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From the glacial era to IoT: the Lyophilization grand adventure

Original
From the glacial era to IoT: the Lyophilization grand adventure / Fissore, D.; Pisano, R.; Barresi, A. A.. - STAMPA. - (2019), pp. ix-xiii.

Availability:
This version is available at: 11583/2786114 since: 2020-01-28T21:55:55Z

Publisher:
CRC Press

Published
DOI:

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12 October 2024

Freeze Drying of Pharmaceutical Products

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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487–2742

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Printed on acid-free paper

International Standard Book Number-13 978-0-367-07680-1 (Hardback)

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Library of Congress Cataloging-in-Publication Data

Names: Fissore, Davide, editor. | Pisano, Roberto (Of Politecnico di Torino), editor. | Barresi, Antonello, editor.
Title: Freeze drying of pharmaceutical products / edited by Davide Fissore, Roberto Pisano, Antonello Barresi.
Other titles: Advances in drying science & technology.
Description: Boca Raton : CRC Press, [2020] | Series: Advances in drying science and technology | Includes bibliographical references and index. | Summary: "Pharmaceuticals typically rely on compounds that are unstable as aqueous solutions and therefore need to be dried for an extended shelf lifetime. While lyophilization remains the gold standard in dehydration technology, it is among the most expensive and time-consuming unit operations in pharma manufacturing. This book provides an overview of the most recent and cutting edge developments and technologies in the field, focusing on formulation developments and process monitoring and considering new technologies for process development like the micro freeze dryer. Case studies from freeze dryer manufacturer and pharmaceutical companies are discussed"—Provided by publisher.
Identifiers: LCCN 2019026901 (print) | ISBN 9780367076801 (hardback ; alk. paper) | ISBN 9780429022074 (ebook)
Subjects: MESH: Technology, Pharmaceutical | Freeze Drying—methods | Freeze Drying—trends | Pharmaceutical Preparations
Classification: LCC RM301.25 (print) | LCC RM301.25 (ebook) | NLM QV 778 | DDC 615.1/9—dc23
LC record available at https://lccn.loc.gov/2019026901
LC ebook record available at https://lccn.loc.gov/2019026902

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and the CRC Press Web site at
www.crcpress.com

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Preface

FROM THE GLACIAL ERA TO IOT: THE LYOPHILIZATION GRAND ADVENTURE

Lyophilization is naturally occurring in nature, even if it is quite a rare phenomenon, as it requires extreme conditions: low temperature, an energy supply and an extremely dry environment (very low water partial pressure). Several anecdotal examples can be reported: from lithopanspermia theory, with living cells quite certainly freeze-dried while travelling space on rock fragments until they hit Earth, to Greenland mummies. In the preface to his book's second edition, Rey mentions mammoth meat from northern Siberia (offered in 1902 at the banquet of the International Congress of Paleontology) and reports of a big "mammoth steak with its fur still attached to the skin," received in the late 1960s from the USSR Academy of Science, which turned out not to be frozen, but naturally and perfectly freeze-dried: the animal was buried under snow, relatively close to the surface, where it was sublimed for millennia. In recent times, it has been reported that the poor quality boots of the Italian Alpine Corp in Russia during World War II underwent freeze-drying, losing mechanical properties, because of the extremely dry environment.

In previous centuries freeze-drying was employed by some populations for food conservation: the origins of this process are generally traced back to the 15th century in Peru, where Incas were freezing tubers and potatoes above Macchu Picchu, leaving them to be sublimated by the effects of the sun's radiation in the dry and low-pressure environment. Japanese monks on Mount Koya, south of Osaka, similarly prepared "kodayofu", preserved tofu, by packing bean curd into the snowy mountainside during the Kamakura period (AD 1185 to 1333), and Vikings in northern Europe used triangular wooden racks to freeze-dry codfish.

Despite these early applications, this technique for food preservation was forgotten. It appeared again as an innovation in food technology in 1955, and it is currently a technique used by some renowned chefs in exclusive restaurants or to prepare food for astronauts.

Much more recent is the use of lyophilization in the pharmaceutical and medical fields. Here, we summarize its use in these fields from early applications to current market perspectives.

Lyophilization was substantially unknown in Western countries until the early 1900s: the first attempt to lyophilize a biological product was documented by the German histologist Richard Altmann in 1881 (Altmann 1894), but only in the 1920s did lyophilization become an established laboratory tool for preserving live microorganisms or tissues (Jennings 1999). In 1933, Flosdorf and Mudd at the University of Pennsylvania performed lyophilization of blood serum under full aseptic conditions; they called that material lyophile (from the Greek λύος and φιλεῖν, solvent-loving) because of its ability to be rehydrated (Flosdorf and Mudd 1935).

The first industrial application of lyophilization dates back to World War II; this application was developed independently by Flosdorf and coworkers in the United States and by Greaves in England, for the production of dried plasma for wartime use and then for the production of penicillin (Flosdorf et al. 1945). The equipment used consisted of a single chamber for sublimation and condensation of vapor, vacuum pumps, and mechanical refrigeration apparatus. This plant configuration was used until the 1980s. Today, the vapor released by ice sublimation is generally condensed in a separate chamber.

Early commercial lyophilized products were Hemin by Abbott and Corticotrophin by Parker Davis and Rorer Pharmaceuticals. In the 1970s, new lyophilized products included antibiotics (penicillin G procaine by Wyeth Development, aminoglycosides by Wyeth, cephalosporins by Lilly, cefazolin by SKB and Lilly, β-lactams and vancomycin HCl by Lilly, tetracycline by Pfizer), vaccines (IBV H-52 and H-120 for infectious bronchitis), oncolytics (dactinomycin by Merck, cisplatin by BMS), two corticosteroids by Upjohn Company, hydrocortisone sodium succinate by Cortef, and methylprednisolone sodium succinate by Solu-Medrol.

In the 1980s and 1990s, new products were introduced for bacterial (Azactam by BMS, imipenem/cilastatin by Merck) and viral infections (acyclovir by GSK, ganciclovir by Syntex/Roche, interferons ra-2A by Roche, interferons ra-2B by Schering), treatment for multiple sclerosis (interferon rB1b by Bayer) and heart attack (alteplase by Genentech), and new vaccines (Cervarix by GSK for HPV prevention, Pentacel by Sanofi Pasteur for DPT + polio and hemophilus influenza B, Zostavax by Merck for herpes zoster) (Trappler 2013).

Nowadays, 40% of commercial biotherapeutics, including recombinant proteins, plasma, vaccines, and antibodies, and more than half of FDA-approved parenteral drugs require lyophilization (Akers 2010). Moreover, BCC Research reported that 16 of the top 100 (based on sales) pharmaceutical drugs are lyophilized (LaTorre-Snyder 2017). The single most lucrative product in 2017 was Enbrel (etanercept), a biologic product for autoimmune disease by Amgen and Pfizer, which generated global sales of $9 billion and that will lose its patent protection in 2019. Other examples of high-revenue products include the following: Remicade (infliximab) produced by Johnson and Johnson and Merck ($8 billion; patent expired in 2018); Herceptin (trastuzumab), a monoclonal antibody produced by Roche ($6.5 billion; patent expires in 2019); Copaxone (glatiramer acetate) manufactured by Teva Pharmaceuticals ($4.2 billion; patent expired in 2014).

In the last 20 years there has been a big change in how academia and industry approach research in the field. Kawasaki et al. (2019) described the evolution well, reporting that "the optimization study of the lyophilizer has been roughly developing by the order of (i) trial-and-error approach, (ii) process modeling using mathematical models, (iii) scalability, and (iv) quality-by-design."

The first breakthrough was the use of the mathematical approach to improve process understanding and to allow off-line optimization; the use of a mathematical model enabled the calculation of the "design space" with limited experimental effort, and to guide in safe and reliable process transfer and scale up. Process control also benefits from good modelling approaches, even if it has only been in the last years that the concepts of intelligent control have been applied to freeze-drying of pharmaceuticals.

The second breakthrough is process analytical technology (PAT), allowing the development of new PAT tools for monitoring the process, and innovations to allow control of the freezing step, enabling achievement of quality by design. According to Kawasaki et al. (2019) "a combination of PAT tools with a model/scale-up theory is expected to result in the QbD, i.e., a quality/risk management and an in-situ optimization of lyophilization operation. As important principles might be hidden behind the big data, for effective analysis, the use of the Internet of things (IoT) together with big data from PAT tool and the models including CFD would bring the rapid decision-making well fused with the practitioner's experiences." In addition, the use of advanced modelling tools, like molecular dynamics, has been recently proposed to better understand the complex interactions between active molecules and excipients or solid–liquid interfaces during both freezing and drying; these approaches offer a powerful tool for the "in silico" development of formulations to be lyophilized and reduce time and cost of experimentation.

The lyophilization equipment market is forecasted to double its value from $2.7 billion to $4.8 billion in 2020 as a consequence of development in the biopharma industry and the introduction of new drugs. The registration of new products with an expected high return, in particular, can be beneficial for introducing new technologies to production plants. Continuous freeze-drying might be one of these: this technology was developed for the coffee industry in the 1960s, but it has been object of recent interest by the pharmaceutic industry, as it has been shown that it can strongly reduce production time and is easily scalable, and enables quality control in each vial.

The new challenges, and the increasingly sophisticated approaches developed to respond to them, together with the new problems faced and solved by upcoming technologies, stimulated the production of new books or new editions.

This was the case for the second and third edition of Rey and May's book, *Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products*, published in 2004 and 2010, respectively (Rey 2010). The editors of the present book contributed to that and various other books, including the five-volume series *Modern Drying Technology*, edited by Tsotsas and Mujumdar and completed in 2014, with chapters focusing on several of the previously mentioned breakthrough topics: the use of mathematical modeling and PAT for QbD, in-line product quality control, process monitoring, design space development, and equipment design (Barresi et al. 2010; Fissore and Barresi 2011; Fissore 2012, 2015; Fissore et al. 2015), management of non-uniform batches and scale-up (Pisano et al. 2011; Barresi and Pisano 2013), process intensification by means of combined technologies, use of organic solvents and control of nucleation (Pisano et al. 2014; Barresi et al. 2015; Pisano 2019), and advanced control (Barresi et al. 2018).

But in order to present organically the most recent advancements at the cutting edge of freeze-drying research and technology, from formulation design to process optimization and control, from new PAT monitoring tools and multivariate image analysis to process scale-down and development, from use of CFD for equipment design to development of continuous processes, the editors of the present volume were happy to accept Mujumdar's invitation to contribute to the series *Advances in Drying Science and Technology*, writing or co-writing several of the chapters and

editing the book on *Freeze Drying of Pharmaceutical Products*. Thanks to the contribution of some lyophilization experts, this review work was carried out effectively.

Antonello Barresi
Roberto Pisano
Davide Fissore

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