



FIGURE 1 Example of primary drying design space.

Another important aspect is the extent of product characterization and identification of all relevant product quality attributes. In considering changes to an established product's manufacturing conditions, one must often take another look at product attributes that are not part of routine release or stability testing—especially product crystallinity by powder X-ray diffraction. Acceptance ranges for routine tests such as moisture and reconstitution time may need to be adjusted once sufficient data are accumulated.

An excellent example of a primary drying design space can be found in a paper by Chang and Fischer (5). Figure 1A is a sketch representing the nature of their findings. Process conditions are the chamber pressure on the x-axis and shelf fluid inlet temperature shown as a family of curves. Outputs are product temperature (family of dashed curves) and sublimation (drying) rate on the y-axis. This way of presenting the design space for primary drying, which will look slightly different for each product, is that it gives prominence to the drying (sublimation) rate by putting it on the y-axis. Observations that can be made from this figure are

1. Increasing chamber pressure (up to a point) leads to higher sublimation rate but also higher product temperature.
2. Increasing shelf fluid inlet temperature also leads to higher sublimation rate and product temperature.
3. At a given product temperature, the highest sublimation rate can be found at combinations of lower chamber pressure and higher shelf fluid inlet temperature.

Minimizing primary drying time means maximizing the sublimation rate during primary drying. Chang and Fischer measured primary drying rate by removing vials through the cycle and weighing them. The third observation above is a cornerstone of this chapter—the drying rate can be maximized “for a given product temperature” by using combinations of lower chamber pressure and higher shelf fluid inlet temperature. It has long been known that there is a maximum product temperature for primary drying, above which the product will collapse. This maximum allowable temperature constitutes a “boundary”