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Book review

Protein Formulation and Delivery, E.J. McNally, J.E. Hastedt. Informa Health Care, New York, NY (2008). 351 pp., US\$ 229.

In the face of the enormous progress in the field of therapeutic protein research and development, nine years after the first edition of "Protein Formulation and Delivery" now a second adapted and extended one has been published. On 350 pages, divided into 14 chapters, more than 25 contributors give a detailed overview of the basic elements of protein formulation and demonstrate new trends in protein delivery addressing both the beginning and experienced protein formulators. The large number of examples of use and that of cited references reveal the authors' huge expertise.

Chemical and physical stability of proteins, established analytical methods, preformulation development, the basics of protein formulation and innovative protein delivery systems are the main topics of this volume. After a short introduction (chapter 1), two chapters follow dealing extensively with stability aspects which are very useful, since (even slight) alterations in proteins can have serious consequences like diminished biological activity or increased immunogenicity. The complex mechanisms of deamidation, oxidation and acylation are precisely explained in a comprehensive way with both taking promoters and effective inhibitors of these reactions into consideration. Thus, possible strategies to minimize the common degradation pathways are provided. But also physical instabilities as aggregation, unfolding/denaturation and adsorption phenomena are treated including thermo-dynamic theories. The next two chapters list the most important analytical methods used for protein characterization (e.g. RP-HPLC, circular dichroism, differential scanning calorimetry, FT-IR-/UV-/fluorescence-/mass spectroscopy, isoelectric focusing, ion exchange chromatography, SDS-PAGE, size exclusion chromatography and bioassays) by describing their principles, advantages and limitations. Various examples help realizing which specific methods are most appropriate for (pre)formulation development, product release and stability testing, respectively. Then the focus is set on preformulation development: studies and methods are discussed which allow understanding the critical quality attributes of a protein in a very early state of development. Finally, two interesting preformulation case studies deliver an insightful view on how the results of several analytical methods can be interpreted and used to define threshold limits for a robust production process.

Chapters 6–9 present an extensive review of the basics of traditional protein formulation, including the formulation of protein solutions, the formulation of high-concentration protein systems, the freeze-drying process and the rational selection of excipients for use in lyophilized formulations. First, the formulation of protein solutions is considered by discussing critical factors such as solubility, buffer effects, temperature and shaking, as well as the requirement of adding stabilizing excipients and the need for manufacturing under aseptic conditions. The development of a highly concentrated Leuprolide formulation (~400 mg/mL) is described, which is used in combination with the Duros® implant, an osmot-

ically driven drug delivery system achieving constant release rates over one year. The subsequent chapter 8 is devoted to the freeze-drying concept and certainly belongs to the highlights of this volume. Besides a detailed presentation of the single parts of this complex process, the challenge of scale-up to production size is so excellently prepared that even inexperienced readers are instantly capable of conceiving the subject matter. Reading this chapter really was a pleasure. General considerations about the reasonable use of excipients for lyophilization complete this part.

To date the vast majority of therapeutic proteins is administered via s.c./i.v.-injection. However, there is a strong ambition to develop more patient-friendly drug delivery systems, which are reflected in chapters 10–12, where three innovative ways of protein delivery are pointed out: pulmonary delivery, needle-free injection and oral delivery. Chapter 10 elucidates the formulation of liquid and solid protein formulations for aerosol delivery with regard to their special requirements and preparation (particle diameter and shape, excipients, stability, spray-drying, appropriate device), whereas chapter 11 concentrates on formulations for needle-free injectors, which are still waiting for their breakthrough on the market. Another rather unusual route of protein administration is exhibited in chapter 12. It describes the successful oral delivery of insulin by the Eligen® technology, showing that an oral application of proteins is not impossible.

Chapter 13 provides valuable information about the reasonable setting of quality-assuring specifications and determination of expiration dates for biotechnological products, mentioning the most relevant definitions and regulatory guidances. Lastly, both editors, Eugene McNally and Jayne Hastedt, compare the formulation development of protein biologicals with that of small synthetic molecules, with the result that there are many amazing similarities.

This updated volume gives a wide overview of the dynamically developing field of protein formulation and delivery. The different aspects are explained comprehensively, illustrated by numerous examples and very well-referenced. In this context, especially chapter 8 treating the freeze-drying process should be pointed out. Although some facts are already outdated (e.g. the distribution of Exubera® has been stopped), this volume can be highly recommended for both students who are beginning to work with proteins and to experienced scientists who want to refresh their knowledge.

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