Book Reviews

Oral Drug Absorption: Prediction and Assessment, Drugs and the Pharmaceutical Sciences, Volume 106, Jennifer B. Dressman and Hans Lennernäs, Eds., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 1006-0602, http://www.dekker.com/, 2000, x, 330 pp., illustrations, $165.00.

This book contains a nice summary of methods to assess and characterize drug release from dosage forms and in vitro and in vivo drug absorption. An additional aspect is the prediction of absorption from in silico and in vitro data and the correlation between in vitro and in vivo data. The book is divided into 16 chapters related to gastrointestinal variables, membrane permeability, solubility and drug dissolution and in vivo–in vitro correlations. The book is well illustrated with figures and each chapter has a series of adequate references.

In the section of gastrointestinal variables an overview is given of the various absorption and retention sites in the GI-tract and the importance of the time of dosing is stressed particularly with respect to absorption under fasting and non-fasting conditions. The permeability of the GI-tract in patients is studied with a perfusion technique using the Loc-I-Gut technique. The influence of dosage form performance and GI-diseases is discussed with respect to malabsorption, maldigestion and Crohn's and celiac disease, AIDS enteropathy, systemic diseases, drug- and irradiation induced malabsorption, aging and surgery.

Membrane permeability is characterized by calculated and experimental molecular properties culminating into Lipinsky' rules of five. In addition, the correlation between log-D and absorption data obtained in epithelial cell culture systems and animal models is discussed. Further biological in vitro methods for the assessment of permeability are summarized and discussed with respect to predictability of in vivo absorption. Perfusion techniques in animals to assess drug absorption are extensively reviewed and discussed particularly with respect to regional factors influencing drug absorption and the influence of efflux transporters and drug metabolism.

In an additional chapter human perfusion of the GI-tract with the Loc-I-Gut system is described and illustrated with several examples indicating its applicability in studying drug absorption. The role of permeability studies in preclinical evaluation is stressed particularly with respect to the time and place in drug development and discovery screens. This is illustrated with some case histories.

Solubility and drug dissolution is treated in 5 chapters. In the first solubility is studied as a limiting factor in drug absorption. Starting from the biopharmaceutics classification system a theoretical approach is described and correlated with human permeability data. The application of micellar systems in oral drug absorption is discussed and briefly in vitro–in vivo correlation. A subsequent chapter discusses extensively the dissolution testing of immediate release products and its predictability for in vivo. Many examples are given including suggestions for the proper choice of equipment. In a next chapter the dissolution testing and its physiological relevance of extended release systems is treated with respect to in vitro–in vivo correlations, the biopharmaceutics classification system and the influence of post-approval changes and food effects, while in a subsequent chapter the place of dissolution testing in the development of oral drug products is discussed and illustrated with case examples including the prediction of food effects. Analysis of dissolution data is extensively treated including multipoint assessment of dissolution characteristics by moment analysis and according to the Noyes-Witney and the semi-emperical Weibul approach. Comparison of dissolution profiles is discussed including the prediction of in vivo profiles.

The last part of the book describes in vitro–in vivo correlations. Convolution and deconvolution techniques including mass balance, direct numerical methods, transformation methods, least squares methods, maximum entropy methods and constrained direct sequential estimation with iterative improvement. A subsequent chapter describes the in vitro–in vivo correlation of dissolution profiles and residences times by the statistical moment method and by a point-by-point comparison between in vitro drug dissolution data and the in vivo profile obtained by deconvolution. Examples are given to illustrate both methods. The last chapter describes a useful approach to implement and apply in vitro–in vivo correlation methodology based on statistical moments and deconvolution.

The overall feeling of this book is that it contains a comprehensive and state of the art number of methods and procedures to test in vitro and in vivo drug dissolution and absorption and its correlation and the in vivo prediction from in vitro data. The book is a must for people who start in this area of research but is also very suitable and convenient as a reference.

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Circular Dichroism Principles and Applications, Second Edition, Nina Berova, Koji Nakanishi, and Robert W. Woody, Eds., John Wiley & Sons, Inc., 605 Third Avenue, New York, NY 10158-0012, 2000, xix, 877 pp., illustrations, $195.00.

Circular dichroism (CD) is a classic spectroscopic technique that examines the symmetry of chromophores in the molecule of interest. This text covers topics related to CD ranging from the theoretical basis for optical activity to the application of CD to the development of molecules of phar-

0724-8741/01/0400-0551$19.50/0

maceutical importance. The use of CD to study inorganic complexes, polymers, peptides, proteins, DNA, nucleic acids is discussed. Several chapters are devoted to emerging techniques related to circular dichroism, including vibrational circular dichroism (VCD) and Raman Optical Activity (ROA).

With such a breadth of topics covered, I found that not all of the chapters were relevant for all readers. The theoretical discussions were fairly high level, and a reader without an extensive background in either quantum mechanics or group theory could easily be lost. While some of the analogies used in the introductory chapter do help the reader to visualize asymmetry, the text quickly jumps to a mathematical discussion of the spectroscopic techniques that can leave the reader behind if he does not have the background knowledge in this.

Despite my reservations regarding the theoretical discussions, there are several chapters that I believe the readers of *Pharmaceutical Research* would find very useful. The chapter on circular dichroism of peptides and proteins by Sreerama and Woody is exceptionally well written and discusses several of the programs used to calculate the secondary structure fractions of proteins. Contact information to obtain these programs is provided in this section. The chapter by Brittain on the application of CD to the study of pharmaceutically relevant molecules discusses three areas in which CD may aid drug development, including the use to study the interaction of drugs with serum proteins. A discussion of HPLC-CD by Salvadori, Di Bari, and Pescitelli demonstrates the strength of the use of a polarimeter in conjunction with a UV detector in the analysis of chiral molecules during chromatographic separation. Chapters on the related techniques of VCD and ROA serve to educate the reader about how these techniques may supplement knowledge gained from traditional vibrational spectroscopic methodologies and CD.

Overall, this book serves as an excellent resource for information regarding circular dichroism. It should not be considered as a text from which to learn the basic technique, but rather a source to learn more than is typically covered in books on this subject.

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Good Manufacturing Practices for Pharmaceuticals, Fifth Edition, Revised and Expanded, Drugs and the Pharmaceutical Sciences Series, Volume 109, Sidney H. Willig, Ed., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 1006-0602, http://www.dekker.com/, 2001, xii, 732 pp., illustrations, $135.00.

The fifth edition of *Good Manufacturing Practices for Pharmaceuticals* has been expanded in certain areas and compressed in others because of the considerable material that has been used in prior editions. This edition brings further insights into the multi-national activities of various manufacturers. The text contains guidelines that address the many factors and also includes questions that the reader may want to analyze in detail. The audience for this reference is broad. It involves personnel from those operations manufacturing pharmaceuticals as well as information for private and independent inspection personnel, local and state inspection agencies and quality assurance organizations contracted by distributors. It also emphasizes the growing role of pharmacists in whatever their capacity may be to apply elements of quality control. It is noted that the CGMPs for pharmaceuticals addresses the quality issue from the foundation element that is adulteration of pharmaceuticals.

The text begins with an analysis of the status of U.S. regulations as far as the CGMPs are concerned in the manufacturing processing, packaging and holding of drugs. Chapter 1 reviews the many elements to establish this status which can be drawn from Section 210.1 of the regulations. This chapter discusses the various definitions that appear in this section of the regulations and clearly sets the stage for moving on further into the regulations. Chapter 2 clearly defines the status of finished pharmaceuticals and the CGMPs. It considers all facets of drug products being marketed within the United States as well as elements involving medical devices.

Suitable references are given for individuals who need more information about the device area. Chapter 3, as before, completely outlines the organization and personnel requirements as established by the regulations. Clear information is given to establish the rules. Chapters 4–10 establish all of the necessary information needed to proceed with compliance to the regulations. This goes from buildings and facilities on through all of the necessary control documents that one must have for compliance to the regulations. Each of these chapters are well documented as to what is required of the regulations and those necessary bits of information one would need to follow through as far as compliance or to understand what the regulations are about. The explanations as far as batch production control records and other records are clearly discussed and give full information as to what is needed. Chapter 11 concerns complaint files and what is necessary to have them in compliance. In this chapter examples of observations from FDA 483 citations are given.

A section is given on returned and salvaged drug products. It is necessary to clearly understand what is required by law and to suitably comply. Chapter 13 discusses repackaging and relabeling giving clear-cut information including policies that must be followed to comply with the CGMPs. Suitable labeling instructions are also given in this particular chapter. Of importance is a section on bulk pharmaceutical chemicals. In recent years there has been emphasis on the CGMPs in this particular area and this chapter outlines not only U.S. requirements but European requirements for bulk pharmaceutical chemicals. Chapter 15 discusses the pharmacy and total quality control. It gives information that can be used to instill upon the practitioner his or her role in maintaining total quality control of pharmaceuticals either in community practice or in the hospital. It also emphasizes the impact that the pharmacist will have on total quality control. Additional information concerning recalls, control substances, safeguards, inspection procedure for compliance and a very informative section involving the FDA and its preapproval inspection/investigations. Other GMPs are discussed later in the text. An important appendix is Appendix A that is a discussion of the FDA Modernization Act of 1997. This gives all the elements

that are in that particular act and the expectations that Congress has with this particular revision.

This text is an invaluable text for anyone involved with current good manufacturing practices. It would be an excellent text for use in any course on the regulations. It is an outstanding resource and would help any individual or student learn the application of the CGMPs.

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Medicine Quest: In Search of Nature's Healing Secrets, Mark J. Plotkin, Ed., Penguin Putnam Inc., 375 Hudson Street, New York NY 10014, 2000, xvi. 224 pp., illustrations, $22.95.

In this interesting book, ethnobotanist Mark Plotkin takes the reader on an extensive tour of the numerous drugs already in use, and those that presently show promise, from plants and animals. The tour is both detailed and comprehensive. After two introductory chapters, Plotkin reviews the drugs, potential drugs, and various medical uses of fungi, insects and arachnids, leeches and maggots, snakes, cone snails, sponges, and coral. He goes on to discuss the medicinal use of plants by chimpanzees and other animals, and concludes with a chapter on the role of shamans. In the latter, he describes his participation in a ceremony featuring the consumption of the hallucinogenic beverage, ayahuasca. Some of his tales are very familiar—Fleming's discovery of penicillin; others are much less so—Toto Olivera's discovery of conotoxins in cone snails. Occasionally, Plotkin uses suspense as a tool to keep the reader reading. He notes on page 5 that poison dart frogs raised in captivity contained no toxic epibatidine but does not explain why this is so until page 162. (The most likely explanation is that the poisons are sequestered in the animals from a component of their diet, possibly insects.)

Obviously written for laypersons, the author intentionally misuses the term antibiotic to describe all antimicrobial agents (not just those obtained from microorganisms) and omits many, not all, of the Latin scientific binomials that would precisely define the species being discussed. Such misuses and omissions will prove bothersome to readers with scientific backgrounds. The scientific names could have been included in an appendix if the author and/or his editor thought they might prove distracting to some of the readership if included in the text. The book is relatively error free, but once in a while the author nods. Felix Hoffman did not synthesize acetylsalicylic acid in 1897. Credit for that belongs to Von Gerhardt in 1853. Actually, Hoffman simply took the chemical from a shelf at Bayer to treat his father's rheumatism when his stomach could no longer tolerate sodium salicylate, thus discovering aspirin's beneficial effect for that condition. In discussing snakes and medicine, Plotkin notes that the symbol of medicine, the caduceus, is derived from the symbol of Hermes (Mercury), the winged messenger of the gods. He fails to note that Mercury was also the patron thieves and merchants. He also overlooks completely the bowl of Hygeia, the daughter of Asclepius, with its accompanying sacred serpent. It has become one of the universal symbols of pharmacy. Warfarin was not renamed Coumadin. The former retains its generic status; the latter is simply a tradename.

In his concluding chapter, the author argues that herbs and dietary supplements will prove to be an integral part of the new Western healing tradition but notes that environmental degradation and destruction pose major threats to the discovery of new drugs from nature. I agree with both these conclusions. I do wish he had taken the time to write a few more pages explaining why it is that so few of the scores of potential medicines that he has identified so well in his book have ever been approved as drugs by the Food and Drug Administration and entered into widespread use in mainline medical practice. Aside from the antibiotics, there is only a handful of approved natural medicines of post-World War II vintage. The reasons are well-known to scientists—patent problems, supply problems of raw materials, the mind-set of synthetic organic chemists, current enamourment with combinational chemistry and high throughput screening, which to date have yielded few positive results—the list could go on and on. But Plotkin's book is written for laypersons, and it would have been useful to explain these problems to those readers. I think it would also have been appropriate to note that about 25% of the prescriptions filled in 1991 contained one or more natural drug products. And even more important, the fact that almost all the synthetic drugs sold today are based on natural product prototypes. So I believe that the author missed a golden opportunity to supplement the tales of the discovery of natural drugs, which he does very well indeed, with an explanation to laypersons of the stumbling blocks involved in taking these products from the jungle and the oceans into mainstream medical use.

The book is well pointed in easily readable Aldus type on acid-free paper, but the pages have so-called perfect, that is, glued binding. That means the pages will come loose from the hard cover long before the paper deteriorates. Illustrations are found on the first page of every chapter. I highly recommend Mark Plotkin's book as an interesting and comprehensive story of the search for new drugs from nature. It belongs in the library of everyone interested in this fascinating subject.

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Handbook of Pharmaceutical Controlled Release Technology, Donald L. Wise, Ed., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016, 212-696-9000, http://www.dekker.com, 2000, x, 890 pp., illustrations, $225.00.

This book consists of 42 chapters that are categorized into 6 parts, such as polymers, mechanisms, particulate systems, administration sites, peptides and proteins, and medical applications of or for controlled release. Several constituting chapters of some parts are not strictly classified based on

above categories. The chapters are either extensive review contributions or summary of the research experiences of a specific subject from contributing authors' research groups. Current controlled release technologies are well classified and their overview is presented with brief description of commercial products in Chapter 22.

The book begins with pharmaceutically important polymers for oral and parenteral controlled delivery formulations, including cellulose derivatives, poly(vinyl alcohol), acrylic polymers, complexing polymers and biodegradable polylactide, polyglycolide and their copolymers. This part describes some material properties of the polymers that are critical for controlled release and is extended to governing mechanisms of drug release of diffusion-, and swelling-, and dissolution-controlled release with mathematical descriptions. The second part of mechanism-based classification of controlled release devices provides the details of swelling controlled systems, osmotic pumps, superporous hydrogels as an oral delivery platform, and bioadhesive polymers. The third part for micro- and nanoparticulate release system (9 chapters) covers particulate fabrication technologies, including interfacial polymerization, coacervation/phase separation, and solvent evaporation methods, with biodegradable and nondegradable synthetic polymers, polysaccharides and solid lipids. However, polymeric micelles and liposomes, which are another important carrier for controlled release and targeting, are missing. The partial characterization and applications of particulate systems to cancer therapy, solubilization of poorly soluble drugs, drug stability issue in the PLGA particles are described in relevant chapters.

The part for classification of controlled release devices according to administration site summarizes oral and transdermal delivery systems with the emphasis on recent research trends, especially in transdermal system such as electrically and ultrasonically assisted delivery with enhancer technology. Transmucosal delivery routes other than oral administration and parenteral routes are not included in this part, but rather scattered throughout the book. Four chapters describe peptide and protein release systems with an overview of the protein stability issue in controlled release formulations and some applications to tissue engineering (growth factor release) and cancer treatment (IL-2 release). The subject is one of the most important future developments of biopharmaceutical delivery. The last part of this book (medical application of delivery system) is attributed to recent technologies of asymmetric membrane-coated osmotic delivery, biodegradable polymer formulations for pain management, birth-control, the treatment of opioid addiction, and biodegradable bone cement with bioactive agents. The last chapter of this book gives us a brief pharmacoeconomic value of controlled release formulations.

This book does not seem to be a true handbook of every controlled delivery technology, although many chapters provide handbook-quality information for specific controlled release technologies. While the book's organization is not ideal, it covers many important aspects of controlled release formulations and recent trends to provide informative reference sources for those pharmaceutical scientists with limited background in developing polymeric controlled release formulations. The book is also useful for graduate students who wish to have an overview of controlled release technology with information on commercially successful controlled release products.

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Tumor Suppressor Genes in Human Cancer, David E. Fisher, Ed., Humana Press, 999 Riverview Drive, Suite 208, Totowa, NJ 07512, http://www.humanapress.com, 2001, xii, 386 pp., illustrations, $125.00.

Many anticancer agents are developed by screening a number of chemical compounds, but the efficacy of such drugs is sometimes diminished because of the concomitant cytotoxicity in normal cells. To overcome this painful situation, genomics and proteomics, such as DNA microarray and analytical mass spectrometry, are defined as unique and powerful technologies to identify cancer-specific gene expression profiles. However, as most proteins are post-translationally modified, gene expression profile and functional analysis of proteins should complement each other to better understand the pathways by which cells become cancerous.

Since the discoveries of p53 and Rb tumor suppressors, basic cancer research has tremendously improved our understanding on cell proliferation, differentiation and even programmed cell death in cancer. In the book, Dr. David Fisher and spirited scientists representative in the field have summarized the mechanistic bases of divergent roles of tumor suppressors in cell growth regulation and introduced loss of tumor suppressors by a number of reasons, such as point mutation, gene deletion and transcriptional inactivation. They highlighted the promising link of mechanistic understanding of tumor suppressor pathways to the improved application in cancer chemotherapy. One of the most important objective of basic cancer research is to develop and establish a mechanism-based strategy to selectively eradicate cancer. This monograph can serve as a compact and contemporary source of fundamental knowledge of tumor suppressor-dependent biological functions, such as apoptotic cell death, which is potentially applicable for the design of new anticancer drugs.

This book is separated into two parts: general remarks of tumor suppressor functions in Part I, which allows the readers to gain general ideas about tumor suppressor pathways, and itemized discussions of each tumor suppressor pathway in Part II. In addition to the general discussions about tumor suppressors in Part I, Dr. Allex Matter has provided a unique and informative resource entitled "Drug Discovery in Oncology." It very effectively guided the reader to novel integrated strategies of drug discovery that combine chemistry, biophysics, molecular cell biology and computational mechanical technologies. This book is highly recommended for senior-level pharmacy and medical students who are interested in cancer cell biology, carcinogenesis and clinical oncology. I also found it more than satisfactory for basic laboratory researchers, registered pharmacists and medical oncologists who are working in this exciting and rapidly moving research

area, where the discovery of a cancer-specific cytotoxic drug may be achieved in the near future.

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Books Received

Molecular Biology

DNA Topoisomerase Protocols: Enzymology and Drugs. Methods in Molecular Biology Volume 95, Neil Osheroff and Mary-Ann Bjornsti, Eds., Humana Press, 999 Riverview Drive, Suite 208, Totowa, NJ 07512, http://www.humanapress.com, 2001, xvi, 333 pp., illustrations, $79.50.

Amino Acid Analysis Protocols. Methods in Molecular Biology, Volume 159, Catherine Cooper, Nicolle Packer, Keith Williams, Eds., Humana Press, 999 Riverview Drive, Suite 208, Totowa, NJ 07512, http://www.humanapress.com, 2000, xi, 265 pp., illustrations, $84.50.

Polymers

Adhesion Promotion Techniques: Technological Applications, Materials Engineering Series Volume 14, K. L. Mittal and A. Pizzi, Eds., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 1006-0602, http://www.dekker.com/, 1999, ix, 403 pp., illustrations, $195.00.

Development and Manufacture Pressure-Sensitive Products, István Benedek, Ed., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 1006-0602. http://www.dekker.com/, 1999, viii, 682 pp., illustrations, $195.00.

Handbook of Elastomers, Second Edition, Revised and Expanded, Plastics Engineering Series Volume 61, Anil K. Bhowmick and Howard L. Stephens, Eds., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 1006-0602, http://www.dekker.com/, 2001, xii, 922 pp., illustrations, $250.00.

Others

Pharmaceutical Innovation: Revolutionizing Human Health, Ralph Landau, Basil Achilladelis and Alexander Scriabine, Eds., Chemical Heritage Foundation, 315 Chestnut Street, Philadelphia, PA 19106-2702, http://www.chemheritage.org, 1999, xxiii, 409 pp., illustrations, $44.95.

Billmeyer and Saltzman's Principles of Color Technology, Third Edition, Roy A. Berns, John Wiley & Sons, Inc., 605 Third Avenue, New York, NY 10158-0012, 2000, ix, 247 pp., illustrations, $99.95.

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