

is perfectly preserved. Figure 6F shows the retention of crystalline cake structure when lyophilization was performed at a sample temperature at -15°C . Clearly, the observation agrees with the DSC results described above, that is, with an annealing step, glycine crystallizes out and freeze-drying can be done at a much higher temperature.

So far we have described how to use DSC and a freeze-drying microscope to determine (i) the necessity of annealing in freezing and (ii) the highest allowable product temperature in primary drying. With these two different methods, we can confidently design the freezing cycle and primary drying cycles. For the crystalline matrix-type formulation discussed in this chapter, it is clear that annealing is necessary to crystallize glycine. The annealing temperature should be at -20°C . After the glycine crystallizes out, the highest allowable product temperature is elevated and, therefore, primary drying can be done with a much higher efficiency. Determining the highest allowable product temperature is the most critical factor in developing a primary drying cycle. During the primary drying the product temperature must be kept lower than the highest allowable temperature to avoid collapse and melt-back of the cake. The melt-back here includes both the melt-back of a solid, such as glycine described above, and the melt-back of ice, which occurs at a much higher temperature than that of glycine. In addition, during primary drying, both heat transfer and mass transfer are important in affecting product temperature. In other words, we can achieve a product temperature lower than the highest allowable temperature by using many different combinations of shelf temperature and chamber pressure. Figure 7 demonstrates the possible combinations for the crystalline matrix-type formulation. This provides very important information not only for designing a primary drying process, but also for bracketing process parameters during validation. For example, if -16°C is the highest allowable temperature for the formulation, Figure 7 illustrates that all combinations of shelf temperature and chamber pressure resulting in a product temperature lower than -16°C would be acceptable process parameters. In practice, we usually take at least 2°C to 5°C as a safety margin, and we always optimize the process by looking for the combinations that result in the highest sublimation rate and, consequently, the shortest drying time.

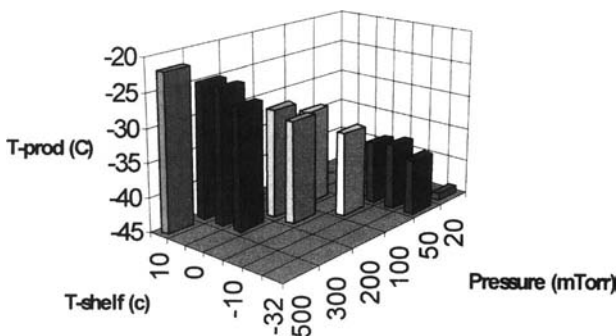


FIGURE 7 Relationship of product temperature as a function of shelf temperature and chamber pressure.