**Z-FDM: Micro-Sample Impedance Spectroscopy for Freeze-Dried Formulation Development**

For many years, freeze-drying microscopy (FDM) has been the method of choice for the determination of the critical product temperature above which a formulation collapses at the sublimation interface. Recent developments in image processing techniques such as TASC (2) have enabled a more objective assessment of this temperature, with less reliance on the operator’s experience and skill, while the inclusion of an Optical DSC stage has allowed other thermal events to be recorded, such as the glass transition.

This work presents one further development, which integrates impedance spectroscopy with pixel analysis of FDM images to create a new instrument called Z-FDM. The instrument comprises an inter-digitated electrode (IDE) array placed within the cryo-microscope stage of a standard freeze-drying microscope (in our case the Lyostat5 from Biopharma Process Systems, Winchester, UK) connected to a Sciospec ISX3 impedance analyser. The cabling between the IDE (within the cryo-stage) and the analyser (outside of the cryo-stage) passes through a KF-flanged end-plate, attached to the side arm of a T-piece that is placed in-line with the hose that connects to the vacuum pump.

The talk focusses on a number of applications for Z-FDM in the determination of (i) ice nucleation temperature and ice solidification time, (ii) eutectic crystallization, (iii) glass transition temperature and collapse temperature, and (iv) primary drying rate.  In order to explore the significance of these parameters to the development of the final formulation, the talk also describes a series of case studies where the impact of several parameters were investigated: sample size and a range of formulation variables, such as crystalizing and glass forming excipients, salts and buffers.

1. Ward, K.R. and Matejtschuk, P., (2019). In: K. R. Ward and P. Matejtschuk, eds, Lyophilization of Pharmaceuticals and Biologicals: New Technologies and Approaches. 1 edn. Humana Press, New York, pp. 1-33.