DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 137

Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products

Second Edition, Revised and Expanded

edited by
Louis Rey
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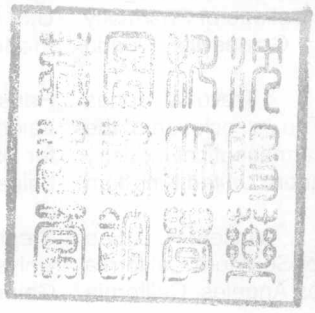
Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products



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DRUGS AND THE PHARMACEUTICAL SCIENCES

Foreword

Like most of today's technological success stories, the history of freeze-drying has been pretty much limited to the 20th century. Whereas Altmann (1), in 1890, reported drying frozen tissues to make histological sections, it was not until 1909 that an application to biologicals was first reported (2). Although the first patent was filed in 1927 (3), there appears to have been little interest in commercial uses until 1935 with a publication by Flosdorf and Mudd (4) that introduced the concept of the cold trap. In the early 1940s Flosdorf et al. (5) in the United States and Greaves (6), working quite independently in England, constructed plants for the large-scale production of dried plasma for wartime use, establishing both the principles and the commercial potential of a new industry.

During the subsequent half-century, the potential of freeze-drying captured the imagination of both scientists and industrial engineers, often without full appreciation of the economic limitations imposed by the immutable thermodynamic costs of freezing and the subsequent sublimation of the frozen water. The food industry in particular was attracted by the potential of prolonged room-temperature storage at a time when home freezers were not yet a staple in every kitchen. It is surprising how long it took to recognize the inappropriateness of this demanding technology for use with a low-cost, high-volume product.

It is the biological and pharmaceutical industries that have been best able to capitalize on the unique virtues of lyophilization and that have stimulated continuing research into the biophysics of both freezing and freeze-drying, some of which is displayed in the initial chapters of this volume. These are the studies that are progressively converting the pioneering and somewhat "brute force" demonstrations by Flosdorf and Greaves into modern, more finely tuned procedures, the importance of which cannot be underestimated. At present it is the pharmaceutical industry with its high-cost product that drives the development of this demanding technology that is increasingly delivering great benefits to our society.

This volume provides clear evidence of the mature state of freeze-drying technology, from the mundane to the sophisticated, all of which are essential to a quality product. And, paradoxically, it is the potential for a high-quality product that will stimulate efforts for still higher quality. The more faithfully the lyophilized product resembles the starting material, the more the focus will fall on the quality of the starting material.

The ability to maintain the complex and delicate structural relationships of biologically active compounds during storage at ambient temperatures has been a boon to manufacturers but with an impact well beyond the manufacturing process itself. Analyses of the freeze-drying process are beginning to shift from the physical aspects of freezing and sublimation to a more sophisticated examination of the effects of the process on the chemical structures and the biological properties of the products themselves.

It is here that the technology of freeze-drying may ultimately make its greatest contribution. Protein function and protein conformation are inexorably linked, and the forces that maintain functional conformations can be substantially and often irreversibly altered by cold and by dehydration (7,8). As those in the pharmaceutical industry look more closely at how these forces may be altering the structure and jeopardizing the function of biologicals during lyophilization, they will inevitably find that many of these alterations, particularly those induced by cold, are not limited only to the freeze-drying process but are inherent in many of the isolation and purification procedures conducted well before final processing begins.

An active site on a protein may be a very small proportion of the total molecule. Is maintaining the function of the active site good enough? Why is the rest of the molecule there? Does it make an unrecognized contribution and should we worry about its integrity? The human body is exquisitely designed to reject malformed and altered proteins. Will denaturation of "inactive" portions of a protein alter its physiological function? Can such denaturation be responsible for unrelated side effects? The resolution of technical concerns such as freezing rates, drying temperatures, and product solubility will permit a more critical reassessment of product quality.

As the technology of lyophilization is perfected, it is creating an environment in which attention will be increasingly focused on the stability of product at the molecular level, not just after or even during lyophilization but throughout the entire manufacturing process. The benefits to society of safe and more effective pharmaceuticals are indisputable and for those of us

who have participated in the development of freeze-drying technology, it is a privilege to have been part of that history.

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Foreword

When I first became aware of the freezing process, some 30 years ago, the process appeared to me to be rather simple and straightforward. At that time I was employed by a major manufacturer of freeze-dryers but working in the field of microelectronics. Given my background in physical chemistry, I found myself becoming increasingly involved in the field of freeze-drying. I must admit I was surprised and somewhat puzzled to learn that some of those using this process were experiencing difficulties. Many formulations of lyophilized products were made isotonic and contained a host of other recipients such as bulking compounds, cryoprotectants, surfactants, and pH modifiers. It was then that I started to read publications concerning the freeze-drying process, particularly those that offered any explanation regarding why some freeze-drying processes were not successful. It was at that time that I realized that the freeze-drying process was more complex than my first impression. That viewpoint has not been altered and perhaps has only been reinforced as the years have passed. However, a great deal of research has been and continues to be done in this field to enhance our understanding.

The actual number of factors we should take into account with a freeze-drying or lyophilization process I simply never stopped to count. But I am certain that they will exceed the 10 fingers on our hands. While not wishing to examine every possible aspect of this process, let me just share with the reader just three areas that I feel to be of major concern.

The first and foremost is the thermal properties of the formulation, without which one is reduced to process development by trial and error. With knowledge of the thermal properties, one is able to quickly develop and validate a lyophilization process. Without such knowledge one has no reference point on which to rely should a change occur in the properties of the formulation. Knowledge of the thermal properties is paramount to the development of a lyophilization process.

The stability of a lyophilized product will be dependent on the residual moisture content. The industry is certainly very much in need of a means

of determining the residual moisture in a product that is both nondestructive and noninvasive. The method should determine the moisture without destroying the dried product, nor should the measurement cause any changes in the product properties such as a loss in activity.

Finally, although the equipment should only provide a safe environment for the product and the necessary operating parameters for the lyophilization process, differences in freeze-drying equipment can affect the process. One should be aware of such differences, especially when transferring a process from one dryer to another. So in any discussion of the lyophilization process, the freeze-drying equipment should not be overlooked.

It is the intent of this Foreword to provide the reader with an appreciation that considerable efforts are being made to enhance our knowledge of the lyophilization process and its associated instrumentation and equipment. While admittedly we will need more information to complete our knowledge of this process, the advances described in this book will take us closer to achieving this final objective.

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Preface

In the middle of the 1950s, when I was actively engaged in low-temperature preservation of living tissues and organs, and tissue banking, I discovered with surprise that in 1902, in St. Petersburg, the participants of the International Congress on Paleontology were given mammoth meat at the banquet. That curiosity actually came from Iakoutia, where a whole frozen mammoth suddenly appeared in the collapsed bank of a Siberian river. Apparently this body had been stored there in the permafrost for 15,000 years and the wolves still found it palatable, as did the conference participants.

I learned then that this discovery was not uncommon and that, from time to time, well-preserved mammoth were found in Northern Siberia. Quite excited by this news I started to investigate whether I could get a sample of that unique material. Numerous requests made at all levels of the administration were fruitless and I had almost forgotten the issue when, in the late 1960s, I received in Switzerland a big box from the USSR Academy of Sciences and—what a surprise—inside there was a big mammoth steak with its fur still attached to the skin. Instead of being frozen it was perfectly freeze-dried and, of course, naturally so. Apparently the big animal had broken its backbone falling into a crevasse and was buried under snow, almost immediately and relatively close to the surface, where it sublimed for millennia, which kept its anatomical features almost intact. We made many scientific investigations of this sample and obtained excellent electron micrographs of the dried muscles. Less successful, by far, was the "stew" that the Nestlé cooks managed to prepare with it: it definitely was no delicacy!

Much more recently, when opening a microbiological conference in Morocco, I came across in my preparation work, on several interesting papers dealing with lithopanspermia, the fantastic ride of living cells in suspended animation, dashing throughout outer space on a rock's back. Quite certainly freeze-dried, they traveled there for maybe millions of years before being captured by the earth's gravity field and falling into the depths

of the ocean, where—it is claimed by some scientists—they "seeded" life on our planet. Freeze-drying, as a natural phenomenon, was again in the limelight.

A scientific curiosity for almost 40 years after the publication of Bordas and d'Arsonval in 1906, freeze-drying, later called lyophilization by Earl Flosdorf at the time of World War II, has bloomed again within the past 20 years to become an almost unavoidable technology to preserve rare and sensitive biochemicals and drugs. Concomitantly, new challenges appeared in basic and applied engineering fields and required more and more sophisticated approaches.

This is the reason that Joan May and I found it useful, if not compulsory, to prepare a second edition of our 1999 book *Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products*. Indeed, our understanding of the fundamentals of freeze-drying has been continuously improving in such areas as confined water, annealing, NMR assessment of mobility in dried products, formulation, protein stabilization, and the role of additives. We witness rising interest in some fields which have been long considered as collateral but which are of prime importance today: properties and behavior of glass and elastomeres in the always present container-closer system. In parallel, industrial operations are becoming more diversified and offer numerous different problems: scaling up towards production from the laboratory bench throughout the pilot plant, cleaning and environmental concerns, and sterile handling of bulk material with the associated qualification and validation strategies. Moreover, new technologies are starting to develop: the use of co-solvents and irradiation. However, in all cases, an absolute duty of care still remains for the operators to provide both security and quality and keep their outgoing products in line with the international standards, a field which is quickly expanding.

Thus, year after year, lyophilization is becoming a vast, diversified field for research and development, engineering, and production, still under the close eye of the administration and of the compliance officers.

Therefore, it comes as no surprise that the publisher and the editors decided to prepare this revised and expanded second edition. In so doing, it is a privilege and pleasure for Joan May and I to extend our warm appreciation to all our devoted, competent contributors and acknowledge once more the generous support and professional skill of the staff at Marcel Dekker, Inc.

Louis Rey, Ph.D.

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