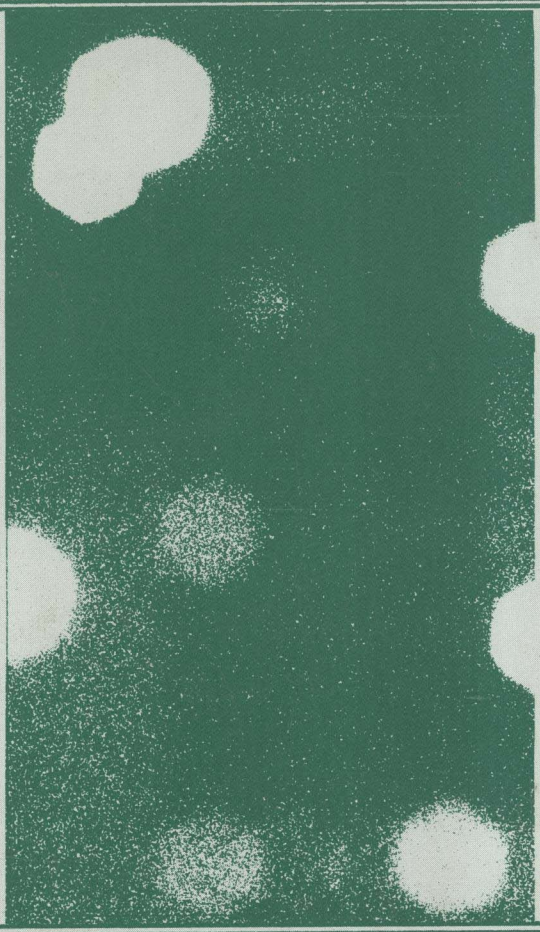
POLYMER SCIENCE AND TECHNOLOGY • VOLUME 38

Edited by
Charles G. Gebelein,
Charles E. Carraher, Jr., and Van R. Foster



APPLIED BIOACTIVE POLYMERIC MATERIALS

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PLENUM PRESS • NEW YORK AND LONDON

Library of Congress Cataloging in Publication Data

ACS Symposium on Applied Bioactive Polymeric Materials (1987: New Orleans, La.)
Applied bioactive polymeric materials / edited by Charles G. Gebelein, Charles E. Carraher, Jr., and Van R. Foster.
p. cm.—(Polymer science and technology; v. 38)
"Proceedings of an ACS Symposium on Applied Bioactive Polymeric Materials, held August 30–September 2, 1987, in New Orleans, Louisiana."
Includes bibliographical references and index.
ISBN 0-306-43101-7
1. Biopolymers—Congresses. 2. Drugs—Dosage forms—Congresses. 3. Biopolymers—Physiological effect—Congresses. 4. Biopolymers in medicine—Congresses. I. Gebelein, Charles G. II. Carraher, Charles E. III. Foster, Van R. IV. Title. V. Series.
RS201.B56 27 1987 88-39216
615'.19—dc19 CIP

Proceedings of an ACS Symposium on Applied Bioactive Polymeric Materials, held August 30–September 2, 1987, in New Orleans, Louisiana

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PREFACE

The biological and biomedical applications of polymeric materials have increased greatly in the past few years. This book will detail some, but not all, of these recent developments. There would not be enough space in this book to cover, even lightly, all of the major advances that have occurred. Some earlier books and summaries are available by two of this book's Editors (Gebelein & Carraher) and these should be consulted for additional information. The books are: "*Bioactive Polymeric Systems*" (Plenum, 1985); "*Polymeric Materials In Medication*" (Plenum, 1985); "*Biological Activities of Polymers*" (American Chemical Society, 1982). Of these three, "*Bioactive Polymeric Systems*" should be the most useful to a person who is new to this field because it only contains review articles written at an introductory level. The present book primarily consists of recent research results and applications, with only a few review or summary articles.

Bioactive polymeric materials have existed from the creation of life itself. Many firmly believe that life could not even exist unless polymeric materials are used to form the basic building blocks. Although this assumption can not be rigorously proven, it is a fact that most, if not all, of the major biochemical pathways involve polymeric species, such as the proteins (including enzymes), polysaccharides and nucleic acids. Among the many reasons for this fact, must be the observation that the natural polymeric materials can be made into an enormous variety of *different*, but inter-related, species. It is now well established that a DNA chain, which only contains four different primary repeating units, can encode an enormous wealth of data permitting not only the replication processes, but protein synthesis and the entire life scheme as well.

It is not surprising, therefore, that many of the applications of bioactive polymeric systems involve interactions with the natural polymeric materials. Likewise, the use of many natural polymers as the base materials for these bioactive systems can hardly be considered a surprise. They are not only readily available, they are also normally more biocompatible and/or biodegradable than the usual synthetic polymer. This book contains several chapters in which natural polymers are the main theme, but there are far more chapters which involve synthetic polymeric materials. There is probably a place for either type of material in the vast realms of biological and/or biomedical applications.

Historically, the earliest "man-made" bioactive polymeric systems utilized a natural polymer (or a modification) in some manner. The advent of the totally synthetic polymers is a more recent innovation. Like many things, however, this pattern appears to be cyclic and we are seeing a renewed interest in the use of natural polymers. This is due, in part, to the perceived need to use renewable resources and, in part, to the desire

to eliminate non-biodegradable materials from the environment, whether that environment is medical or biological.

The twenty three chapters of this book largely are concerned with biomedical considerations. This too is a quirk of history; much of the original impetus for the bioactive polymer research was aimed at agricultural applications. Unfortunately, these important applications could not bear the increased cost of the polymeric materials, regardless of whether they were significantly better or not. In the long run, however, many of the pressing environmental concerns may mandate the utilization of bioactive polymeric systems. Fortunately, much of the technology is about the same. A controlled release system could be readily tailored to release a drug or a herbicide. A bioactive polymer could be designed to interact with either the human environment or the biosphere. In short, the knowledge and technology reported herein could be a harbinger of many unexpected future applications.

The design of this book is simple. Chapter 1 (Gebelein, Carraher & Foster) is a summarizing overview of the field and includes several applications not otherwise covered in the book. Chapter 2 (Kurtz & Hassett) considers the use of polymers in pest control, while Chapter 3 (Hirano, et al.) describes the use of chitin and its derivatives as a plant growth activator. Chapters 4 (DiBenedetto, et al.) and 5 (Wang) consider controlled release systems from biodegradable polymers, while Chapter 6 (Pitt, et al.) describes the metal-mediated controlled release of chelating agents. Chapters 7 (Gettings & White) and 8 (Jansen, et al.) cover the release of anti-microbial agents from different types of polymeric systems. Chapter 7 is also mainly concerned with some non-medical applications of this technology. Chapters 9 (Ghosh) and 10 (Kesler) are concerned with bioactive polymeric systems that contain steroidal sex hormones in completely different ways.

The next seven Chapters involve polymers with potential anti-tumor and other medicinal properties. Chapter 11 (Carraher & Strothers) deals with the release of methotrexate and/or chloroplatinate while Chapter 12 (Gebelein, et al.) describes the release of 5-fluorouracil from a biodegradable polymer. Chapter 13 (Matsuzaki, et al.) reviews much research on polysaccharides that have anti-tumor properties, and this theme is enhanced in Chapter 14 (Carraher, et al.) which describes tin-modified polysaccharides. The use of nucleic acid analogs in chromatography is the main theme of Chapter 15 (Inaki, et al.), but these same materials also have potential anti-tumor properties. Poly(ICLC), Chapter 16 (Levy & Bever) is also a nucleic acid analog with some anti-tumor potential. Finally, Chapter 17 (Trombley, et al.) covers polymers with anti-tumor and other medical properties.

Chapter 18 (Singh & Gaber) describes research on polymers that can form bioactive bilayers. Chapters 19-22 report various types of grafted polymers with varied potential medical applications. Thus, Chapter 19 (Daly & Lee) covers grafts of poly(amino acids) onto various proteins while Chapter 20 (Dworjanyn & Garnett) reports on research showing how to prepare grafts using radiation and/or photochemical methods. Chapters 21 and 22 are concerned with preparing anti-thrombogenic polymeric surfaces. In Chapter 21 (Wrobelski, et al.) this is attempted by the modification of poly(methyl methacrylate) with poly(vinylpyrrolidone), which had once been used as a blood plasma extender. In Chapter 22 (Chandy & Sharma) the approach is to graft thrombus lyzing agents or thrombo-resistant proteins onto the polymer surface. The books closes with Chapter 23 (Yannas, et al.) which updates important research on burn wound treatment using collagen modifications which interact with the natural body tissues. This paper by I. V. Yannas was given the Doolittle Award by the Division of

Polymeric Materials: Science & Engineering as the best paper presented in the Division at the American Chemical Society National Meeting, New Orleans, August, 1987.

This is a rapidly changing area of research and new developments will no doubt change some of the conclusions reported in these chapters, but much of this research will ultimately lead to many new applications of polymers in the biological and/or biomedical environments, both of which are of considerable practical human importance. The Editors wish to thank the American Chemical Society Division of Polymeric Materials: Science and Engineering who sponsored the symposium from which this book was derived. Likewise, we wish to thank the individual authors whose excellent research has made this book the challenging volume that it is. Finally, we wish to thank our wives, families and/or friends for their help and patience while we were bring this book into existence. This book was word-processed by CG ENTERPRISES.

Charles G. Gebelein
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CONTENTS

OVERVIEW OF SYNTHETIC AND MODIFIED NATURAL BIOACTIVE POLYMERS

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The area of applied bioactive polymeric systems includes such diverse entities as controlled release systems (erodable systems, diffusion controlled systems, mechanical systems and microcapsules), and biologically active polymers, such as natural polymers, synthetic polypeptides, pseudo-enzymes, pseudo-nucleic acids and polymeric drugs. The area can also include immobilized bioactive materials, such as immobilized enzymes, antibodies and other bioactive agents and the area of artificial cells. This Chapter reviews the general field of biologically active synthetic and modified natural macromolecules with an emphasis on their common characteristics, problems and applications. The areas reviewed include both medical and non-medical applications for both controlled release systems and polymers that exhibit direct biological activity.

INTRODUCTION

Many synthetic and natural macromolecules have some biological activity, although often inhibitory or toxic in nature. This well known biological activity of natural proteins (including enzymes), nucleic acids and polysaccharides actually forms the basis for both plant and animal life. While some material applications require a lack of biological activity (such as prosthetic hip joints, protective coatings), other applications require at least some biological activity (e.g., biodegradable materials, which generally require sensitivity to radiation, moisture, air and/or microorganisms; controlled drug release).[1-3] This Chapter concentrates on biologically active synthetic and modified natural macromolecules.

BIOACTIVITY DEFINITION

In this paper, bioactivity will be considered to be the interaction of some chemical agent on a biological system. Examples of bioactivity would include: (1) the action of a drug on a disease center, (2) the action of a herbicide on weeds, (3) the action of an insecticide on insects, and (4) the prevention of conception by a chemical agent. In this sense, an applied bioactive polymeric system is one that utilizes any kind of polymeric material in producing, enhancing or controlling bioactivity.

TYPES OF BIOACTIVE POLYMERS

Many distinctively different types of bioactive polymeric systems exist and some of these are summarized in Table 1. For convenience, these are divided into the three classes of (1) controlled release systems,

Table 1. Classes of bioactive polymeric systems.

CONTROLLED RELEASE SYSTEMS
erodible systems. diffusion controlled systems: a. reservoir b. monolithic mechanical devices. microcapsules.
BIOLOGICALLY ACTIVE POLYMERS
Natural Polymers:
proteins enzymes polysaccharides nucleic acids
Synthetic Polymers:
modified polypeptides enzyme-mimetic polymers nucleic acid analogs polymeric drugs polymeric herbicides polymeric pesticides
IMMOBILIZED OR ENCAPSULATED BIOACTIVE MATERIALS
living cells hemoglobin enzymes hormones antigens antibodies chloroplasts mitochondria plant growth regulators

(2) biologically active polymers, and (3) immobilized or encapsulated bioactive materials. The potential applications of the biologically active polymers are far too numerous to list exhaustively. Some of the applications are summarized in Table 2. It should be noted that any given application could be accomplished by more than one type of bioactive system, and vise versa. For example, cancer might be treated using controlled release systems, bioactive polymers or bound enzymes.

MODIFIED NATURAL BIOACTIVE MACROMOLECULES

Natural polymers have been widely employed as the polymeric matrix for controlled release systems and as a carrier for other bioactive agents. Part of this wide usage is due to three factors. First, the natural macromolecules themselves may exhibit biological activity that could be utilized to make a modified system more specific.[4-7] Second, depending on the specific natural macromolecule, the polymer may exhibit greater biological acceptance or rejection, such as in synthetic skin applications.[8] Third, most biological macromolecules are biodegradable allowing an avenue for controlled release and moderating unwanted concentration buildups.[9] (Controlled release is discussed in the next section.) Synthetic polymers have been used as the carriers in most drug delivery systems, which were designed to be inert and nondegradable, employing diffusion as the primary factor regulating the drug release.[10,11] The study of biodegradable systems is of more recent origin and with added difficulties - namely, specified rates of degradation and biocompatability of the degradation products. Such biodegradable systems have also been referred to as bioerodible and bio-absorbable drug delivery systems.

Poly(lactic acid), PLA, was first described in the literature in 1913 and was reported in 1966 as a material suitable for use in biodegradable surgical implants.[12] The first description of the use of PLA as a biodegradable implant for the delivery of the narcotic antagonists cyclazocine, naltrexone and naloxone was made by Yolles and coworkers in 1971.[13,14] Shortly afterwards, this polymer was tried in a contraceptive system.[15] Following the investigations with PLA, additional hydroxy-containing polypeptides were investigated. Poly(glycolic acid), PGA, has been widely used in surgical sutures, and copolymers of PLA and PGA have been used in delivery systems for drugs, insecticides and fertilizers. Various other copolymers of PLA, PGA, polyamides and polyesters have been synthesized and investigated as delivery systems.[16-19] Bio-lifetimes can be varied from several weeks to over a year.

CONTROLLED RELEASE SYSTEMS

A controlled release system is one which regulates or controls the release of some type of biologically active agent. Most, but not all, of these systems involve some type of polymeric material to restrict the concentration of this agent within a fairly narrow concentration range in order to elicit the desired bioactivity without the potentially dangerous side effects of the agent. Many examples of this behavior can be found in nature. For example, some complex polypeptides release a controlled amount of a subsection of the polypeptide which has some specific biological activity, and this is controlled by the body's chemistry.[20] Recently, hundreds of synthetic polypeptides have been developed, and many have shown biological activity.[5,21,22] Often these polypeptides have been mimics of those that occur naturally.

The basic concepts of controlled release systems will be considered below under the headings: (a) erodable systems, (b) diffusion controlled

systems, (c) mechanical systems, and (d) microcapsules. In all cases considered, a polymeric material is used to regulate the bioactive agent.[23,24]

Erodable Systems

An erodable system contains the biologically active agent within some polymeric system which will dissolve or be destroyed by the biological media in which it is placed. Among the oldest medical examples are the

Table 2. Applications of biologically active polymers.

MEDICAL	cancer treatment disease treatment transplants blood replacement contraception control narcotic control
AGRICHEMICAL	mildew control rust & rot control pest control weed control plant growth regulation seed coating
VETERINARIAN	livestock protection pets protection wild animal control
WOOD PRESERVATION	fungus prevention color protection pest control
FOOD PROCESSING	enhanced yields better preservation flavor enhancement coloring
HOME USES	pest control insect control rodent control mildew control furniture preservation food preservation

enteric coated drugs in which a drug is protected from the stomach fluids and enzymes by a polymer which is then hydrolyzed in the intestines releasing the drug agent. In a similar manner, copper salts have been placed within natural, biodegradable polymers and have controlled barnacles adhering to ships.[25] More recent examples include timed-release capsules for cold and/or headache remedies. The polymers that have been used in this approach include polyacetals, polyesters, poly(orthoesters), polysaccharides, polypeptides and polyketals. The most commonly used synthetic polymers are the poly(lactic acids) and poly(glycolic acids), and their copolymers. Possibly the chief advantage of these systems is that the polymeric material is usually biodegradable and would not have to be removed from a patient. In addition to the enteric coatings and the timed-release capsules, erodable systems have been explored in drug addiction control, contraception, cancer treatment and a wide variety of drug release systems.[10,19,26-28]

Diffusion Controlled Systems

There are two basic types of diffusion controlled systems: (a) the reservior (depot) and (b) the monolithic. Most examples have used a non-degradable polymer, such as poly(dimethyl siloxane), natural or synthetic rubber, a vinyl polymer, or an acrylic polymer, although some examples of devices based on biodegradable polymers have been reported. The release rate of the bioactive agent normally follows first order kinetics in the reservior system, but is proportional to the square root of time in the monolithic systems (Higuchi kinetics). In either case, the specific rates are dependent on the composition of this polymeric material and on the chemical nature of the bioactive agent. In both systems, the release rate shows a steady decrease with time. Both systems usually give a high initial release of the active agent which is termed a "burst effect".[10,11,29,30]

The design of biodegradable implant devices based on PLA and PGA, noted earlier, have been mainly limited to reservoir types where the drug, in suspension or crystalline state, is sealed within a polymeric capsule so that the rate of release is regulated by diffusion characteristics. Another approach involves the use of poly(α-amino acids) in which the drug is encapsulated in polymeric shells, intermixed with the polymer, or covalently bound to the polymer backbone.[31-34]

The difussion based systems have found a variety of non-medical applications such as flea repellant collars, insecticide releasing strips and several agricultural applications. Some medical uses include the release of pilocarpine from a ethylene-vinyl acetate copolymer (Ocusert^{R}, Alza Corp.) for the control of glaucoma, and the release of progesterone from the same polymer to control fertility (Progestasert^{R}, Alza Corp.). Diffusion systems have also been utilized to release narcotic antagonists and anti-cancer agents.[35-38] Although most of the early examples of this technology were non-medical, nearly all of the recent emphasis has been in the medical areas. One of major areas of medically related activity is in fertility control and several potential systems are currently in advanced clinical trials, often funded by the World Health Organization. The controlled release of birth control agents has been reviewed recently.[39]

Mechanical Devices

A mechanical device would be one that utilizes any form of control, other than direct diffusion or erosion, to regulate the release of the

biologicaly active agent. This catagory includes pumps and extracorporeal devices as well as osmotic pressure powered devices and transdermal membrane systems. Ordinary intravenous devices would also be included under this heading, but will not be considered further.

A number of external or internal pumps have been developed as insulin infusion pumps, or an artificial pancreas, which gives a more precise control over the body's insulin level. These devices normally inject the insulin solution directly into the patient's blood. Many of these "artificial pancreas" devices are able to vary the rate of insulin administration, and much progress has been made to couple these pumps with a microprocessor controlled glucose sensor which would closely approximate normal pancreatic activity. Most of these infusion pumps utilize poly-(dimethylsiloxane).[40,41]

Many devices currently on the medical market are simply a solution of a drug agent enclosed within a semi-permeable membrane. These systems have been reviewed recently.[42,43] Several of these devices operate by allowing water to diffuse into the drug-containing chamber and the diluted solution is forced out through a small orifice by the osmotic pressure that develops. The Oros^{R} System (Alza Corp.) is an example.[35,36,44] Some other recent developments include the use of magnetic fields to moderate drug release.[45]

Transdermal patches, which utilize a semi-permeable membrane to regulate the release of a drug directly through the skin into a specified region of the body, have been developed for the administration of nitroglycerine (for treating angina pectoris) and scopolamine (for treating motion sickness).[35,36,42,46,47]

Microcapsules

A microcapsule is a minature membrane system in which the combination of high permeability and large surface area can confer some unusual properties and have made microcapsules of interest for drug release systems and for some artificial organs. Hundreds of different materials have been enclosed within microcapsules for both biomedical and non-medical use. The classic non-medical example would be the carbonless "carbon" papers which are in wide use today. Medically, microcapsules have been used to enclose various enzymes, such as catalase or L-asparaginase (which can be used to treat some forms of cancer), and have been shown to maintain the enzymatic activity for prolonged time periods.[48-50] Microcapsules have been utilized as artificial cells to enclose the beta-cells from the Islets of Langerhans, and such a system can function as a source of insulin (artificial pancreas).[51-55] Other research has centered on the use of such devices for artificial red blood cells.[56]

Market for Controlled Release

At this time, the market for controlled release systems is about \$2.16 x 10^{9}/year and is growing with an expected market in excess of \$3.80 billion by 1991. At the present time, 51% of the controlled release market consists of pharmaceutical and related applications and this is projected to increase to about 63% by 1991. The second largest sector is in industrial applications which is currently about 40%, but is expected to decline to only 29% by 1991. The agricultural and food applications of controlled release is currently only about 9% of the total market and is expected to decline to about 7% by 1991.[57]

This decline in the agrichemical applications is especially interesting to note because much of the early impetus in the field of controlled release technology was in potential agricultural applications. One only has to examine the tables of contents of the papers published at the Annual Meeting of the Controlled Release Society to note a distinct shift in this emphasis. The major reasons for this shift is economics, not the unavailabilty of the technology. The use of any controlled release system will add an expense which can not be tolerated readily in agriculture but can be absorbed in medicine.

In the present markets for controlled release systems, microencapsulation is the dominant technology accounting for about $1.31 billion annually (61%), followed by coatings at $0.55 billion (25%) and polymer/membranes at $0.30 billion (14%). By 1991 these figures are expected to increase to $2.06, $0.69 and $1.05 billion for the microencapsulation, coatings and polymer/membranes, respectively. (The percentages are expected to be 54, 18 and 27, respectively.)[57]

PROTEINS AND ANALOGS

Proteins, enzymes, polysaccharides, and nucleic acids are natural biologically active polymers, but no attempt will be made to review these diverse systems here; several recent books and review articles are available.[20-22,58-60] Synthetic analogs have been prepared of essentially every type of natural macromolecule and many of these have exhibited biological activity. These analogs will be considered briefly in the next several sections.

Samanen and Whiteley have recently reviewed the area of biomedical polypeptides with respect to synthesis, problems and possibilities for developing new drugs.[5,60,61] Sequences can be assigned different roles, such as message sequences, prohormone sequences, and stability sequences. Research in this area illustrates attempts to employ naturally occurring (although typically synthetic) sequences to produce synthetic "nature-like" macromolecules. More than 200 clinical trials have been conducted using such natural peptides and their analogs. Whiteley and Petersen have reviewed the use of proteins and peptides as carriers.[4,6] The research on the endophins and enkephalins is now a classical example of such an effort and artificial derivatives have been synthesized with more than 28,000 times the analgesic activity of the natural materials.[62] Natural polymers, usually polypeptides, have been used as the polymeric matrix or as carrier controlled release systems.[5,6,60]

ENZYMES AND ENZYME-MIMETIC POLYMERS

Hundreds of examples of modified, natural polypeptides have appeared in the literature, many of which have high biological activity.[5,21,22,61] Enzyme-mimetic polymers (also referred to as enzyme-analogs, synzymes, or pseudo-enzymes) have been studied by many workers and these artificial analogs often show some activity, although much less than a typical enzyme.[63-66] This field was pioneered by Overberger,[63] and has been reviewed extensively by Imanishi.[65,66] In some recent research, enzyme activity has been created in otherwise inert protein molecules by chemical modification.[67,68] The potential medical applications of enzyme-mimetic polymers could include the treatment of enzyme deficiency diseases such as as phenylketon uria, tyrosinosis or histidinemia. If the missing enzyme is used to treat the patient, the body rapidly destroys this enzyme as a foreign protein. An enzyme-mimetic polymer might be able to by-pass the body's defense system and treat the enzyme deficient