The freezing process will also be important; snap freezing by placing product on precooled shelves can result in heterogeneous crystal formation and final product appearance (12). This has been particularly apparent to us when freeze-drying plasma where shelf freezing on precooled shelves (−50°C) resulted in up to 60% of ampoules having freeze-dried cakes with a markedly striated appearance and some having a heterogeneous appearance, partially uniform (noncrystalline) and partially striated.

For plasma, to prevent this heterogeneity, we routinely use shelf freezing from 4°C down to −50°C at a modest rate of cooling (0.2–1°C/min) and then perform primary drying from shelf temperatures of −30°C to −40°C. This controlled freezing results in a homogeneous cake without marked crystalline appearance.

However, if there is a tendency for freeze-induced damage in a biological then there may be no alternative to rapid freezing, achieved by loading product on to precooled shelves at −50°C Historically, snap freezing in liquid nitrogen was used but this is neither safe nor practical at the scale of current manufacture, often resulting in a high proportion of ampoules breaking and leading to the crystalline problems described above. Materials that contain adjuvant suspension or cellular components are also loaded on a precooled shelf to minimize the time taken to achieve a frozen state and so the likelihood of sedimentation. There is evidence that rapid freezing of cellular or viral materials may also minimize the damage caused by ice crystal formation as the crystals will be smaller (13).

Primary Drying

The aim of primary drying is to remove the crystalline water ice. As freeze-drying commences, the products must be held below these temperatures to avoid collapse as drying commences and a visually unacceptable cake or, worse still, loss of functional activity. The initial product temperature during primary drying must not exceed the T_g' or T_{eu} points while not being so low that the sublimation rate is too slow. Product temperatures 0°C to 10°C below the T_g' or T_{eu} are chosen and maintained for sufficient time for an inflexion in the temperature profile to be evident and the product temperature to rise to equal or above that of the shelf (Fig. 7). During the early stages of freeze-drying, the product temperature is at a temperature lower than the shelves due to sublimative cooling; the heat loss from the product exceeds the heat flow into the product, primarily from the shelf. The inflexion in the product temperature profile represents the stage at which this cooling loss finishes and the product temperature rises and so gives a coarse indication of the end of primary drying, at least for the ampoules being monitored.

During primary drying, should a processing equipment failure occur, it is important that the shelf temperature and therefore the product temperature be rapidly lowered to ensure that the product retains biological activity. Routinely, low shelf temperatures have been used at NIBSC, with prolonged primary drying periods. Under such conditions, although sublimation rates are slow, the likelihood of product temperature exceeding the product T_g' is low. This, although not optimal in terms of the duration of the freeze-drying process, does allow the processing of a wide variety of formulations with minimal cycle development. Chamber vacuum is maintained typically at 30μbar to 100 μbar during the primary drying process in most of our operations.