ADVANCES IN POLYMERIC BIOMATERIALS SERIES

Absorbable and Biodegradable Polymers

Shalaby W. Shalaby
Karen J.L. Burg

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Preface

For the past two decades, the fast-growing interest in synthetic absorbable polymers has lured most authors to focus on this family of polymers while practically ignoring biodegradable materials of natural origin. Revival of interest in natural polymers by contemporary investigators compelled the editors of this volume to develop it in a form that provides integrated accounts of most of the recent developments not only in synthetic absorbable polymers but also in biodegradable polymers of natural origin. Hence, the theme of this volume is based on the fact that technology of absorbable/biodegradable polymers (A/BP) has evolved in two independent areas which need to be treated in an integrated manner because of their common end use in clinical applications.

The evolution of natural polymers takes place through chain modification of existing materials, mostly by using chemical means to impart certain physical and/or functional properties. Meanwhile, the evolution of synthetic A/BP has been achieved through modulating their chemical composition using different polymerization schemes and, to a lesser extent, chemical modification of presynthesized polymers. In concert with this theme, the book begins with an introduction (Section A) to prepare the reader for the three main sections (B, C, and D) comprising 15 chapters which are based mostly on evolutionary materials developments, processing methods, and characterization/evaluation methods, as well as clinical and newly sought applications that have become available over the past decade. Section B deals with development and applications of new systems. Section C pertains to development in preparative, processing, and evaluation methods. Section D addresses growing and newly sought applications.

It is to be emphasized that the diverse topics presented in this book are integrated in such a fashion as to yield a coherent source of diverse but interrelated information for use by scientists, engineers, and clinicians who are interested in the use of A/BP in pharmaceutical and biomedical applications. The clinical components of the book are prepared by clinicians who are also well-versed scientists to maximize the effectiveness of integrating clinical with preclinical information.

The editors express gratitude to all contributors for their highly informative chapters on cutting-edge technologies and their enthusiastic response to making contributions to the book. The comprehensive nature of the chapters and their extensive biographies will make this volume a valuable source well-suited for use by students, industrialists, and educators with interest in development and/or investigation of A/BP for use in pharmaceutical and biomedical applications.

Acknowledgment

The editors express their gratitude to Dr. Joanne E. Shalaby of Poly-Med, Inc., for her guidance and valuable contributions during the compilation and integration of the diverse segments of the book.

The Editors

Shalaby W. Shalaby is currently president and director of R&D at Poly-Med, Inc., Anderson, South Carolina. After completing his undergraduate training in chemistry and botany as well as pharmacy in Egypt at Ain Shams University and Cairo University, he enrolled at the University of Massachusetts at Lowell to complete his graduate studies toward an M.S. degree in textiles, a Ph.D. in chemistry, and a second Ph.D. in polymer science. Following the completion of his graduate training, 2 years of teaching, and a postdoctoral assignment, Dr. Shalaby spent four years as a senior research chemist at Allied Signal, Polymer Research Group. Subsequently, he joined Ethicon/Johnson & Johnson to start an exploratory group on polymers for biomedical applications, with some focus on new absorbable and radiation-sterilizable polymers. Before joining Clemson University in the summer of 1990, Dr. Shalaby headed the Johnson & Johnson Polymer Technology Center. Dr. Shalaby's previous research activities pertained to the molecular design of polymeric systems with a major focus on biomedical and pharmaceutical applications. At Clemson University, Dr. Shalaby's research activities addressed primarily the molecular and engineering design of bioabsorbable systems, high performance composites, radio-stabilization of polymers, and new aspects of radiation processing. He has supervised or cosupervised 30 M.S. and Ph.D. thesis projects. After joining United States Surgical Corporation in 1993 as a corporate research scientist/senior director, Dr. Shalaby directed his efforts toward the establishment of new R&D programs pertinent to surgical and allied products and assessment of new product opportunities through technology acquisition. In late 1994, Shalaby directed his industrial efforts, as president of Poly-Med, Inc., toward focused R&D of polymeric materials for biomedical and pharmaceutical applications. Since 1994, he has been an adjunct or visiting professor at four universities. He has over 100 patents and 250 publications, including eight books.

Karen J. L. Burg earned a B.S. in chemical engineering with a minor in biochemical engineering from North Carolina State University in 1990, an M.S. in bioengineering from Clemson University in 1992, and a Ph.D. in bioengineering with a minor in experimental statistics from Clemson University in 1996. She completed a tissue engineering postdoctoral research fellowship in 1998 at Carolinas Medical Center in Charlotte, North Carolina, and is currently associate professor of bioengineering at Clemson University and an adjunct research faculty member at Carolinas Medical Center.

Professional affiliations include membership in Sigma Xi, Society for Biomaterials, Tissue Engineering Society, and American Institute of Chemical

Engineers; she also serves on the ASTM Tissue Engineering Standards Development Committee.

Awards include the 2001 National Science Foundation Faculty Early Career Award, 2001 Clemson University Board of Trustees Award for Faculty Excellence, 2001 Presidential Early Career Award for Scientists and Engineers, and 2003 Clemson University Outstanding Woman Faculty Award.

Among her research interests are the optimization of absorbable biomaterials processing for tissue engineering applications, application of magnetic resonance imaging in tissue engineering, development of absorbable composites for orthopedic and soft tissue applications, surface modulation of absorbable implants to enhance biocompatibility, and evaluation of physicochemical changes in absorbing systems.

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Section A

Introduction Notes

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Absorbable/Biodegradable Polymers: Technology Evolution

Shalaby W. Shalaby and Karen J.L. Burg

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1.1 Introduction

Egyptians sutured wounds as early as 3500 B.C. using a variety of natural polymers including treated intestines, which are the early versions of collagen-based surgical gut sutures.[1] Synthetic, absorbable polyesters based on

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2-hydroxyacetic acids were developed for preparing less tissue reactive alternatives to surgical gut sutures in the early 1970s. In addition to collagen-based polymers, other natural, absorbable polymers, such as albumin, chitosan, and hyaluronic acid and derivatives thereof have been used for many pharmaceutical and biomedical applications for several decades.[2] Of these polymers, the application of chitosan and hyaluronic acid–based polymers has received a great deal of attention in the past 15 years for use in controlled drug delivery systems, tissue repair, tissue engineering, and controlling certain biological events.

1.2 Technology Evolution of Absorbable/Biodegradable Polymers as Materials

Technology of absorbable/biodegradable polymers (A/BP) has evolved in two independent areas. The evolution of natural polymers took place through chain modification of existing materials using chemical means or modulating the biosynthetic process for fermentation to impart certain physical and/or functional properties. On the other hand, the evolution of synthetic A/BP has been achieved through modulating their chemical composition using several polymerization techniques and, to a lesser extent, chemical modification of presynthesized polymers.

1.2.1 Evolution of Natural Absorbable/Biodegradable Polymers

Evolution and development of absorbable/biodegradable polysaccharides was associated mostly with chitosan and hyaluronic acid. Chitosan is among the most important members of the absorbable/biodegradable polymer family. It is a partially deacetylated chitin where 70 to 90% of the monosaccharide sequences carry free amino groups and the balance is retained with its original acetamido side groups. Most of the research to develop novel A/BP products was directed to reaction of the chain amine and/or hydroxyl groups.[2] In an interesting approach to developing absorbable drug delivery systems, Shalaby and co-workers acylated chitosan with mono- and dicarboxylic acids, anhydrides and conjugated the carboxylated products with bioactive amine-bearing oligopeptides.[3,4]

Hyaluronic acid is a naturally occurring polysaccharide comprising monosaccharide sequences with carboxylic or acetamido side groups. Early production of hyaluronic acid, a biodegradable polymer similar to chitosan, was achieved through extraction of natural tissues, and the evolution of hyaluronic acid technology was made possible after its successful production in sufficient quantities as a fermentation product.[2] The key evolution of

hyaluronic acid technology commenced with its chemical modification and crosslinking.[2] These entailed:

- Esterification with monohydric alcohol to improve its film-forming properties and lower its solubility
- Reaction with basic drugs to control their release profiles
- Crosslinking to produce water-swellable systems as surgical implants

Evolution in the development of proteins for novel pharmaceutical and biomedical applications was directed towards the modification of:

- Collagen to decrease its hydrophilicity by acylation with long chain alkyl-substituted succinic anhydrides
- Insulin to increase its iontophoretic mobility and bioavailability as part of a transdermal delivery system by acylation with succinic anhydride, or to improve its enzymatic stability by acylation with certain fatty acid anhydrides
- Epidermal growth factor (EGF) to improve its enzymatic stability and hence bioavailability by acylation with fatty acid anhydrides[5–11]

Bacterial polyhydroxyalkanoates (PHA) are among the most important biodegradable polymers produced via biosynthesis.[12] Initial production of the PHA was focused on poly(2-hydroxybutyrate) (PHB). However, the high melting temperature and crystallinity of PHB prompted the evolutionary development of copolymers having about 15 to 20% of the chain sequences as 2-hydroxyvalerate through controlling the composition of the feed during the fermentation process. The resulting copolyesters (PHBV) were suggested to have more suitable properties for conversion by traditional processing techniques into biomedical devices.

1.2.2 Evolution of Synthetic Absorbable/Biodegradable Polymers

Interest in synthetic absorbable polymers has grown considerably over the past three decades, principally because of their transient nature when used as biomedical implants or drug carriers. The genesis of absorbable polymers was driven by the need to replace the highly tissue-reactive, absorbable, collagen-based sutures with synthetic polymers, which elicit milder tissue response. This led to the early development of polyglycolide as an absorbable polyester suture. In spite of the many polymeric systems investigated as candidates for absorbable implants and drug carriers, ester-based polymers maintain an almost absolute dominance among clinically used systems and others that are under investigation.

In addition to ester-based polyesters, a great deal of research activity has been directed to other types of absorbable polymers, but the clinical relevance of their properties practically halted their evolution beyond the exploratory phase. Typical examples of these polymers have been covered in a review by Shalaby and include those based on polyanhydrides, polyorthoesters, polyphosphazenes, and certain polyamidoesters.[13]

With the development of absorbable cyanoacrylate systems, the classification of synthetic, absorbable polymers into the traditional heterochain polymers (e.g., polyesters and polyanhydrides) and less-conventional homochain polymers (e.g., cyanoacrylate polymers) became inevitable.[14–16] Meanwhile, since ester-based systems are most important among both the heterochain- and homochain-type synthetic, absorbable polymers, they are given special attention in this chapter.

1.2.2.1 Heterochain Ester-Based Absorbable Synthetic Polymers

Detailed accounts of this class of absorbable polymers were a subject of a review by Shalaby and Johnson.[17] The review dealt with:

- Polymerization of lactones such as glycolide (G), *l*-lactide (LL), *dl*-lactide (DL-L), *p*-dioxanone (PD), trimethylene carbonate (TMC), ε-caprolactone (CL), 1,5 dioxepan-2-one (DOX), glycosalicylate (GS), morpholine-2,5-dione (MD)
- Polyalkylene oxalates and their isomorphic copolymers
- Polyoxamates
- Partially aromatic, segmented glycolide copolymers

The authors discussed briefly what were then considered as new trends. These included:

- Segmented copolymers as low modulus materials comprising polymeric CL or TMC soft segments
- Fast-absorbing polylactones containing MD-based sequences
- Segmented copolyester as hydrophilic substrates based on end-grafted polyethylene glycol (PEG)
- Polymeric prodrugs including those containing GS-based sequences
- Radiation-sterilizable, segmented copolyester made by end-grafting radiostable aromatic prepolymers with glycolide
- The early use of polyglycolide and 90/10 G/LL copolymer in braided forms as scaffolds for tissue engineering

Over the past 8 years, impressive advances have been made toward the development of new absorbable systems for novel or improved applications