20 Process Analytical Technology in Industrial Freeze-Drying

Antonello A. Barresi, Davide Fissore, and Daniele L. Marchisio
Dipartimento di Scienza dei Materiali e Ingegneria Chimica, Politecnico di Torino, Torino, Italy

INTRODUCTION

Process analytical technologies (PAT) are intended to be systems for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. PAT tools are thus required to implement a true QbD (quality-by-design) manufacturing principle, rather than the classical QbT (quality-by-testing) approach: quality is no longer tested into products, but it is built-in or is by design. This is the framework described by the Guidance for Industry PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance issued by U.S. FDA in September 2004. This guidance encourages the design and implementation of innovative pharmaceutical development, manufacturing, and quality assurance to support innovation and efficiency, with the goal to have safe, effective, and affordable medicines. In fact, besides a proper design of the formulation containing the active pharmaceutical ingredient (API), a comprehensive understanding and design of the manufacturing process is required to guarantee product quality.

Pharmaceuticals freeze-drying is a process where significant improvements can be obtained if PAT tools are used. In fact, although regarded as a soft dehydration process, due to the low operating temperatures, the API can be damaged as a series of stresses are applied to the molecules of the product, which can be rather labile, both during freezing, due to the large variation of solute concentration, ionic strength, and, eventually, pH, and during drying (1). Moreover, in case of pharmaceutical products also the final appearance and the reconstitution time, which can be strongly affected by processing, must be taken into account (2). To this purpose, during the process, product temperature has to be carefully maintained below a limit value that is a characteristic of the product. In case of solutes that crystallize during freezing, the limit value corresponds to the eutectic point to avoid formation of a liquid phase and successive boiling due to low pressure. In case of solutes that do not crystallize during freezing, the maximum allowed product temperature is close to the glass transition temperature to avoid the collapse of dried cake. This collapse as well as the shrinkage (that is generally due to limited and localized collapse phenomena) can be responsible for a higher residual water content in the final product, a higher reconstitution time, and the loss of activity of the pharmaceutical principle; besides this, a collapsed product is often rejected because of the unattractive physical appearance. Finally, the residual water content at the end of secondary drying has to match a target value, which is dependent on the product considered.