measure, predict, or model mathematically, including variations in temperature, pressure, and radiative heating effects within the freeze-dryer, the effect of the temperature probe on the sample with regard to the nonprobed samples within a batch, and a whole plethora of scale-up issues. These issues are discussed in later chapters in this volume.

Critical temperatures can still be employed during freeze-drying, even if no possibility exists to probe product temperature directly. This is the case for products that are frozen in pellets prior to sublimation or where a simplistic freeze-dryer is used in the early stages of product development. In such instances a "safe"—yet perhaps somewhat inefficient—cycle may be devised by employing shelf (or chamber) temperatures that are several degrees below the critical temperature of the frozen material under sublimation and relying on the sublimation cooling effect to maintain the product temperature below its critical temperature; this approach should work, provided the source of heat into the material does not exceed the cooling effect of the sublimation process on the product.

For an amorphous material, collapse occurs at the drying front while the remainder of the frozen material remains unaffected (unless a different transition occurs within the frozen structure in the same temperature range). Therefore, if the base of a product is probed, the drying front will, by definition, be colder because of the sublimation cooling effect at the front itself. Therefore, during the sublimation process, if the base of the material is kept below the collapse temperature of the interface a safety margin already exists, but which will reduce in magnitude as the rate of drying decreases over time (because of the increased resistance to vapor flow from the dried layer). Contrastingly, for crystalline materials, if the temperature anywhere in the frozen material exceeds the eutectic temperature part of the eutectic solid will melt and may evaporate under vacuum, leading to eruption of the material and resulting in a product with poor aesthetic appearance. Therefore, although there will be a temperature gradient between the base of the material and the drying front, this does not constitute a safety margin as it does with amorphous materials, since the base of the material is at risk of melting. Thus the use of a greater safety margin may be advisable when freeze-drying crystalline materials.

ELECTRICAL IMPEDANCE ANALYSIS: A NOVEL METHOD THAT MAY ALLOW GREATER INSIGHT INTO MICROCOLLAPSE/ MICROMELTING

The use of electrical resistance (ER) analysis or freezing resistance analysis (FRA) has been widely reported for the study of frozen materials that are subsequently to be freeze-dried (21,54–58). Here, the ER of a material to a low-voltage alternating current is measured, as it is cooled and rewarmed. Traditional devices that measure ER (often termed "eutectic analyzers") have often been observed to miss subtle changes that may turn out to be significant and do not tend to give clear indications of changes in nonionic materials such as proteins, polymers, and saccharides. Furthermore, the term eutectic analyzer may often be considered a misnomer, since a high proportion of materials that are lyophilized do not give a true eutectic but instead persist in a glassy state. To this end, on the basis of observations made by Rey (59), who established that analysis using a function of impedance ($Z\sin\varphi$) can provide more detailed information about the behavior of the frozen solute, a novel instrument has been