Rational Design of Stable Protein Formulations: Theory and Practice

Rational Design of Stable Protein Formulations

Theory and Practice

Edited by

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and

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Preface to the Series

A major challenge confronting pharmaceutical scientists in the future will be to design successful dosage forms for the next generation of drugs. Many of these drugs will be complex polymers of amino acids (e.g., peptides, proteins), nucleosides (e.g., antisense molecules), carbohydrates (e.g., polysaccharides), or complex lipids.

Through rational drug design, synthetic medicinal chemists are preparing very potent and very specific peptides and antisense drug candidates. These molecules are being developed with molecular characteristics that permit optimal interaction with the specific macromolecules (e.g., receptors, enzymes, RNA, DNA) that mediate their therapeutic effects. Rational drug design does not necessarily mean rational drug delivery, however, which strives to incorporate into a molecule the molecular properties necessary for optimal transfer between the point of administration and the pharmacological target site in the body.

Like rational drug design, molecular biology is having a significant impact on the pharmaceutical industry. For the first time, it is possible to produce large quantities of highly pure proteins, polysaccharides, and lipids for possible pharmaceutical applications. Like peptides and antisense molecules, the design of successful dosage forms for these complex biotechnology products represents a major challenge to pharmaceutical scientists.

Development of an acceptable drug dosage form is a complex process requiring strong interactions between scientists from many different divisions in a pharmaceutical company, including discovery, development, and manufacturing. The series editor, the editors of the individual volumes, and the publisher hope that this new series will be particularly helpful to scientists in the development areas of a pharmaceutical company, (e.g., drug metabolism, toxicology, pharmacokinetics and pharmacodynamics, drug delivery, preformulation, formulation, and physical and analytical chemistry). In addition, we hope this series

will help to build bridges between the development scientists and scientists in discovery (e.g., medicinal chemistry, pharmacology, immunology, cell biology, molecular biology) and in manufacturing (e.g., process chemistry, engineering). The design of successful dosage forms for the next generation of drugs will require not only a high level of expertise by individual scientists, but also a high degree of interaction between scientists in these different divisions of a pharmaceutical company.

Finally, everyone involved with this series hopes that these volumes will also be useful to the educators who are training the next generation of pharmaceutical scientists. In addition to having a high level of expertise in their respective disciplines, these young scientists will need to have the scientific skills necessary to communicate with their peers in other scientific disciplines.

RONALD T. BORCHARDT
Series Editor

Preface

The need to improve drug development approaches has become even more important in this post-genomic era. The number of drug candidates is escalating in most companies. As a result, every aspect of drug development must become more efficient and accurate. This volume is intended as a treatise on the state-of-the-art in formulation and stabilization of protein pharmaceuticals. As we approach the twentieth anniversary of the introduction of a recombinant protein therapeutic agent (human insulin, 1982), it is timely to summarize the advances made in formulation of proteins. The earlier two volumes in this series dedicated to protein stability continue to be widely used in the industry as reference works. However, this volume is intended to move beyond that work. Rather than providing a traditional description of mechanisms and concepts, this volume is intended to be more practical, trying to emphasize that our understanding of protein stability has evolved to the point where rational design of some formulations can be achieved. Furthermore, two of the chapters introduce new stabilization and formulation strategies that may provide future directions in this field. We believe the modern practitioner of protein formulation should find this volume of use, whether they are experts or neophytes.

The first chapter, authored by Byeong Chang and Susan Hershenson from Amgen, is entitled "Practical Approaches to Protein Formulation Development". This chapter will not only talk about modes of decomposition of protein but provides readable and practical guide on how to turn theoretical insight into a manufacturable, stable product. It also provides the reader with insight into the practical constraints placed on scientists actually doing formulation development.

Chapter 2, by Tsutomu Arakawa, Tiansheng Li, and Linda Nahri, introduces the reader to critical issues of refolding proteins produced in *E. coli*. For someone new to this field, the authors provide a number of experimental details and clearly describe the current approaches towards obtaining high yields of

native proteins from inclusion bodies. By providing such great detail, the reader can quickly identify the prior work that is most relevant to their current needs.

The third chapter, entitled "Physical Stabilization of Proteins in Aqueous Solution", is written by Brent Kendrick, Tiansheng Li, and Byeong Chang. A fundamental principle in protein stabilization is the ability of additives (excipients) to alter the thermodynamic stability of a protein's structure. These thermodynamic effects arise from preferential binding or exclusion of the additive from the surface of the protein, as first described by Serge Timasheff and coworkers. This chapter provides a detailed tutorial on the theory and then proceeds to outline the impact of these effects on the stability of protein pharmaceuticals. These effects are important in development of liquid formulations, stabilization during lyophilization, and protein aggregation.

The next chapter introduces an emerging appreciation that susceptibility to chemical degradation can be modulated by the conformation of the protein (or even peptide). Entitled "Effects of Conformation on the Chemical Stability of Pharmaceutically Relevant Peptides", by Jeffrey Meyer, Bert Ho, and Mark Manning, summarizes the data in the literature that indicate it is possible to minimize chemical degradation by altering conformation. One possible method for accomplishing this would be to add preferentially excluded solutes (as described in chapter 3) to compact the structure of the protein. This has worked to diminish aggregation and is now being shown to be effective at slowing chemical decomposition as well. Altogether, this approach could provide a new strategy for developing liquid formulations of peptides and proteins.

The one area where our understanding of protein behavior has truly advanced is for freeze-dried formulations. The authors of the next chapter, John Carpenter, Byeong Chang, William Garzon-Rodriguez, and Theodore Randolph, provide an overview of what is required to produce a stable formulation of a protein in a lyophilized cake. Not only do the authors provide an excellent summary of the advances that have been made in understanding the behavior of proteins during freeze-drying, they translate that theoretical insight into a step-by-step guide to producing reasonable, practical formulations that should work for most any protein pharmaceutical.

Chapter 6, authored by Geoff Lee, is an overview of the development of spray-dried protein formulations. This process has received a large amount of attention in recent years, and this chapter describes the process, the equipment, and formulation concerns that need to be addressed if one is to use this approach to make dried powders of proteins that will retain native structure and activity.

Chapter 7 focuses on the role of surfactants in stabilizing proteins. Over the past few years, an increasing number of mechanisms by which surfactants can stabilize proteins have been described. This chapter, by Theodore Randolph and LaToya Jones, provides an overview about the behavior of this important class of excipients. Even the most experienced formulation scientist probably

does not appreciate all of the subtleties of protein-surfactant interactions. Understanding these mechanisms will allow for a more rational choice of which surfactant (if any) to use and at what concentration.

The last chapter is intended to spur discussion about new strategies to designing formulations of protein pharmaceuticals. Although the drug discovery field has been revolutionized by combinatorial libraries, high throughput screening, and genomics, similar high throughput approaches have not received much attention in the drug development field. This chapter, written by Rajiv Nayar and Mark Manning, will hopefully cause workers in this field to examine their current approaches and seek to find more efficient modes of operation. It is the authors' belief that the demand to develop more products simultaneously with less material and in less time will ultimately transform the field of formulation science.

For anyone who wishes to learn the state-of-the-art in formulating and stabilizing protein drug products, this book should provide information on all aspects, covering not only what is well established, but also where we are and where we are going. The goal to ensure that the reader has the mechanistic understanding of how proteins degrade and can be stabilized rationally, and then provide practical advice on how to translate that knowledge into action.

JOHN CARPENTER
MARK C. MANNING

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