Then this material can enter the freeze-dryer. Altogether, it is a rather simple online galenic process.

Thermal and Electric Properties

A fundamental paradigm of freeze-drying is to understand that, in almost every case, there is no direct correlation between the structure of a frozen product and its temperature since all structural features depend essentially on the "thermal history" of the material. In other words, the knowledge of the temperature of a frozen solution is not enough to allow the operator to know its structure since this latter depends, essentially, on the way this temperature has been reached, that is, on the freezing cycle.

For instance, we did show in 1960 that an aqueous solution of sodium chloride at −25°C could be

either a sponge-like ice network soaked with highly concentrated fluids if the system has been cooled progressively from +20°C to −25°C

or a totally frozen solid where all the interstitial fluids have crystallized as eutectics if the system has been cooled, first to −40°C and then rewarmed to −25°C

Actually, when water separates as pure ice, as is the case for diluted solutions, there might be a considerable degree of supercooling in the remaining interstitial fluids. It is then compulsory to go to much lower temperatures to "rupture" these metastable states and provoke their separation as solid phases. This, indeed, has a great significance because it is precisely within those hypertonic concentrated fluids that the "active substances" soak, whether they are virus particles, bacteria, or delicate proteins, and there they can undergo serious alterations in this aggressive environment. This is the reason why we advised to cool the product at sufficiently low levels to reach what we have called T_{cs}, the maximum temperature of complete solidification. However, when frozen, the material will only start to melt when it reaches either eutectic temperature or what we called T_{im}, the minimum temperature of incipient melting.

Differential thermal analysis (DTA) and differential scanning calorimetry (DSC) are useful techniques to proceed to this determination. They can be very advantageously coupled with low frequency (LF) electric measurements since the impedance of the frozen system drops in a spectacular way when melting occurs (Figs. 5 and 6). In other terms, a high electric impedance is always related to a state of utter rigidity. Moreover, the electric measurements are more reliable than DTA/DSC alone. Indeed, when we are dealing with a complex system—more particularly when it contains high molecular weight compounds—the material hardens progressively during freezing and, often, in the course of rewarming shows incipient melting only at relatively high temperatures. Until that point the DTA curve remains "silent." Unfortunately, this is not always a sign of absolute stability since, quite often, a "softening" of the structure appears much earlier. It is our experience that a sharp decrease in electric impedance is a clear warning for an operator who should try and maintain the product during primary drying at temperatures below this limit. Figure 7 demonstrates this phenomenon in the case of U.S. standard for pertussis vaccine lot 9, and Figure 8 shows the same behavior for the Saizen mass 10 mg from Serono. In both cases it is quite obvious that sublimation has to be