The Saga of Freeze-Drying

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Though recognized by the public since freeze-dried coffee hit the market 30 years ago, lyophilization remains far from mature and deserves more research.

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Drying from the frozen state is not uncommon in nature. In the winter, snow vanishes along the roads in dry cold air without melting. In Central Siberia, scientists have found the large bodies of mammoths that have been progressively freeze-dried during the past 15,000 years. In the Peruvian high plateau, the Incas reportedly stored, in their tambos, meat that had been dried in the sun at the reduced pressure of the Andes. And freeze-drying is in no way restricted to water systems. Dry ice, for example, can sublimate at −78.8 °C.

Scientific interest in freeze-drying began at the turn of the twentieth century with a publication by Bordas and d'Arsonval at the French Academy of Sciences. Following that publication, Altman and later Gersh used this technique to prepare undistorted dry samples for microscopy. Indeed, freezing and drying from the frozen state was particularly appropriate for the preparation and preservation of sensitive materials, especially biologicals.

Ronald Greaves, in Cambridge, UK, began his work along those lines in the 1930s by preparing dry

suspensions of living bacteria. However, this technique still was only familiar to a handful of scientists in isolated laboratories.

Then came World War II. With tens of thousands of casualties on the battlefields, human plasma was in great need, and freeze-drying again entered the limelight. Thanks to Greaves in England, François Henaff in France, and Earl Flosdorf in the United States, thousands of liters of blood were processed to isolate plasma, which was then preserved by freezing and drying.

As the use of lyophilization expanded, the process began to be industrialized. Loire, Stokes, Edwards, and others designed and built the first equipment for the purpose. Called "lyophilization" by Flosdorf, the process faced its first major challenge under Sir Ernst Boris Chain, who used the technique to preserve antibiotics. Given Chain's results, it is no wonder that Charles Mérieux turned to lyophilization to prepare vaccines and, later on, to refine blood fractions.

By the mid-1950s, many industries were already using freeze-drying to preserve pharmaceutical and biological products, as were the physicians and surgeons who developed tissue-banking for plastic and reconstructive surgery. Drs. Hyatt, Bassett, and Meryman of the United States Navy were among the early pioneers in the field. At the time, the process was quite simple, and the equipment was robust and unsophisticated. Because freeze-drying was still considered an expensive operation, however, its extension to the food industry, though potentially feasible, remained almost nonexistent.

Today, lyophilization is thriving and is even recognized as an everyday technology thanks to the introduction of freeze-dried coffee 30 years ago.

In the pharmaceutical industry, freeze-dried drugs are well-recognized products. At the same time, in some specialized laboratories, scientists are developing more-sophisticated processes that combine freeze-drying technology with electron microscopy, biochemistry, and refined surgery.

In parallel, equipment manufacturers continually search for more-reliable automated systems capable of handling many different products in large batches under fully sterile conditions. They compete to improve efficiency and safety and reduce costs.

At the same time, the cosmetics industry is increasing its use of lyophilization to help prepare beauty masks, hair dyes, and sophisticated supports for face creams. Chemical industries also are beginning to use freeze-drying to prepare refined chemicals, catalysts, and selective filters.

At first sight, the health profile of lyophilization looks good, because it appears to be a ubiquitous technology strictly controlled both by manufacturers and operators. This view is short-sighted, however, because freeze-drying is facing difficult challenges as the sensitivity, complexity, and price of treated products steadily rise. New antibi-

otics and drugs, immunological products, substances derived from genetic engineering, high molecular weight proteins, and sophisticated peptides are very fragile, difficult to freeze, and all highly sensitive to residual moisture content. As a result, each product deserves a dedicated process and sometimes dedicated equipment as well (as in the case of oncolytic drugs).

In-depth knowledge of each product's thermodynamic properties at low temperature is compulsory, which means that various product-specific questions must be answered. For example, how does it freeze? Does it form metastable glassy structures, which often need to be annealed? How far can its water content be reduced without disrupting its steric configuration? What type of bulking agent is required to form a stable plug when the active substance is present only at the milligram level? Will it display "product elegance?" What are the potential surface actions of the container–closure system? Do the glass walls of the vial release undesirable ions or adsorb, irreversibly or not, very dilute active substances? Do the stoppers remain neutral and hermetic to gas and water vapor?

All of these factors must be given appropriate weight in the context of the overall technical and financial budget. This is especially true when it is understood that the whole operation must be sterile, sometimes with the use of isolators that require remote handling and automation. As an alternative, a manufacturer may want to consider whether it would be more advisable to use a hygenic process and then sterilize the finished product by irradiation.

Other key questions also must be answered. For example, can the manufacturer guarantee that all vials in a batch of 50,000 or 150,000 have the same end-moisture content, whatever their respective position in the drying cabinet? Can the manufacturer present to regulatory authorities and compliance officers process and data sheets that are precise and stable enough to obtain validation?

Today, considering all these issues, we can say that lyophilization

- is an increasingly essential tool for the pharmaceutical industry
- although a highly sophisticated technology, still is far from mature and deserves substantial fundamental and applied research
- presents constant challenges for equipment manufacturers that must provide instruments that can process, in a reproducible and reliable way, large batches of high therapeutic and material value. (One batch of a peptide or an oncolytic drug often is worth more than the freeze-dryer itself!)

For all of these reasons, it is an appropriate time to devote this special issue to lyophilization. Lyophilization is a demanding and challenging technology that deserves an educated and multidisciplinary approach. **PT**