



Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice

ABSTRACT:

Design of freeze-drying processes is often approached with a “trial and error” experimental plan or, worse yet, the protocol used in the first laboratory run is adopted without further attempts at optimization. Consequently commercial freeze-drying processes are often neither robust nor efficient.

It is our thesis that design of an “optimized” freeze-drying process is not particularly difficult for most products, as long as some simple rules based on well-accepted scientific principles are followed. It is the purpose of this review to discuss the scientific foundations of the freeze-drying process design and then to consolidate these principles into a set of guidelines for rational process design and optimization.

General advice is given concerning common stability issues with proteins, but unusual and difficult stability issues are beyond the scope of this review. Control of the ice nucleation and crystallization during the freezing step is discussed, and the impact of freezing on the rest of the process and final product quality is reviewed. Representative freezing protocols are presented. The significance of collapse temperature and the thermal transition, denoted T_g' , are discussed, and procedure for the selection of the “target product temperature” for primary drying are presented. Furthermore guidelines are given for selection of the optimal shelf temperature and chamber pressure settings required to achieve the target product temperature without thermal and/or mass transfer overload of the freeze dryer. Finally guidelines and “rules” for optimization of secondary drying and representative secondary drying protocols are presented.