Book Reviews

Prodrugs. Topical and Ocular Drug Delivery. Edited by Kenneth B. Sloan. Marcel Dekker, New York and Basel, 1992, 313 pp.

The book represents a complete overview with minimal overlap among various chapters. The editor has done a remarkable job in putting together the fundamental physicochemical properties of prodrugs and their dermal and ocular transport characteristics. The chapter authors demonstrate considerable expertise in their respective areas. The primary focus relates to the application of bioreversible modification of active drugs for enhanced dermal, transdermal, and ocular permeation. The volume contains seven chapters, beginning with the mechanisms of dermal and transdermal absorption and continuing with the practical aspects of prodrug development and applications.

Chapter 1 opens the book with a brief overview of the mechanisms of topical, dermal and transdermal drug delivery. A brief discussion of the routes of transdermal mass transfer is followed by a discussion of the physicochemical variables that are relevant to stratum corneum permeability, including lipophilicity, molecular weight and volume, and solubilities in vehicle and membrane biophase.

An exhaustive review of the prodrug approaches that have been utilized in an attempt to optimize dermal and transdermal topical delivery of compounds is presented in Chapter 2. The functional groups amenable to prodrug derivatization are examined. The author organizes the remainder of the chapter into various functional groups and further divides this into the promoieties that have been used with these functional groups. Numerous experimental results are given for each functional group/promoiety discussed. The interested reader would be forced to sift through dozens of review articles to acquire the information organized in this chapter.

Chapters 3 through 5 describe different mathematical and empirical models of transdermal flux useful in optimizing topical delivery. Chapter 3 explores the modeling of drug flux taking into consideration the effect of molecular size, lipophilicity, and solubility. The thermodynamic contribution of functional groups to the permeability of compounds is also explored. This chapter offers experimental support for the models developed and concludes by detailing the experiments utilized to optimize the topical dermal delivery of various nonsteroidal antiinflammant drugs using the prodrug approach. Chapter four compares the utility and predictive value of four models used to describe the transdermal flux of a compound. The experimentally determined flux of 50 compounds are compared to the flux values obtained from the predictive models. A method for utilization of these models to optimize the dermal and transdermal flux of a compound concludes this chapter. Chapter 5 deals with the use of solution theory, theoretically derived solute and solvent activity coefficients, and calculated vehicle/membrane partition coefficients to yield theoretical permeability coefficients for partitioning-driven processes. The author addresses membrane permeability in general, then follows this with discussions on dermal delivery, transdermal delivery, and the use of prodrug modifications. The method of calculating permeability coefficients from theoretically derived activity coefficients in this manner and the extrapolation of these permeability coefficients to multiple vehicles are then discussed.

Chapter 6 provides an interesting caveat to the use of prodrugs in the dermal and transdermal delivery of drugs. Rather than taking an overly enthusiastic stance on the utility of prodrugs, the author examines the success of actual cases of drug absorption enhancement involving the use of prodrugs. While in many cases the permeability coefficient of a compound is increased, the flux and, hence, absorption are only marginally affected. This chapter provides many practical examples and discusses the failure of prodrug approach in greatly increasing the net flux of a compound. The variables influencing the transdermal flux of a compound, solubility, oil/water partition coefficient, and enzymatic hydrolysis are discussed. The chapter details some of the factors that must be overcome if prodrug technology is to be successful as theoretically suggested.

The volume concludes with a chapter on topical ocular drug delivery. The constraints and barriers unique to ocular drug delivery are outlined. The authors present the formulation, physicochemical, and physiologic considerations of corneal drug absorption. The prodrug approaches that have been used to date to enhance corneal absorption are reviewed. Other methodologies commonly used to optimize the ocular delivery of drugs are also discussed.

The stated goal of this work is to organize the abundance of literature available on prodrugs into one concise, well-referenced volume. The book presents the theoretical and practical aspects of prodrug derivatization to enhance topically administered drugs. This work is complete enough to be a valuable reference to researchers involved with prodrugs as well as anyone interested in topical drug delivery. To this end, the book fulfills its stated objectives.

Ashim K. Mitra
Department of Industrial and Physical Pharmacy
School of Pharmacy and Pharmacal Sciences
Purdue University
West Lafayette, Indiana 47907-1336

Protein Folding. Edited by Thomas E. Creighton. W. H. Freeman, New York, 1992, xv + 547 pp., ISBN 0-7167-7027-x, $59.95 (hardback).

Our knowledge of how and why polypeptides fold into specific shapes has progressed a very long way from the early studies by Anfinsen on the denaturation and renaturation of RNase A. The book in hand is an excellent summary of the current state of knowledge in protein folding from the point of view of biophysical chemists.

The book is a collection of chapters on individual topics in protein folding, each chapter written by one or two experts in that area. A masterly introductory chapter by Rich-

0724-8741/93/1200-1812$07.00/0

ards gives an overview of the field, with a brief but critical review of kinetic and thermodynamic models and results. This is followed by chapters on (1) protein structures, (2) the thermodynamics of protein stability, (3) theoretical (i.e., computer-based) modeling of the thermodynamics and kinetics of folding, (4) the details of experimental kinetics of folding, (5) the very interesting topic of "molten globules" and their role as intermediates in folding, (6) the use and role of disulfide bonds in folding studies, (7) the application of modern genetic tools to study the effects of mutations on folding, (8) a summary of the folding and association of large, multidomain proteins, and (9) the cell biology involved in protein synthesis and folding.

The breadth of topics covered here is quite good. The major biophysical chemistry areas of concern are reviewed, and I commend the editor for including the chapter on protein folding *in vivo* as a useful counterbalance to the otherwise heavy physical chemical content of the book.

There are occasionally some lapses in depth of coverage. For example, the chapter by Karplus and Shakhnovich on theoretical modeling of protein folding does not discuss electrostatic interactions to any appreciable extent. One must go to the chapter on mutational analysis of folding to find references to current work in this area. The treatment of the hydrophobic interaction is long on phenomenology, especially in the chapter by Privalov on folding thermodynamics and in the chapter by Ptitsyn on molten globules, though short on a good but simple mechanistic explanation. Apparently the hydrophobic effect *still* is not that well understood. A topic virtually ignored in this book is the folding of membrane-bound proteins, certainly an area of interest to anyone involved in medicinal chemistry, pharmacology, toxicology, etc. One hopes that this is more a result of the lack of progress in this area than an oversight by the editor.

On the other hand, there is an excellent introduction to the molten globule model, a detailed summary of the role of disulfide bonds in folding, and a very complete discussion of the kinetics of single-domain protein folding. The chapter on the folding of multidomain proteins limits its discussion to a few archetypal systems, many of which may not be as familiar to the reader as, for example, aspartate transcarbamoylase. The limited choice, however, serves the author's purpose well in developing a common framework for understanding the overall folding process.

The book's index seems complete and useful. It does not include the names of cited authors. Instead, literature citations appear at the end of each chapter. The literature cited is as current as may reasonably be expected (up through 1991; the editor does manage to cite an article from 1992!). Overlap among the various chapters is kept to a minimum.

In summary, this book emphasizes the biophysical chemistry of protein folding, it is current, and it is authoritative. It is highly recommended to readers with a strong physical chemical background, but not as an introduction to the subject.

Charles P. Woodbury, Jr.
Department of Medicinal Chemistry and Pharmacognosy
University of Illinois at Chicago
Chicago, Illinois 60612