Sustained-Release Injectable Products

Edited by

Judy Senior
Michael Radomsky

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Preface

Sustained-release versions of drugs are an essential part of the formulations repertoire of the Pharmaceutical Scientist in the new millennium. Many important products in this field originated as pioneering research in academic institutions. A critical component of their becoming successful products is the science of pharmaceutical formulation development and the subsequent drug development process, fuelled by the efforts of the industry to satisfy clinical needs.

The scientific work of drug development conducted by companies is largely unpublished partly because publishing is not a priority, especially when regulatory submissions are underway. We are therefore especially privileged to collect together in this volume contributions by excellent scientists who day-to-day nurture drugs through the delicate process of drug development as it applies to sustained-release drug delivery.

Why should the development process for a sustained-release version of a drug be different from its unmodified counterpart? While some aspects of the process may appear similar, there are important differences. This volume illustrates answers by using examples of current types of sustained-release systems

for local injectable applications. Taking it one step further, the second half of the book brings together common threads of scientific aspects that apply to any sustained-release formulation of a pharmaceutical product, such as the scale-up, safety, biocompatibility, analytical challenges, quality assurance, and specific regulatory factors.

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This volume would not have been possible without the generous contributions of the valiant authors, who energetically, patiently, and conscientiously stuck with the process of writing, editing, proofing, and indexing, amid many other pressing priorities.

Judy Senior would especially like to thank her parents, David and Elisabeth Whitehead. They lovingly gave me the tools of discipline, patience, and determination, encouraging me to take my passion for life and turn my dreams into reality. Also my friends and advisors, especially Pramod Gupta, Robert I. Pinsker, Francis Cannon, Paige Lucetti, Ann Thevenin, Pat Drago, András Gruber, Hal Handley, Gregory Gregoriadis, Deborah A. Eppstein, and my colleagues at Syntex, SkyePharma (formerly DepoTech), and Maxim Pharmaceuticals.

Michael Radomsky would like to thank Greg Allen, Andrea Thompson, Bob Spiro, Bach Phan, Junghae Scott, Lynda Sanders, Larry Zeitlin, and Kevin Whaley for their manuscript reviews, technical expertise, and stimulating and encouraging discussions. I am very grateful that I have worked with a number of bright and energetic scientists at Syntex, Orquest, and now Epicyte; these professional and sometimes personal relationships have helped me grow as both a scientist and a human being. Finally, I would also like to thank my parents for their lifelong support and encouragement during both the productive and difficult chapters in my life.

We both would like to thank Dr. Gupta, whose initial sparks ignited this volume. Dr. Radomsky is also grateful that Dr. Senior took the initiative to get him involved in this project. We are also indebted to many small companies that inspire the industry with their innovation, speed to market, and nurturing of employees.

They are where much of the work described in this volume was promulgated.

Finally, we would both like to thank Amy Davis for taking on the initial book idea and Jane Steinmann and Liz Prigge for their expert guidance during the process of realizing the book and bringing it to the attention of readers around the world. We look forward to offering the knowledge and experience collected in this volume for the benefit of a worldwide audience to advance the goal of having effective therapies available sooner through the timely development of effective drugs that reduce suffering in the twenty-first century and beyond.

Judy Senior
Michael Radomsky
January 2000

Contributors

Judy H. Senior, Editor

Dr. Judy Senior is a specialist in drug delivery and drug development cycle management. Over the past 16 years, she has published widely in the fields of liposomes and lipid-based drug delivery systems. Dr. Senior received her BSc in biochemistry from the University of East Anglia and her PhD in drug delivery from the University of London. In 1989, she began to develop liposome-based drug formulations at Syntex Corporation (now Roche Bioscience), where she subsequently gained broad experience in the drug development process with a wide variety of drugs, dosage forms, and delivery systems. In 1993, Dr. Senior joined DepoTech Corporation (now SkyePharma plc) as project leader and later project manager for the company's development programs. Currently at Maxim Pharmaceuticals, Dr. Senior is developing delivery systems for the Maxamine™ and MaxDerm™ family of products. Dr. Senior is active in the AAPS Western Regional planning committee and in a local San Diego pharmaceutical discussion group. She is also a regular scientific contributor in the field of controlled-release and sustained-release technologies.

Michael Radomsky, Editor

Dr. Michael Radomsky is a project leader at Epicyte Pharmaceuticals, Inc. He received his BS in chemical engineering from the Rose Hulman Institute of Technology in 1987 and a PhD in 1991 from The Johns Hopkins University. From 1991 to 1995, he was a staff researcher at Syntex Inc. (now Roche Bioscience) in the Drug Delivery Research and Formulation Development departments. As senior scientist at Orquest from 1995 to 1999, he developed products for the local delivery of proteins in orthopaedic applications. At Epicyte, he is working with transgenic plants to produce antibodies for disease treatment and prevention. His multidisciplinary research interests have included sustained- and controlled-release pharmaceuticals, polymers for controlled drug delivery, mathematical modeling of drug transport and drug delivery systems, design of delivery systems for peptide and protein drugs, local drug delivery, tissue engineering, and antibody technology.

Paul Burke

Dr. Paul Burke received his BS in chemistry from Harvey Mudd College in 1986 and his PhD from MIT in 1992. He is presently laboratory head of sustained-release pharmaceutics at Amgen. From 1993 to 1997, Dr. Burke designed microsphere formulations of several protein therapeutics and antisense oligonucleotides for Alkermes. He coinvented a multiweek formulation of erythropoietin (currently undergoing clinical testing) and developed a patented cryogenic encapsulation process. In addition to protein microencapsulation, his research interests include the characterization of controlled-release systems using magnetic resonance spectroscopy.

Geneva Chen

Dr. Geneva Chen received her BS in chemistry in 1988 from Beijing United University and her PhD in pharmaceutics from the University of Houston in 1995. Dr. Chen was formerly employed by Aronex Pharmaceuticals, Inc., as a research scientist and

served as a postdoctoral research associate at the University of Houston. She has also served as pharmacokinetics lecturer at the University of Houston. Dr. Chen is author and coauthor of many technical articles.

Daan J. A. Crommelin

Professor Daan Crommelin received a degree in pharmacy from the University of Groningen in 1975 and a PhD from the University of Leiden in 1979. After serving as a postdoctoral fellow with Prof. W. I. Higuchi at the University of Michigan, he became full professor and head of the Department of Pharmaceutics in 1984. In 1992, he became managing scientific director of the Utrecht Institute for Pharmaceutical Sciences (UIPS) and in 1993 deputy managing director of the Groningen Utrecht Institute for Drug Exploration (GUIDE). Also in 1993, he was appointed adjunct professor in the Department of Pharmaceutics and Pharmaceutical Chemistry at the University of Utah. In 1995, he became scientific director of OctoPlus, BV, a company focused on providing pharmaceutical formulation know-how. He has published over 200 original articles, reviews, and book chapters. He has served as either an editor or on the editorial advisory board of numerous pharmaceutical journals. He is a fellow of the American Association of Pharmaceutical Sciences (AAPS). He was winner of the Maurice-Marie Janot award in 1995 and received the International Award of the Belgian Society of Pharmaceutical Sciences in 1997. He is involved in organizing meetings in the fields of biopharmaceutics, drug targeting, and the development of biotechnological products all over the world.

Richard L. Dunn

Dr. Richard Dunn received his BS in chemistry from the University of North Carolina and his PhD in organic/polymer chemistry from the University of Florida. He then joined the Beaunit Corporation, synthesizing and characterizing nylon, polyester, polypropylene, and viscose polymers into high-performance and specialty fibers. In 1979, Dr. Dunn joined the Applied Sciences

Department of the Southern Research Institute (Birmingham, Ala.), directing multidisciplinary programs in polymer chemistry; polymer engineering; biomaterials; biomedical engineering; membrane development; and controlled release of biologically active agents from fibers, film, and devices, especially those fabricated from biodegradable polymers.

In 1987, Dr. Dunn joined Vipont Research Laboratories, Inc. (now Atrix Laboratories), and directed the development of a local antibiotic delivery product for the treatment of periodontal disease and a biodegradable barrier membrane for periodontal tissue regeneration. Dr. Dunn invented the in situ polymer system that is used in these projects. Currently, as senior vice president, he is responsible for managing projects involving a proprietary biodegradable polymer system (Atrigel®) for use as a medical device or to deliver biologically active agents. Current applications include the prevention of surgical adhesions and the delivery of local anesthetics to relieve postoperative pain, antineoplastic agents for treating solid tumor cancers, LHRH peptides for prostate cancer, and growth factors for tissue regeneration.

Alexander Florence

Dr. Alexander (Sandy) Florence holds a BSc in pharmacy and a PhD from the University of Glasgow and a DSc from Strathclyde. Dr. Florence is currently dean and professor of pharmacy at the School of Pharmacy, University of London. Prior to this appointment in 1989, he was professor of pharmaceutics at the University of Strathclyde. He has published several textbooks as well as authoring over 230 papers, chapters, and reviews in the area of drug delivery and surfactant and polymer systems.

Maninder Hora

Dr. Maninder Hora received his PhD in 1980 in bioengineering (materials) and was a Fulbright Scholar from 1979 to 1981. Dr. Hora's industrial research experience includes positions at Ayerst-Wyeth Laboratories and SmithKline Beecham Laboratories. He joined the Chiron Corporation in 1986 and became senior director of Pharmaceutical R&D in 1997. His research

interests and experiences encompass the fields of pharmaceutical drug delivery and formulation development. He has approximately 30 publications, 15 patents, and numerous presentations at national and international meetings to his credit. He is a member of the Controlled Release Society (CRS), the American Association of Pharmaceutical Scientists (AAPS), and the American Chemical Society (ACS).

Kunio Kawamura

Dr. Kunio Kawamura received his PhD in pharmaceuticals from the University of Tokyo in 1959. His career at Takeda Chemical Industries includes managing the Quality Control Department in Osaka, directing corporate quality assurance, and managing (as deputy general manager) the Production Department. As project leader for Lupron Depot®, a sustained-release injectable dosage form, he was responsible for the development and construction of the production facility.

As an advisor to the World Health Organization (WHO), Dr. Kawamura helped draft the WHO GMP. He also served on the board of directors of the Parenteral Drug Association (PDA) from 1994 to 1996. Since 1995, as a special advisor for Otsuka Pharmaceutical Co., Ltd., he has been responsible for worldwide GMP–associated technical and regulatory affairs. Dr. Kawamura is also an accreditation auditor for the Japan Accreditation Board for Conformity Assessment.

Joseph Kost

Dr. Joseph Kost completed all of his educational training at the Israel Institute of Technology, receiving a BS in 1973, an MSc in chemical engineering in 1975, and a DSc in biomedical engineering in 1981. Dr. Kost was the head of the Center for Biomedical Engineering at Ben Gurion University from 1988 to 1993 and head of the Program for Biotechnology from 1993 to 1995. He is currently professor of Chemical Engineering at Ben Gurion University and Chief Scientific Officer of Sontra Medical USA. He serves on the editorial boards of several journals and has published 3 books, 23 book chapters, 57 papers, 120 abstracts, and 25 patents, principally in the area of biomaterials. In

1996, Dr. Kost was awarded the Juludan Prize by the Israel Institute of Technology for outstanding scientific research achievements. Dr. Kost was also awarded the Clemson Award by the Society for Biomaterials in recognition of his outstanding contributions to applied biomaterials research.

Johanna K. Lang

Dr. Johanna Lang received her PhD degree in chemistry from the University of Graz, Austria, in 1982. After completing postdoctoral research in biochemistry at the University of Graz and the University of California, Berkeley, she pursued an industrial career in start-up companies in the United States and Germany. In 1987, she joined Liposome Technology, Inc. As head of the assay development group, she designed and implemented release, stability, and bioanalytical assays for the company's key products, Doxil® (liposomal doxorubicin) and Amphocil® (liposomal amphotericin B), now marketed by Abbott Laboratories. From 1993 to 1996, at Pharmacylics, Inc., Dr. Lang directed formulation development, assay development, and GMP manufacturing for a line of synthetic porphyrin-type lanthanide complexes, now in advanced clinical testing for photodymanic therapy of cancer and heart disease. Subsequently, she was Director of Product Development for IDEA GmbH in Munich, Germany. In 1999, Dr. Lang became an independent consultant based in Fremont, California. She is a member of the San Francisco Bay Area Biomedical Consultant's Network and the American Association of Pharmaceutical Scientists (AAPS). She served on organizing committees for AAPS meetings and chaired the Northern California Pharmaceutical Discussion Group (NCPDG).

Jung-Chung Lee

Dr. Jung-Chung Lee received his MS in 1980 and his PhD in 1983 in pharmaceutical chemistry from the University of Kansas. Starting in 1984, Dr. Lee worked in formulation development at Syntex, Roche, and Oread Labs and became director of Pharmaceutical Development at Cytel in 1997. Dr. Lee has been involved in conventional and controlled-release dosage form design and development in both human and veterinary

pharmaceuticals for over 15 years and is currently director of Pharmaceutical Development at Cellegy Pharmaceuticals, Inc. Dr. Lee is a member of the American Association of Pharmaceutical Scientists (AAPS) and the Controlled Release Society (CRS).

LinShu Liu

Dr. LinShu Liu received his BS in 1976 from South China Normal University (Guang Zhou, China), his MSc in polymer chemistry in 1982 from South China Normal University, and his PhD in polymer chemistry in 1990 from Kyoto University (Japan). From 1990 to 1992, Dr. Liu was as a postdoctoral associate with Professor R. Langer at MIT (Cambridge, Mass.). Dr. Liu is a coeditor of 1 book and author or coauthor of 2 book chapters, 21 papers, 45 abstracts, and 6 patents; most of these publications are in the area of biomaterials and the controlled release of drugs.

Natalie McClure

Dr. Natalie McClure received her PhD in organic chemistry from Stanford University and is presently vice president of Regulatory Affairs and Quality Assurance at Matrix Pharmaceutical, Inc. With over 12 years of experience in regulatory affairs, she has experience in all stages of the regulatory process, from pre-IND to postmarketing support. Before branching out into regulatory affairs, Dr. McClure was a process development chemist at Syntex Research.

Sudaxshina Murdan

Dr. Sudaxshina Murdan received a BPharm from the University of Nottingham and was appointed lecturer in pharmaceutics at the School of Pharmacy, University of London, in 1998, following a brief postdoctoral fellowship with Professor A. T. Florence after earning a PhD from the same school. Her current research interests include organogels, amphiphilogels, inverse vesicles and responsive systems for drug delivery, and transdermal immunization. Dr. Murdan is a member of the Royal Pharmaceutical Society of Great Britain, the American Association of

Pharmaceutical Scientists (AAPS), the European Federation of Pharmaceutical Scientists, and the Controlled Release Society (CRS).

Christien Oussoren

Dr. Oussoren studied pharmacy in Utrecht and graduated in 1990. After a short stint as a pharmacist, she began research and obtained her PhD from the University of Utrecht in 1996. In January 1997, she was appointed a faculty member at the University of Utrecht. Her main research interests are in the field of biodistribution and in vivo application of colloidal drug carrier systems.

Leo Pavliv

Mr. Leo Pavliv is a registered pharmacist and received an MBA from Rutgers University. He has 15 years of experience in developing pharmaceutical and biological products, including small molecules, proteins, and peptides in a variety of dosage forms. He has managed the development process of products from preformulation, formulation, and scale-up through manufacturing. He established a clinical supplies group, which was responsible for the manufacturing, packaging, labeling, and distribution of clinical supplies. He has also designed, equipped, and managed a GMP–compliant clinical manufacturing facility.

Michael L. Putnam

Dr. Michael Putnam received his RPh BPhS from the University of Iowa in 1982 and a PhD in pharmaceutics from the same school. For 13 years, he has been involved in veterinary product research and development. Dr. Putnam is currently director of Pharmaceutical Development, Analytical Services, and Technical Services at Fort Dodge Animal Health.

Scott Putney

Dr. Scott Putney received his PhD and postdoctoral training from MIT. He is presently group leader in protein engineering at Lilly Research Laboratories. From 1991 to 1998, he was vice president of protein and molecular biology at Alkermes, Inc., where he led the effort to develop a sustained-release formulation of human growth hormone now awaiting marketing approval from the FDA. From 1983 to 1991, he was vice president of molecular biology at RepliGen Corporation, where he led an effort to develop a vaccine for HIV-1.

Ramachandran Radhakrishnan

Dr. Ramachandran Radhakrishnan received his PhD from Wayne State University in Detroit, Michigan, and was a postdoctoral fellow for 8 years in the laboratory of Dr. H. G. Khorana at MIT, studying lipid-lipid and lipid-protein interactions in biomembranes. As senior scientist at Liposome Technology, Inc., he was responsible for developing liposomal formulations for ocular, inhalational, and parenteral applications. He has been with Chiron Corporation for the past 8 years, dealing with the formulation and delivery of recombinant proteins, vaccines, and genes. He is affiliated with the American Society for Gene Therapy and the American Association of Pharmaceutical Scientists (AAPS). He has authored or coauthored over 40 publications and 12 patents.

Gary Riley

Dr. Gary Riley received his BVS from Sydney University in 1965, an MVS from the University of Melbourne in 1970, and a PhD in comparative pathology from the University of Missouri in 1972. He is a diplomate of the American College of Veterinary Pathologists and the American Board of Toxicology. From 1975 to 1981, Dr. Riley was associate professor of veterinary pathology at Iowa State University. He worked as an experimental pathologist from 1982 to 1993, first in contract research and later as director of Pathobiology at the Medical Research Division of

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Mantripragada B. Sankaram

Dr. Mantripragada Sankaram has a BS and an MS in chemistry and a PhD in molecular biophysics from the Indian Institute of Science. From 1985 to 1989, he was an Alexander von Humboldt and Max Planck fellow at the Max Planck Institute for Biophysical Chemistry in Goettingen, Germany, working on membrane structure and lipid-protein interactions. From 1989 to 1994, he was an assistant professor in biochemistry at the University of Virginia School of Medicine, where he further expanded his research to domains in biological membranes and the interaction of peptides, proteins, and cholesterol with membranes. He held several scientific and management positions at DepoTech Corporation from 1992 to 1999 and was involved in the development of sustained-release injectable products. Currently he directs the Research and Analytical Development departments at SkyePharma plc and is engaged in the research and development of novel drug delivery systems for sustained release. He is a member of the American Association for the Advancement of Science (AAAS), the American Association of Pharmaceutical Scientists (AAPS), the American Chemical Society (ACS), the Biophysical Society, and the Controlled Release Society (CRG).

Gert Storm

Dr. Gert Storm studied biology at the University of Utrecht and received his PhD in 1987. His research interest is in the field of drug targeting. From September 1988 until June 1989, he was a visiting scientist at Liposome Technology Inc. (Menlo Park, Calif.) and visiting assistant professor at the School of Pharmacy, Dept of Pharmaceutics, University of California, San Francisco. From February 1990 until September 1991, he was senior research scientist at Pharma Bio-research Consultancy BV in

Zuidlaren, where he contributed to the design, coordination, and evaluation of clinical pharmacological studies. Dr. Storm has published over 120 original articles, reviews, and book chapters and is involved in organizing conferences in the field of advanced drug delivery. He is member of the editorial advisory board of two journals, acts as a consultant to a number of pharmaceutical companies, and teaches "Liposome Technology", a course organized by the Center for Professional Advancement.

Art Tipton

Dr. Art Tipton received his BS in chemistry from Spring Hill College (Mobile, Ala.) in 1980 and then worked for 3 years at the Southern Research Institute. At the University of Massachusetts, he received his PhD in polymer science and engineering in 1988 and subsequently worked at Atrix Laboratories as a senior polymer scientist and manager of the Polymer Science Department prior to joining Southern BioSystems and Birmingham Polymers in 1993. Dr. Tipton's experience includes research and development at the preclinical and clinical stages as well as the scale-up and manufacture of final products. His research interests include human and veterinary delivery from biodegradable systems, the synthesis of novel biodegradable materials, and systems that function as both medical devices and controlled-delivery matrices. Dr. Tipton holds 16 U.S. patents, numerous corresponding foreign equivalents, and has more than 40 publications in the area of controlled release and biomaterials. In addition to overseeing the executive direction of Birmingham Polymers, Dr. Tipton has participated in the development and introduction of three commercial products. He is a member of the American Chemical Society (ACS), the American Association of Pharmaceutical Scientists (AAPS), the Controlled Release Society (CRS), and the Society for Biomaterials.

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Dr. Steven Tuck received his BSc in chemistry from Imperial College, University of London in 1983 and his PhD in physical–organic chemistry from the same school in 1986, where he studied the endogenous nitrosation of gastric secretions.