LyosenseTM: A method for controlling and/or monitoring process parameters of the lyophilization process

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**Purpose**: To develop an individual vial monitoring system for characterizing lyophile product characteristics and process end points to establish and control efficient lyophilization regimes.

**Method:** A new system has been developed comprising a modified glass freeze-drying vial, with an electrode system deposited on the external surface, coupled to a high precision impedance analyser via miniature coaxial connectors, which are surface mounted at the neck of the vial. The thermal mass of the vial-electrode-connector-system is <0.5% of the mass of the vial/product. Frequency scans of the system impedance were recorded during a range of freeze-drying cycles and placebo formulations (of varying salt loading, in order to simulate the impact of drug loading on the electrical conductivity of lyophile products).

**Results**: Changes in phase (e.g. ice formation) and completion of freezing, the onset of micro-collapse, and the end-points of primary and secondary drying are all detected by this method through changes in the measured impedance of the vial-electrode assembly. These transitions are more easily determined if the impedance is displayed as a complex capacitance or dielectric permittivity, where the cell constant is presumed to equal 1. The imaginary capacitance (dielectric loss) is characterized by a peak in the frequency spectrum, which arises from the composite capacitor of the product in series with the glass vial. It has been demonstrated, in general, that the frequency of the peak is strongly coupled to the temperature of the product (through the interdependency of product temperature and/or phase on the electrical resistance of the product) whereas the height of the peak is dependent on the amount of ice remaining (in primary drying) and the residual surface moisture (in secondary drying). As the cycle progresses the peak height decreases, with a characteristic sigmoid time-dependence, such that the derivative of the time-profile can be used to define the end of the primary drying.

**Conclusions**: In-process control may be established using the Lyosense system, through the definition of set-points (i.e. the product temperature during primary drying, to drive the process at a high temperature while avoiding collapse) and end points (to establish the moisture content of the product).

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