

probe during a freeze-drying run and should be regarded as a source of information and not used to control the system. For the processing of infectious materials, probes are not included due to decontamination concerns.

Given this proviso, temperature probes and vacuum probes can and do provide a useful means of monitoring the progress of the freeze-drying process and to some degree indicate the consistency of process changes within and across the shelves of the freeze-drying chamber. Probes are also useful indicators of equipment noncompliance and system failures—for instance, in terms of pressure leakages, inadequate heating, or cooling steps, etc.

Evidence of ice crystallization (and the degree of supercooling) and the crystallization of excipients can be observed (for the probe-containing ampoules at least) from the temperature profile as inflections in the product temperature profile during the progress of the freezing step (Fig. 10).

Most commercial freeze driers allow for a number of product temperature probes that are usually distributed so as to provide details of temperature profiles across the shelves and between shelves. Even then there may be only six probes (in the case of the Serail CS-100) for instance to monitor the freeze-drying of 10,000 ampoules/vials. Of the types of probes available simple K-type or T-type thermocouples are small, convenient, and inexpensive. We use resistance thermometers, although these are larger (3–4 mm in length and 2-mm wide), as they give more accurate readings with a more linear response than thermocouples. Typically we would aim to place at least one probe in product on each shelf of a run covering multiple shelves.

The primary concern with the location of probes is the reproducibility in terms of the location within the container (centrally or to the side) and the degree to which contact is made with the material to be freeze-dried (see sect. “Impact of Process Scale-up”).

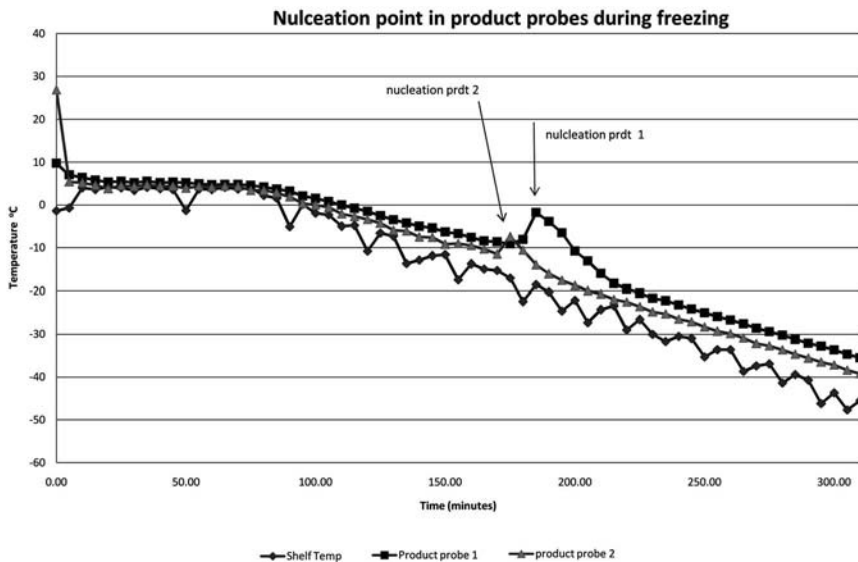


FIGURE 10 Inflection in signal from product temperature probe on nucleation of ice formation during ramped freezing step.