

Fundamentals of Freeze-Drying

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1. INTRODUCTION

The development of freeze-dried injectable pharmaceutical products has traditionally been a process of trial and error, both with respect to the composition of the formulation and the process conditions used during freeze-drying. Although this approach ultimately may result in an acceptable product, it is a time-consuming and labor-intensive process, and is unlikely to result in the highest quality product attainable or in a freeze-dry process which is optimized.

The increased importance of freeze-drying as a pharmaceutical unit operation, in large part caused by widespread development of protein therapeutic agents, has spurred interest in an analytical approach to formulation and process development based on a sound understanding of the physical chemistry of freezing and freeze-drying, the material science of viscoelastic systems, and fundamentals of heat and mass transfer. A growing

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body of scientific literature has demonstrated that the scientific approach can result in improved product quality with minimum trial and error empiricism.

In addition to the need for rapid development of new pharmaceutical products, growing scrutiny of health care costs has focused more attention on minimizing cost of goods by pharmaceutical manufacturers. Among pharmaceutical unit operations, drying operations are, in general, the most expensive. Of these, freeze-drying is generally the most expensive, not only in operating cost, but also in cost of equipment. Development of overly conservative freeze-drying conditions results in long cycle times, added cost of production, and unnecessary consumption of drying capacity. Optimization of the freeze-drying cycle—minimizing drying time without a measurable adverse effect on product quality—should be integrated into the product development plan.

Freeze-drying of proteins often presents a greater challenge to the formulation scientist than that of more traditional, low molecular weight drug compounds, for several reasons. First, proteins are, in general, more susceptible to damage by the stresses involved in freezing and freeze-drying than low molecular weight drugs. Successful freeze-drying commonly requires the use of solutes intended to stabilize the protein against damage by these stresses. Second, the conventional wisdom that “the dryer, the better” with respect to both acute damage caused by freeze-drying and long-term stability does not apply to some proteins. Avoiding overdrying places added importance on careful monitoring of the process, particularly when maintenance of product quality demands keeping the dried product within a “window” of residual moisture activity. Third, the stability of protein formulations as freeze-dried solids is more uncertain than that of most low molecular weight drugs. Freeze-dried protein pharmaceutical products usually require refrigerated storage, and stability of the freeze-dried protein is more affected by seemingly subtle changes in the formulation and in processing conditions than low molecular weight drugs. Finally, the frequent high cost of bulk active material provides added incentive to maximize the yield of pharmaceutically acceptable product.

The purpose of this chapter is to review the basic physical chemistry and material science of freeze-drying, with particular reference to protein formulations, and is geared toward readers unfamiliar with the subject. We also attempt to highlight areas in need of further research. The mechanism of stabilization of proteins against freezing- and drying-induced loss of activity by cosolutes has been thoroughly reviewed by Carpenter *et al.* (1994) and Arakawa *et al.* (1993), and this body of information will not be covered in detail.