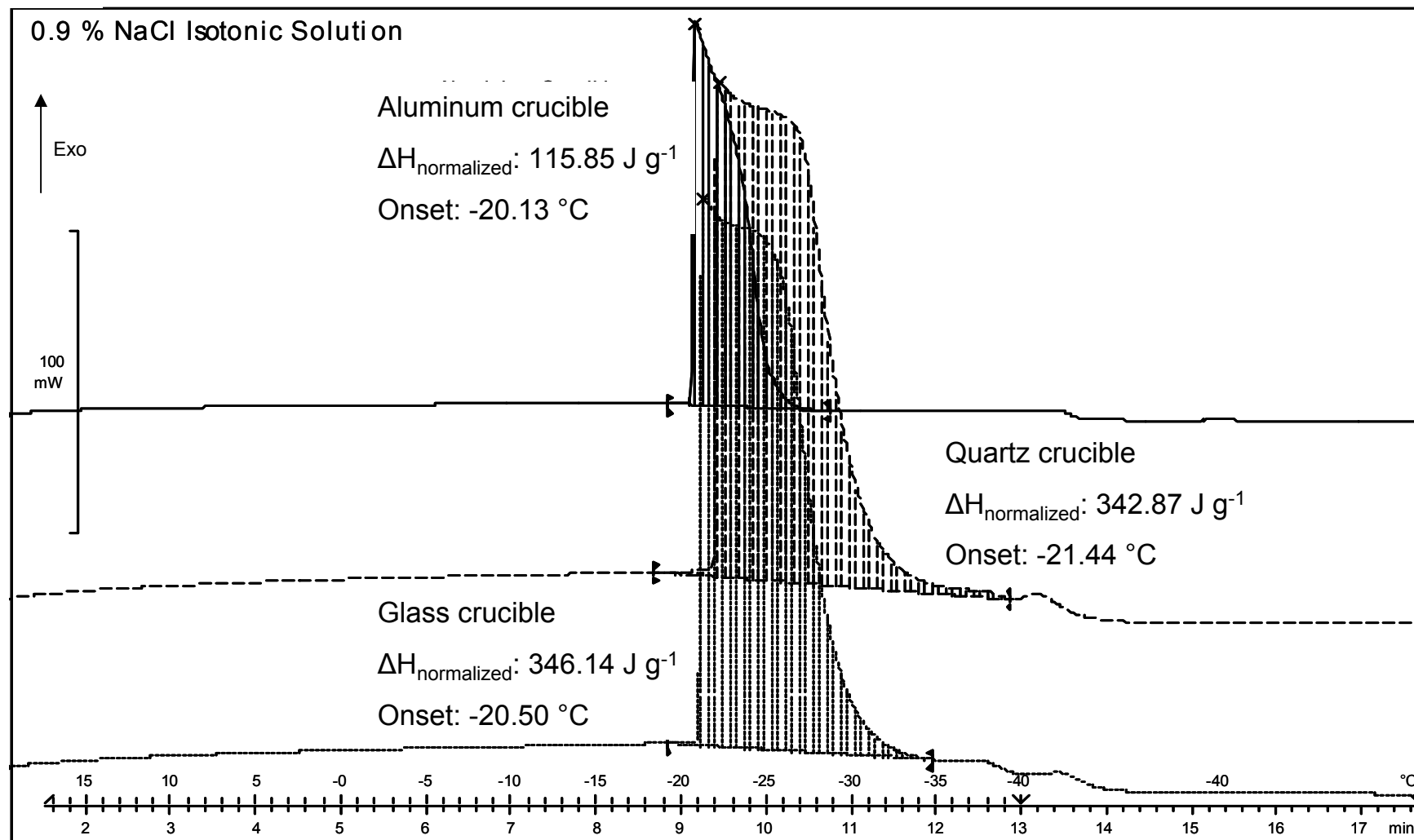


Fig 1a. Crystallization temperature of 0.9% NaCl solution using different crucible materials. The samples were cooled to -50°C at $5^{\circ}\text{C min}^{-1}$.

RESULTS

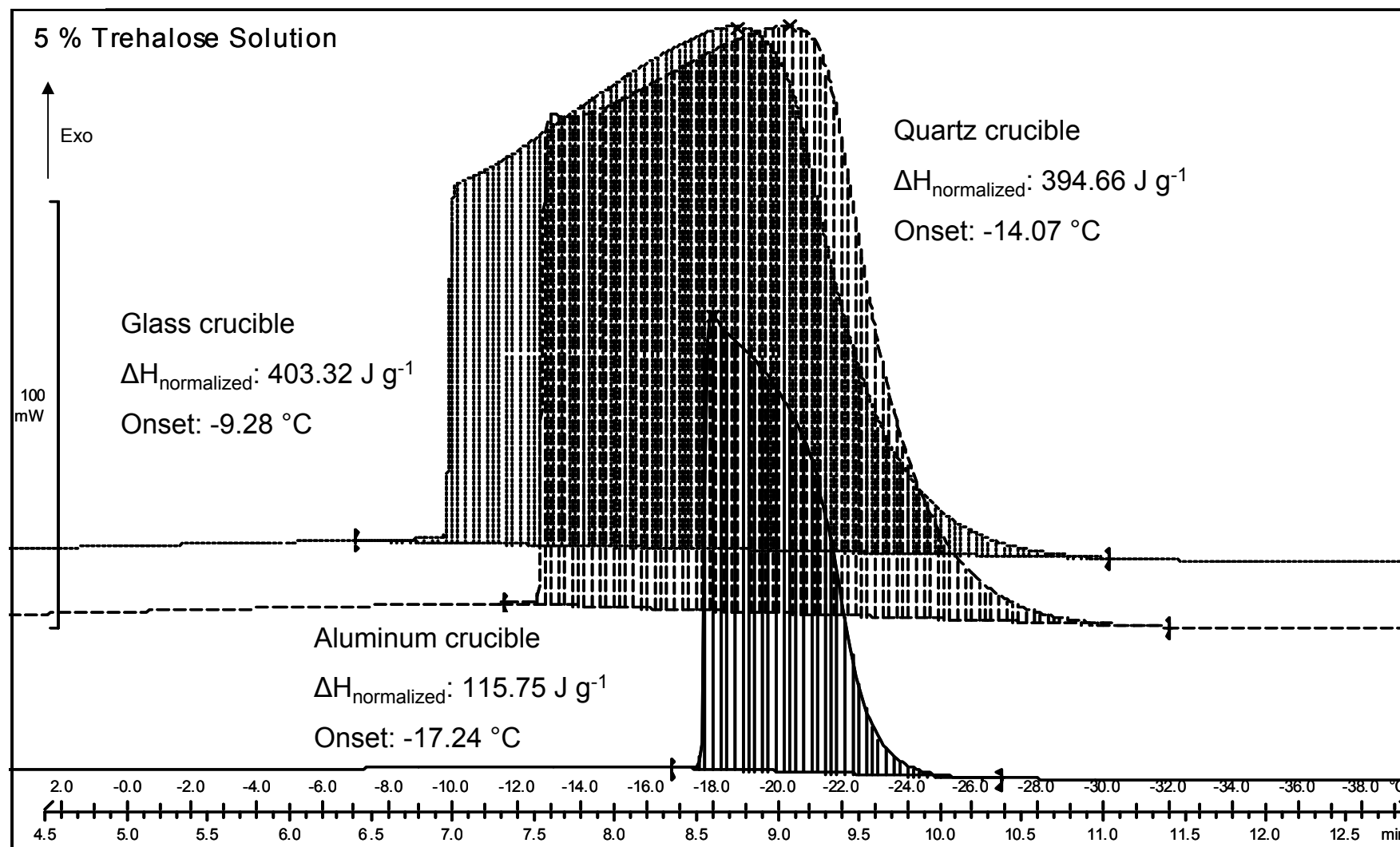


Fig 1b. Crystallization temperature of 5 % trehalose solution using different crucible materials. The samples were cooled to -50°C at 5°C min⁻¹.

RESULTS

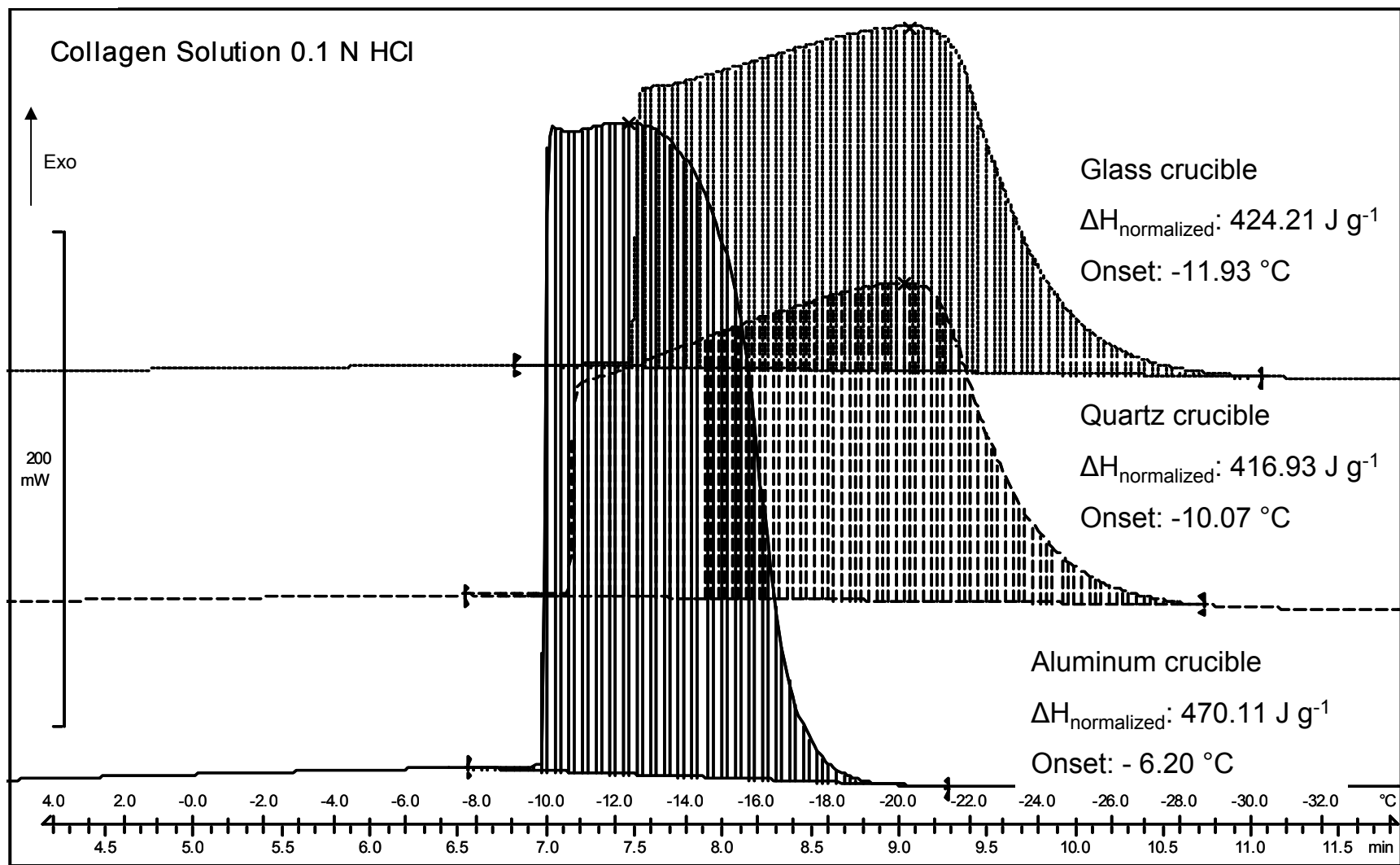


Fig 1c. Crystallization temperature of 0.1 % collagen solution using different crucible materials. The samples were cooled to -50°C at 5°C min⁻¹.

RESULTS

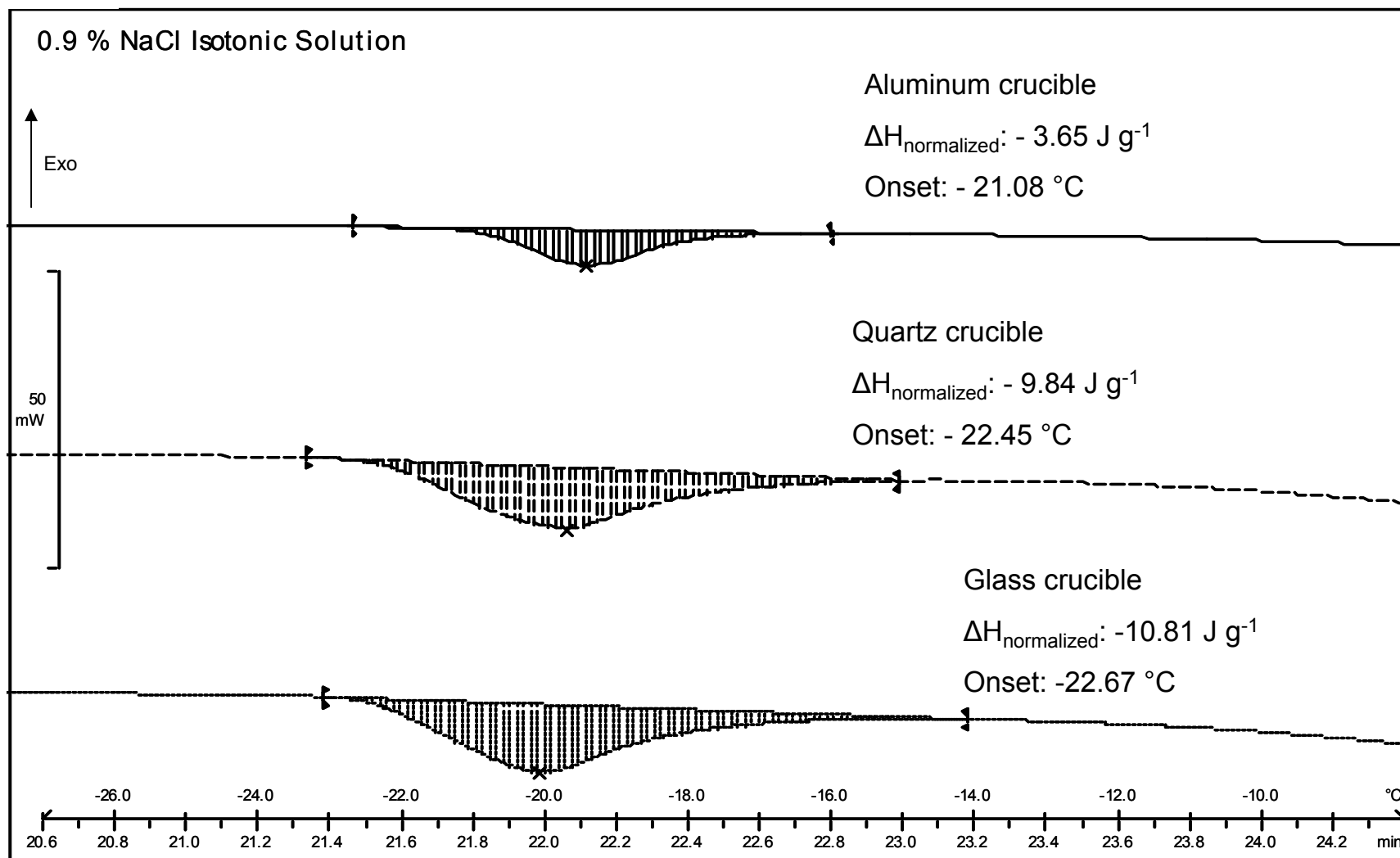


Fig 2 a. Eutectic melting temperature (T_{eut}) of NaCl using crucible of different materials. The samples were cooled to -50°C at $5^{\circ}\text{C min}^{-1}$ followed by a heating at $5^{\circ}\text{C min}^{-1}$ until 25°C .

RESULTS

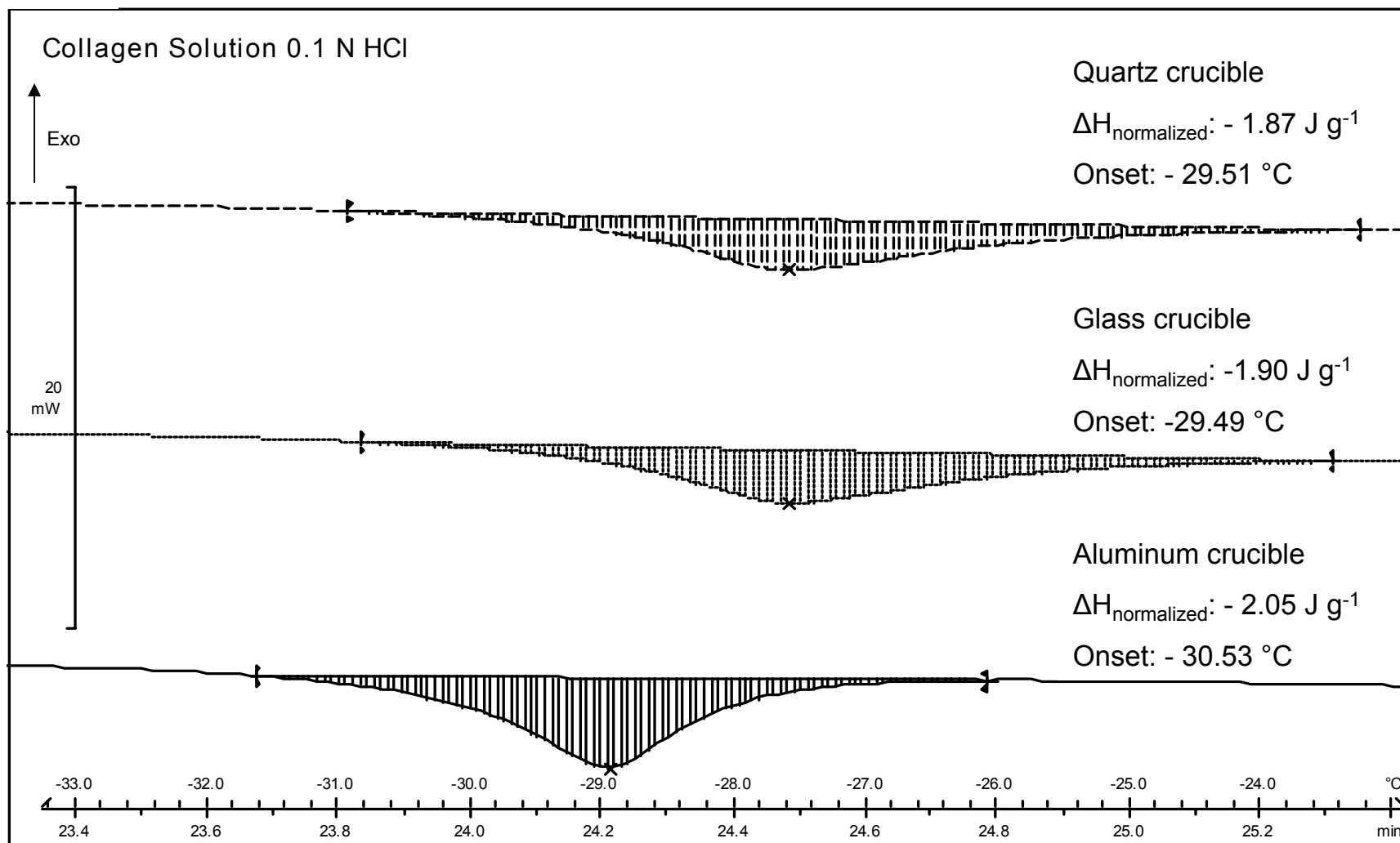


Fig 2 b. Eutectic melting temperature (T_{eut}) of collagen solution using crucible of different materials. The samples were cooled to -50°C at 5°C min⁻¹ followed by a heating at 5°C min⁻¹ until 25°C.

RESULTS

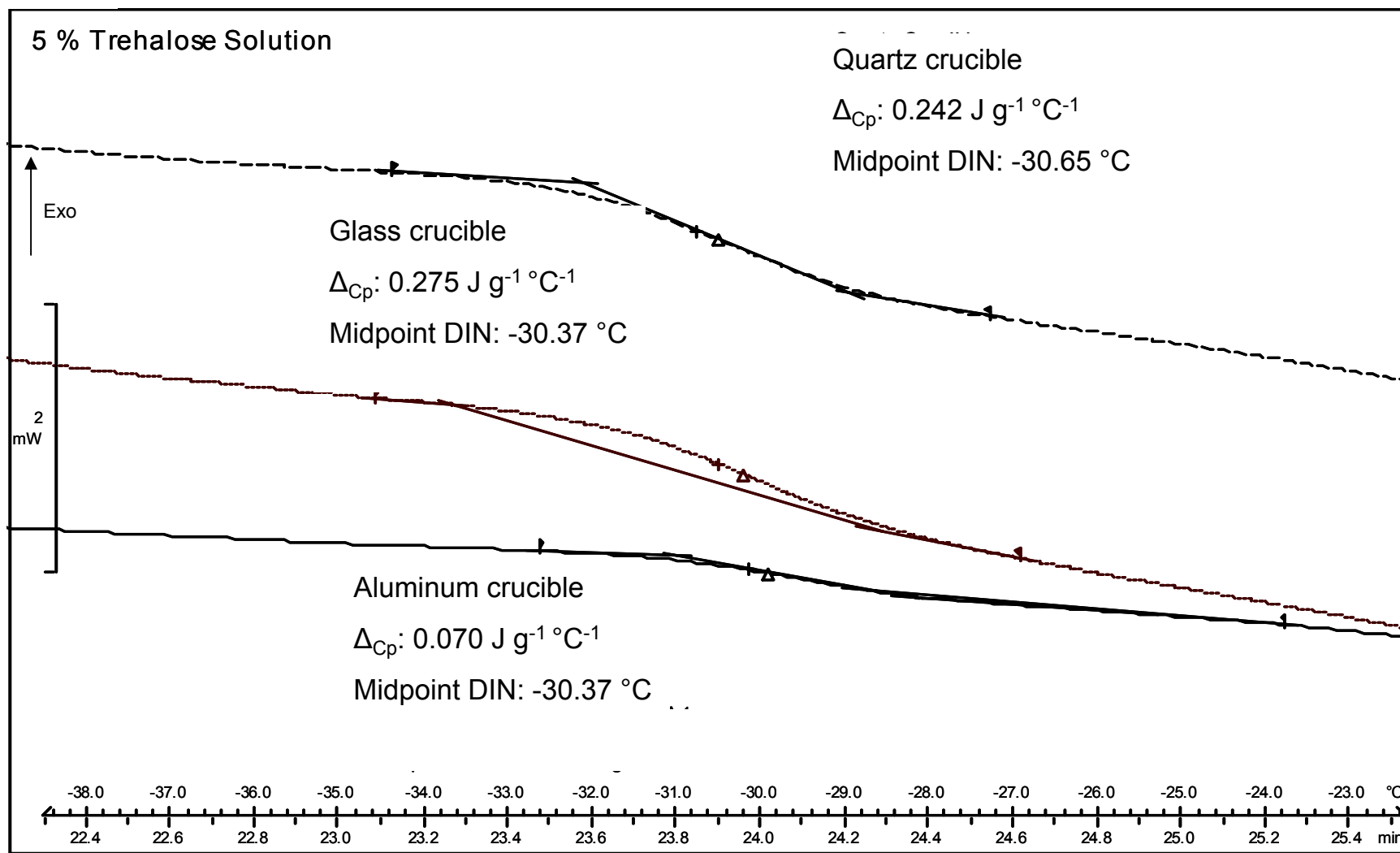


Fig 3. DSC curves showing the Tg' of a 5 % trehalose solution using different crucible materials. The samples were cooled to -50°C at 5°C min⁻¹ followed by a heating rate at 5°C min⁻¹.

RESULTS

- Freeze-drying microscopy

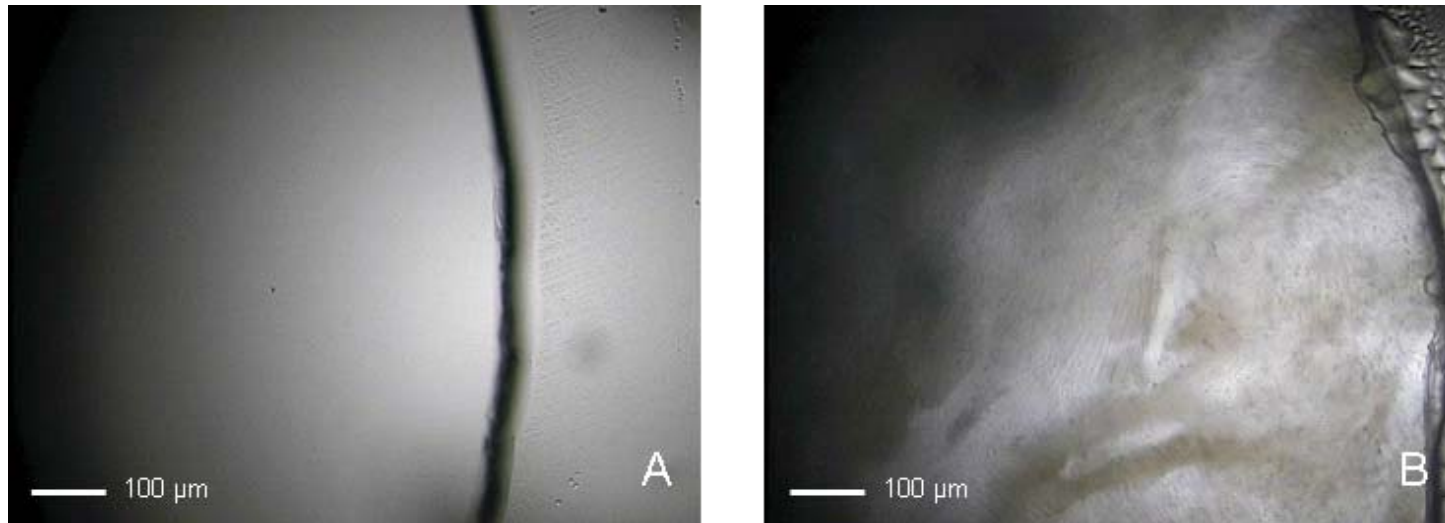


Fig 4. Microscopic observations of freezing 0.1% Collagen solution (0.1 N Acetic acid w/v) :
(A) supercooled solution at -20°C ; (B) Sample crystallization at -22.4°C . The sample was cooled using a freezing rate of $-5^{\circ}\text{C min}^{-1}$.

RESULTS

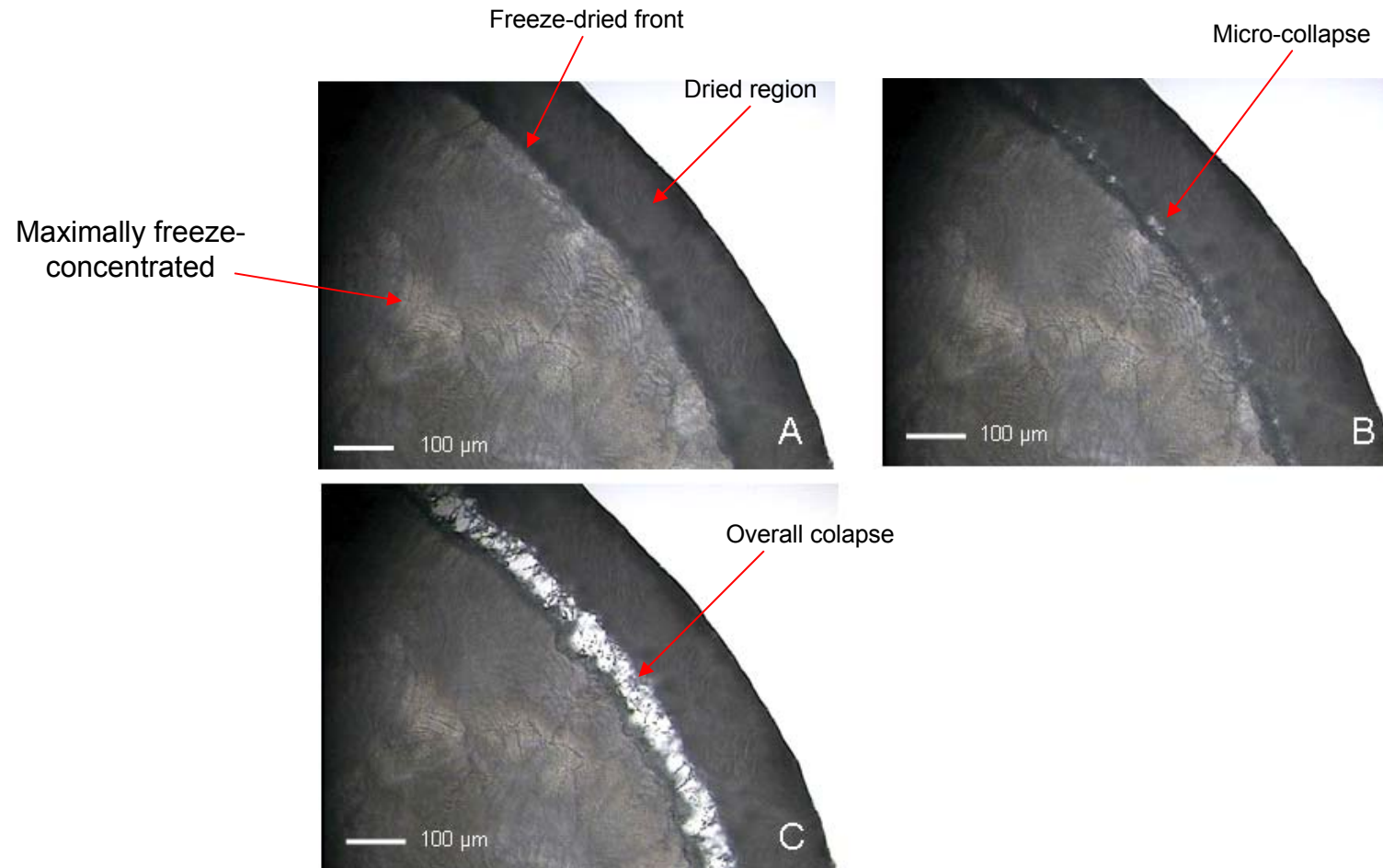


Fig 5. Microscopic observations of freeze-drying 5% Trehalose solution (w/w): (A) structure retention in the dried region (“not collapsed”) at -28°C ; (B) local loss of structure (“microcollapse”) at -25.2°C ; (C) overall loss of structure (“collapse”) at -23.9°C .

RESULTS

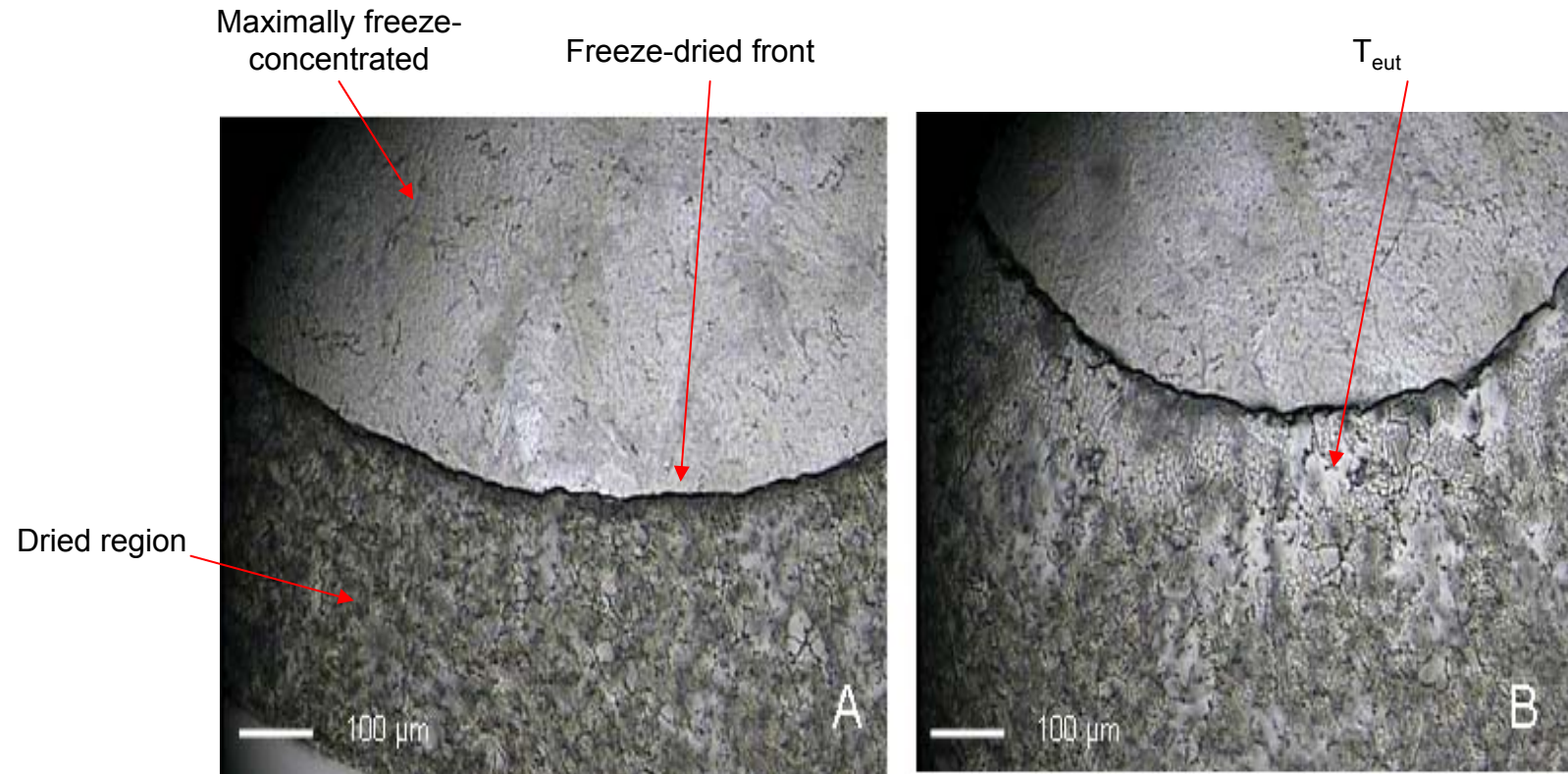


Fig 6. Microscopic observations of freeze-drying 0.9% NaCl solution (w/w) : (A) structure retention in the dried region ("not melted") at -30°C ; (B) T_{eut} at -21°C .

RESULTS

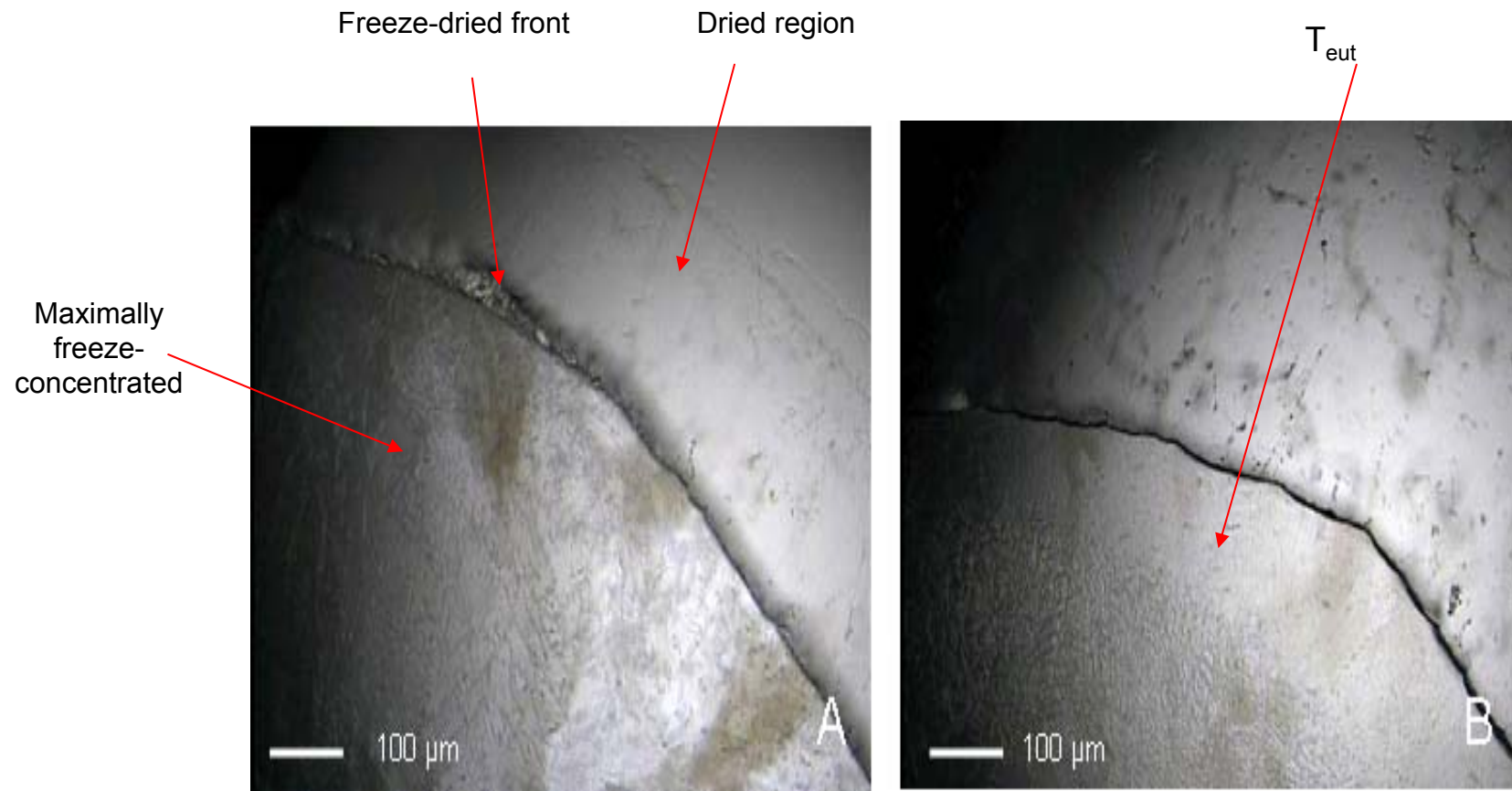


Fig 7. Microscopic observations of freeze-drying 0.1% Collagen solution (w/v): (A) structure retention in the dried region (“not melted”) at -36°C ; (B) T_{eut} at -28°C .

CONCLUSION

- The results showed that T_g' , T_{eut} and T_{cryst} were not influenced by the crucible material type;
- The ΔH involved during the solution crystallization and eutectic melting formulations as well as the ΔC_p involved during the T_g' were affected;
- The aluminum crucible normally used in DSC thermal analysis does not represent the real values involved during the crystallization of a formulation, the eutectic melting and the ΔC_p occurred during the lyophilization of solutions filled into glass vials;

CONCLUSION

- Differences normally observed between T_{cryst} during DSC analysis and freezing during lyophilization process are both directly related to the fill volume and the container material;
- More care should be taken regarding to the concept that T_c is often considered as close to the glass transition temperature (about 1-2 °C above the T_g).

ACKNOWLEDGMENTS

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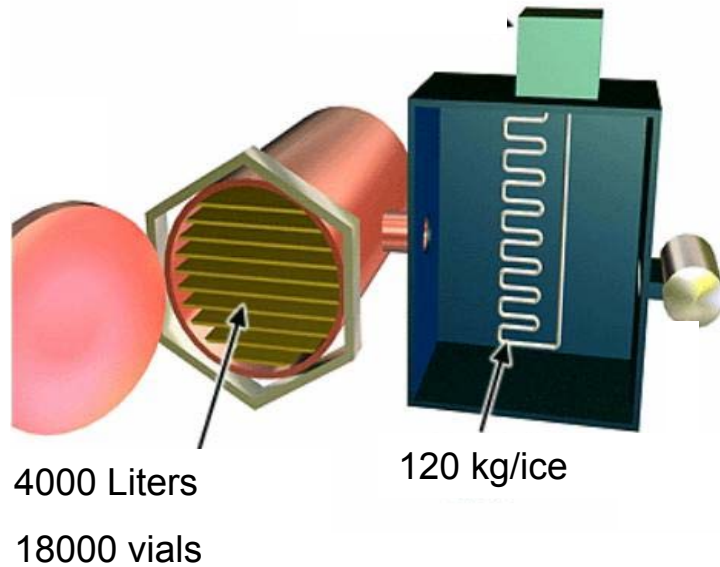
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THANK YOU

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LYOPHILIZATION THE ENERGY CONSUMPTION CONCERN



VS



- Two 2 stage compressors: 32.9 kW/h (each);
- 1 mechanical vacuum pump (175 m³/h): 7.5 kW/h
- 1 roots vacuum pump (1200 m³/h): 3 kW/h
- Circulation pump + Fluid heating: 10 kW/h
- Mean time process: 40 hours

- 25 m² area
- Temperature: 5°C (±3)
- Energy consumption: 14 kW/h
- Product expiration time: 2 years
- Logistic mean time (final user) : 30 days

LYOPHILIZATION THE ENERGY CONSUMPTION CONCERN



~ 1340 kW/process

Lyophilization (freeze-drying)

AN ADVANTAGEOUS PROCESS

VS



~ 10.000 kW/30 days

7-fold increase in energy
consumption