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CONTROLLED RELEASE TECHNOLOGIES: METHODS, THEORY, AND APPLICATIONS

Volume II

Agis F. Kydonieus

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Controlled Release Technologies: Methods, Theory, and Applications

Volume II

Editor

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PREFACE

Delivery of chemical ingredients by controlled release processes occurs in nature. Examples of such processes include the delivery and control of the flow of food and waste across the exterior membrane of one-celled animals and the oxygenation of blood in mammals by the diffusion of oxygen through the alveolar walls. Development of controlled release systems for our modern technology may be considered an attempt to simulate nature's processes and thereby provide more efficient and more effective delivery of chemicals to intended targets. Information and knowledge gained in these exploits form the substance of the two volumes of this treatise.

Intensive research and development by the drug industry in the last 20 years has provided the scientific foundation for this fledging new science. Concern over the administration of high doses of conventional drugs was the impetus toward the development of controlled release oral drugs initially and implantable devices more recently. Applying much the same principles, scientists working in the pesticide field have developed new technologies and formulations to (1) extend the duration of effectiveness of pesticides without increasing rates of application, (2) reduce the hazard associated with the use of highly poisonous chemicals, (3) prolong the effective life of unstable, volatile, or hydrolyzable pesticides, (4) improve pest control efficiency, and (5) minimize pollution of the environment.

The technologies described in these two volumes depend almost exclusively on the use of polymers and polymer technology. Exceptional advancement in polymer science during the past several decades has made possible the creation of delivery systems which previously could not have been conceived. Described herein are dozens of polymers that comprise the elements of delivery systems that control the permeation and release of active ingredients.

The applications, advantages, and fundamental concepts of controlled release have been the subject of many symposia and of several books dealing with formulations: however, all known delivery systems have not been assembled for consideration as they are here.

Our emphasis in these volumes is on the description of the controlled release technologies, their theoretical basis, mechanisms of release, and their advantages and limitations. Many commercial applications, as well as experimental products and formulations, are discussed to illustrate the potential of each of these technologies. Young as this technology may be, many scientists are convinced that it has the momentum and the secure fundamental basis for solving the complex problems of the delivery of drugs to humans and of directing pesticides to targeted biota with minimum disruption of environmental values. Formulations have already been developed that have been proven commercially successful in many fields, including medicine, agriculture, forestry, public health, and products for the consumer and industry. At this juncture, our aim is that this volume will add to the current momentum to explore this already proven technology and that it will help product development scientists choose the proper controlled release technology for their specific product needs.

The fundamental concepts and theoretical background of controlled release processes are given in Volume 1, Chapter 1. Having introduced the subject matter in the introductory chapter, Chapters 2 through 6 and Volume II, Chapters 1 through 12 follow, describing in detail 17 different controlled release technologies; Chapter 13 describes briefly several other controlled release technologies and provides a 1977 to 1978 patent search of controlled release methods and applications. Each chapter was written by an author who either invented a specific controlled release technology or has had a major roll in advancing the state of its art. Representing all the major tech-

nological areas of controlled release, the subject matter is grouped as follows in the chapters indicated:

1. Volume I, Chapters 2 through 6: monolithic devices, membranes, porous and homogenous films, and laminated structures.
2. Volume II, Chapters 1 and 2: erodible, bioerodible, soluble, hydrolyzable, and biodegradable devices.
3. Chapter 3: retrograde chemical reaction systems.
4. Chapters 4 through 8: microencapsulation systems by coascervation, interfacial polymerization, air suspension, and centrifugal extrusion.
5. Chapters 9 through 12: other important controlled release technologies, such as hollow fibers, osmotic devices, starch xanthate matrices, and kraft lignin carriers.

As an introductory background and perspective for the novice or the recent practitioner in the field, the first chapter was included to introduce all the major controlled release technologies and to describe the basic components of controlled release devices and the release characteristics of the controlled release processes. New developments and improvements in existing technologies continue to appear. Described in Chapter 13 are some new and improved technologies and products, actually those found in a review of the Official Gazettes of the U.S. Patent and Trademark Office for 1977 and part of 1978. Several other controlled release technologies which were found in the literature have also been included in Chapter 13. Obviously, in the fast-expanding field of controlled release, several omissions must have occured despite our effort to present all significant developments known by the end of 1977, when most of the manuscripts were collected. Nevertheless, we hope that this effort will prove to be of value to scientists and product development engineers seeking up-to-date information in the field.

Several friends and associates should be given credit for their helpful suggestions and criticisms. Special thanks should go to Dr. Morton Beroza for scrutinizing parts of the manuscript and to Drs. Nate Cardarelli and Bill O'Neill for their guidance and encouragement. I am also indebted to the authors for their cooperation in adhering to strict manuscript specifications and to Ms. Camille Boxhill and Ms. Adriane Chisholm for their efforts in typing and assisting in the editorial endeavors. Finally, I would like to thank the management of Hercon Group and Health-Chem Corporation, who have been strong advocates of controlled release for many years and have given the editor all the support required to complete this undertaking.

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September 1978

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Chapter 1

ERODIBLE MATRICES

S. Yolles and M. F. Sartori

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I. INTRODUCTION

The system most investigated for controlled release comprises incorporating a biologically active agent in a matrix, commonly a polymeric material, shaping the obtained composite into a convenient form, and implanting it into the body tissue or body cavity by surgery or injection.

Early investigations on controlled release delivery systems have used polyethylene film,[1] silicone rubber,[2,3] etc., as matrices. They are effective matrices, but with the disadvantage that, after the implanted composites have fulfilled their functions, the matrices require surgical removal.

Composites of drugs with erodible matrices, which are consumed or biodegraded during therapy, were developed by Yolles[4,5,6] in the study of controlled release of narcotic antagonists.

Specific requirements for a polymeric material to be used as a matrix are (1) compatibility with the environment and with the biologically active ingredient, (2) rate of biodegradation compatible with the projected life span of the composite, (3) ability to provide the desired release rate, and (4) availability of starting material.

Erodible polymers and copolymers investigated most are (1) poly(lactic acid), (2) poly(glycolic acid), (3) copolymers of poly(lactic acid) and poly(glycolic acid), and (4) polyamides and copolymers of polyamides and polyesters. Their uses, preparation and properties are described below.

Several methods have been used to prepare composites containing erodible matrices: dissolving the polymer and the active ingredient with[7] or without plasticizer[8] in a solvent, evaporating the solvent and press-melting the residue between plates in a heated press to produce films; grinding the polymer, mixing with the active ingredient, and compression molding or extruding the mixture into films or pellets[7,9] (pelletizing has been conveniently accomplished with a Marumerizer®[10]); covalently bonding the drug with reactive groups of the polymer and preparing films as above.[11] Films have been reformed into beads, chips, etc. Tubes[12] and rods[9] also have been made.

II. POLY(LACTIC ACID)

Poly(lactic acid) (PLA), sometimes referred to as polylactide, was reported by Kulkarni[13] in 1966 to be a suitable material for surgical implant because it undergoes hydrolytic de-esterification to lactic acid, a normal product of muscle metabolism. At about the same time and independently, Schneider[14] disclosed that PLA was useful for preparing absorbable sutures. The first use of PLA as an erodible matrix for controlled release of drugs was reported by Yolles in 1971.[5] Since then many patents[15,16] and papers[7,12,17,18] have appeared concerning the preparation and the uses of this polymer.

Since lactic acid is optically active, PLA can exist in the following forms: RS, −R and +S forms. Both the +S and RS-PLA have been found to be free of harmful tissue reaction upon implantation.[8]

A. Uses

The most widely reported uses of PLA as a matrix for controlled release is in systems containing the following compounds: (1) narcotic antagonists,[7,21,22] (2) fertility control agents,[12,23] (3) anticancer agents,[18] and (4) herbicides and pesticides.[24]

B. Preparation

Dilactide, the cyclic diester of lactic acid, is polymerized into PLA by heating at 130°C[7] or 170°C[13] under vacuum[12] or at atmospheric pressure[7] and in the presence of

nucleophiles, such as tertiary amines,[12] or of suitable catalysts, such as stannous octoate,[9] stannous chloride,[13] $ZnCl_2$,[13] PbO,[13] SnO,[13] ZnO,[13] tetraphenyl tin,[13] or diethyl zinc.[7] The last two catalysts are preferred. The white fine powder which forms is purified by precipitation from dichloromethane.

C. Properties

Poly(S-lactic acid) is highly crystalline with a mp T_m = 180°C and a glass transition temperature around 67°C. Poly(RS-lactic acid) is amorphous and has a glass transition temperature around 57°C.[12] Poly(RS-lactic acid) is soluble in most common organic solvents, such as benzene, acetone, tetrahydrofuran, and chlorinated hydrocarbons. Poly(S-lactic acid) is soluble in halocarbons, e.g., chloroform and methylene chloride at 50 to 60°C.[12]

The molecular weight of PLA can be controlled by changing the nature or quantity of the catalyst.[13] With tin catalysts PLA can be obtained with $\bar{M}_n$ up to about 400,000 ([η] in chloroform about 7.3 dℓ/g).[20] With diethyl zinc, samples of PLA were prepared with mol wt of 45,000 and 70,000 (calculated from viscosimetric measurements).[7] The intrinsic viscosity of PLA, prepared as in Reference 13, in benzene (100 mℓ/g) varies from 0.5 to 1.18.[13]

The shelf life of poly(lactic acid) is good, although a decrease in molecular weight with time is observed depending on purity of the polymer.[12] Samples prepared by using -S-lactide and diethyl zinc as the catalyst show hydrolytic stability. PLA degrades in vivo, losing 12 to 14% in 3 months, according to Kulkarni,[13] whereas in vivo and in vitro experiments by Schindler[12] show that it takes about 80 days for a PLA composite to halve its average molecular weight. The authors of this paper have found that the life of the polymer is proportional to molecular weight, the higher the $\bar{M}_n$, the slower the erosion in vivo. Carboxyl end groups are given by the equation

$$[COOH] = 1.77 \times 10^{-5} \quad (\Delta E/C_P)$$

where ΔE is the change in optical density at 515 nm and C_P is polymer concentration in g/1.[12] Values of COOH group content, reported in the literature, vary between 2 and 10 mg KOH per gram polymer.[7] Such end group analyses are useful in determining $\bar{M}_n$.

PLA is sensitive to γ-radiation.[12] Histological studies indicate that PLA is nontoxic, nontissue reactive, and biodegradable. The degradation products are not retained in any of the vital organs of animals.[13]

III. POLY(GLYCOLIC ACID)

The preparation of poly(glycolic acid) (PGA) was disclosed by Higgins in 1954.[25] Most of the uses of this polymer are in the preparation of systems for sutures in surgery,[16,26,28] in prosthetic devices,[29] and in storage pellets.[30] Dexon® is the trade name for PGA used as sutures.

A. Preparation

One preferred route to prepare PGA involves the polymerization of glycolide, the cyclic dimeric condensation product obtained by dehydrating glycolic acid. The polymerization occurs by heating at 155 to 241°C in the presence of antimony trioxide[31] or at 150°C in the presence of amines.[32]

B. Properties

The molecular weights of PGA can be controlled by varying the preparation condi-

tions. Preferably the molecular weight is in the range of 10,000 or more.[29] The straight-pull tensile strength is greater than that of catgut and silk of comparable diameter.[33]

Absorption studies in animals show that complete absorption usually occurs within 90 days and no pathologic changes are detectable in various tissues examined in 9 months.[34] It is completely nontoxic upon implantation into animals.[34]

Because of its biodegradability and nontoxic properties, PGA should be a good candidate as a matrix for controlled release. However, its use is limited because of difficulties in fabricating composites, e.g., its low solubility in common solvents.

IV. POLY(LACTIC ACID)/POLY(GLYCOLIC ACID)

The first use of this copolymer (PLA/PGA) as an erodible matrix was reported in 1967.[35] Since then various patents[36,37,38] and papers[39,40,41,42] have been published concerning the preparation of these copolymers and their use for the controlled release of drugs, fertilizers, and insecticides.

A. Preparation

Lactide and glycolide are polymerized into PLA/PGA copolymers by heating at temperatures varying from 115 to 135°C under vacuum and in the presence of stannous octoate as the catalyst.[38,39]

Copolymers of lactic acid (LA) and glycolic acid (GA) ranging from 75 LA/25 GA,[9] 90 LA/10 GA[5,9] and 50/50 RS/lactide/glycolide[39] have been prepared.

B. Properties

Copolymer 90/10 is an opaque, snow-white crystalline material, whereas the 50/50 copolymer is an orange transparent material.[39] The temperature range at which these copolymers become rubbery is 55 to 60°C.[5] The molecular weights determined by gel permeation chromatography, membrane osmosis, and light scattering, range from 40,000 to 200,000.[8] Intrinsic viscosities measured at 37°C in tetrahydrofuran, range from 0.4 to 1.0.[8]

V. POLYAMIDES AND POLYAMIDE-POLYESTER COPOLYMERS

Numerous articles and patents are reported in the literature describing properties and uses of polyamides and of copolymers of polyamides and polyesters.[43,44,45,46,47] However, very little is reported on the erodibility of these polymers.[48] Mixtures of polyamides and ethylcellulose have been used as suture material.[49] Collagen polymers are reported to be completely resorbed without toxic actions.[50] Sidman, et al.[51] investigated glutamic acid/leucine copolymers in the preparation of biodegradable delivery systems for narcotic antagonists. The composition of the copolymers varied from 10% glutamic acid/90% leucine to 40% glutamic acid/60% leucine. The preparation of composites with naltrexone in the forms of films, rods, and tubes is described.[51]

An erodible intrauterine device has been made by crosslinking gelatin with ketones and incorporating prostaglandin.[52]

VI. MISCELLANEOUS MATRICES

In searching the literature for erodible matrices, very few references have been found on the following polymers and copolymers and their use as matrices: polyester from succinic acid and ethylene glycol;[53] poly (ε-caprolactone);[54] copolymer of dilactide and ε-decalactone[54] and copolymer of ε-decalactone and ε-caprolactone.[54] However, inves-

tigation in this field of controlled release is going forward at a feverish rate, including the search for new and patentable bioerodible polymers.

Recently one of the authors[11] of this paper has developed an erodible system in which the active ingredient is covalently bonded (ester linkage) to water-soluble Klucel®[55] (hydroxypropyl cellulose). The compound is water-insoluble. The release mechanism occurs by hydrolysis of the ester linkage (enzymatic in vivo), followed by diffusion of the active ingredient from the polymer. After the drug has been delivered, the polymer matrix becomes water-soluble again and disappears from the injection site. The same principle is now being investigated using an amide bond between drug and water-soluble cellulosic.

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Chapter 2

THE BIODEGRADATIVE CONTROLLED RELEASE OF PESTICIDES FROM POLYMERIC SUBSTRATES

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