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Electrical Impedance Methods for Developing a Lyophilization Cycle

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Abstract

This work describes the theroretical and practical basis for the *in-line* use of impedance spectroscopy in the determination of various critical process parameters (ice nucleation temperature, solidification time, eutectic formation and melt, and the glass transition). A key advantage of the spectroscopy approach, whereby the impedance of the test object (i.e. a glass vial or ampoule containging the product to be freeze-dried) is measured across a range of discreet frequencies (in the range 10 Hz to 1 MHz), is that one can select certain measurement frequencies, and in effect tune the instrument, for the determination of these different facets of the freeze-drying process

Introduction

The electrical impedance of materials has been used for many years in the study of the various processes associated with freeze drying. However, these studies have been restricted to the off-line determination of critical temperatures by laboratory-based analysers that measure at a frequency of 1 kHz[1]. More recently, a new impedance spectrometer has been designed specifically for non-invasive measurements on glass vials used as the product containers for the freeze-drying of injectable drugs. This development has enabled impedance spectroscopy to be implemented as an in-line process analaytical technology (PAT) for product and process development purposes.

Materials and Methods

A bespoke 5 channel impedance analyser was used to measure the 10 Hz and 1 MHz impedance spectrum of a single glass vial (the standard container for the drug solution) which has been modified by conforming two copper-foil electrodes to the outside of the vial, on opposite sides to one another, and soldering two thin/flexible coaxial wires (50 cm in length) that have MCX type coaxial connectors. The cables on the vial are connected to the impedance analyser (located outside the freeze-dryer) via a junction box (located inside the freeze-dryer) via one of the pre-existing ports on the dryer on which is connected a pass-through that has vacuum-tight electrical connections. In separate experiments, water and various solutions of sucrose, lactose and mannitol were either freeze-thawed or freeze-dried inside the impedance measurement vial and, in each experiment, spectra were recorded every 2 min while tracking the temperature using a thermocouple placed in a nearest neighbor vial.

Results & Discussion

Illustrated here (Fig. 1) are those impedance spectra recorded during the re-heating phase of an annealing cycle of frozen water. A number of features of these plots are then extracted for the purpose of demonstrating the applications for this non-invasive impedance technique.

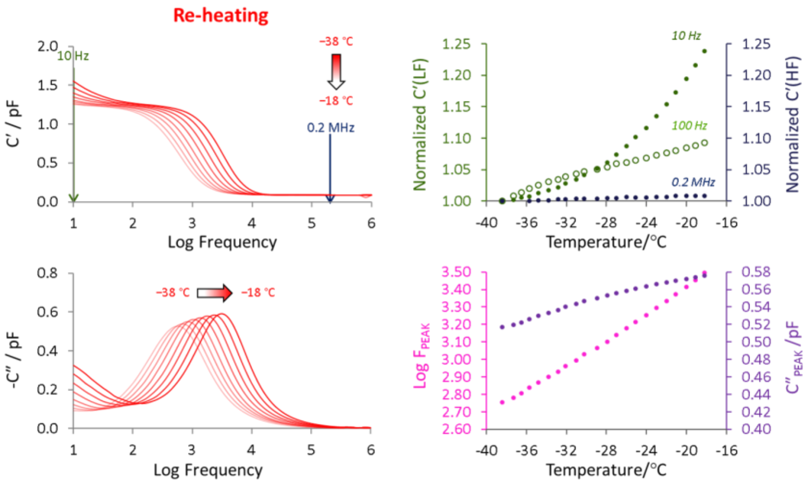

Fig. 1 *(LEFT) Real and imaginary capacitance spectra; (RIGHT) Extracted parameters: TOP real part capacitance C' at selected frequencies, BOTTOM peak frequency (F_{peak}) and peak amplitude (C"peak)*

The conference talk will discuss how: (1) the low frequency region of the real part capacitance spectrum (e.g. 100 Hz) is sensitive to the nucleation temperature and the thermal equilibration time of the vial with the shelf; (2) higher frequencies (e.g. 200 kHz) enables the determination of structural changes inthe frozen solution such as the end of crystallization of water and eutectic solutes, the glass transition and eutectic melting.

Conclusions

This work has demonstrated the importance of the measurement frequency and the choice of real or imaginary capacitance in the determination of critical process parameters.

References

[1] K.R. Ward, P. Matejtschuk, Freeze Drying/Lyophilization of Pharmaceutical and Biological Products, 3 Edn. Informa Healthcare, London, pp. 111-135