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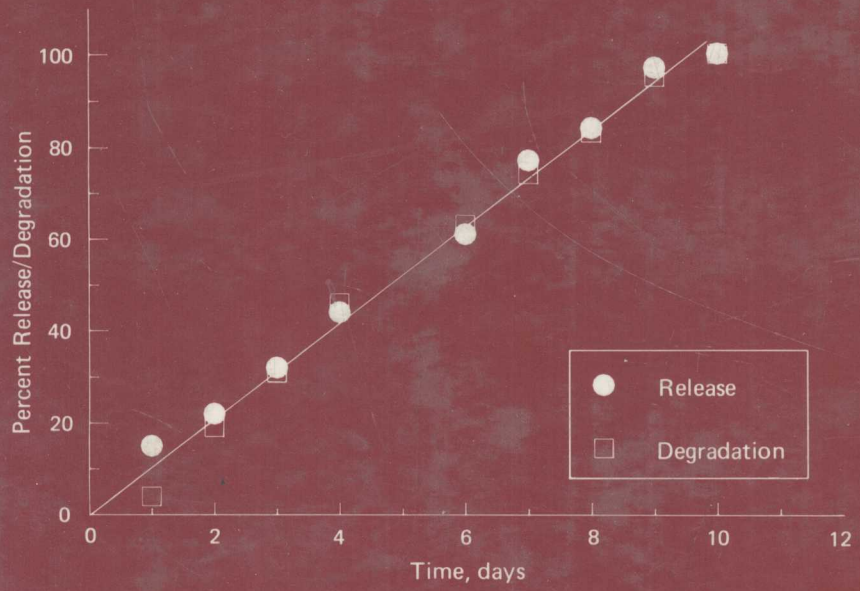
Biodegradable Polymers as Drug Delivery Systems



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Biodegradable Polymers as Drug Delivery Systems

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Preface

Over the past decade, the use of polymers for the administration of pharmaceutical and agricultural agents has increased dramatically. This field of controlled release technology has changed from being merely useful in research to having a significant clinical impact. As we look ahead toward advances in the next decade, one of the areas of greatest practical consequence in medical therapeutics of controlled release technology will be the development of biodegradable polymer systems. Such polymers offer the great advantage of enabling either site-specific or systemic administration of pharmaceutical agents without the need for subsequent retrieval of the delivery system. These polymers offer many other advantages as well.

While this book is focused on drug delivery, the value of biodegradable polymers is not limited to this field. Biodegradable polymers will be useful in other areas of medical therapeutics, such as sutures and bone plates and other types of prostheses. The polymers will also be useful in nonmedical fields, for disposable plastics, bottles, diapers and many other entities.

It was our intention in formulating this book to take selected polymers that have been widely studied and provide a comprehensive review of their properties, synthesis, and formulations. We hope that this will be useful to individuals who have been in the field for a long time and who would like to have all the information together in one place, as well as to individuals who are new to the field and would like to understand more about the various properties of biodegradable polymers.

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Biodegradable Polymers as Drug Delivery Systems

Contents

1

Controlled Release of Bioactive Agents from Lactide/Glycolide Polymers

DANNY H. LEWIS Stolle Research and Development Corporation, Decatur, Alabama

I. INTRODUCTION

For more than two decades, the delivery of bioactive agents from polymeric materials has attracted the considerable attention of investigators throughout the scientific community. Polymer chemists, chemical engineers, pharmaceutical scientists, and entomologists are among those seeking to design predictable, controlled delivery systems for bioactive agents ranging from insulin to rodenticides. This challenge has been a formidable one to date as evidenced by the small number of fully developed products based on this concept. One must realize, however, that only in the past 10 years with the onsurge of biotechnology has research in controlled drug delivery benefited from the intense dedication of resources. With the availability of new molecules, often with short biological half-lives and relatively high molecular weights, the need for reliable controlled release systems has been apparent.

The trend in drug delivery technology has been toward biodegradable polymer excipients requiring no follow-up surgical removal once the drug supply is depleted. The advantages of biodegradable polymers have been described (1-3). Unfortunately, investigators seeking advanced drug delivery systems are severely limited in candidate polymeric materials as evidenced by the relatively small number of systems described in this text. Historically, designers of drug delivery systems have "borrowed" polymeric materials originally developed for other applications. Only one or two synthetic polymers have been developed specifically for use in controlled release formulations.

The most widely investigated and advanced polymers in regard to available toxicological and clinical data are the aliphatic polyesters based on lactic and glycolic acids. The family of homo- and copolymers derived from these monomers has received considerable attention since about 1973 as excipients for drug delivery. Features such as biocompatibility, predictability of biodegradation kinetics, ease of fabrication, and regulatory approval in commercial suture applications have attracted investigators to lactic/glycolic polymers. During the 1970s, a wealth of literature on polyglycolic acid sutures became available. Much of this pioneering work resulted from studies at U.S. suture companies including American Cyanamid and Johnson and Johnson, and also at the U.S. Army Institute of Dental Research (4,5). Those early studies clearly demonstrated the nontoxic nature of the polymers and provided biodegradation data for various types of implants. Although the bulk of this work was aimed at suture applications, the potential for drug delivery from these polymers became quite obvious.

The biodegradable polyesters have attracted attention in a variety of biomaterial applications including tracheal replacement (6), ventral herniorrhaphy (7), ligament reconstruction (8,9), dental repairs (101), fracture repair (11-15), and surgical dressings (16). Among the first reports of polylactic acid used for controlled release were those of Boswell (17), Yolles (18), Wise (19), Sinclair (20), and Beck (21). These research teams were seeking delivery systems for such agents as narcotic antagonists, contraceptive hormones, and other conventional drug compounds. Early efforts were directed to the homopolymer of lactic acid rather than the copolymers. This was primarily due to the limited availability of the glycolide comonomer. Recently, the full range of monomers and polymers has become rather easily accessible through major chemical companies. DuPont now provides the lactide/glycolide polymers under the trade name Medisorb. This availability of materials has greatly broadened the scope of possibilities for designing drug delivery systems.

II. SYNTHESIS

The homo- and copolymers of lactic and glycolic acids are synthesized by the ring-opening melt condensation of the cyclic dimers, lactide and glycolide (22,23). Due to the asymmetrical β carbon of lactic acid, D and L stereoisomers exist, and the resulting polymer can be either D, L, or racemic DL. The polymerizations are usually conducted over a period of 2–6 hr at about 175°C in the melt. Organotin catalysts are normally utilized with stannous chloride and stannous octoate being the most common. Other catalysts such as p-toluene sulfonic acid and antimony trifluoride have been successfully employed on a limited basis. Lauryl alcohol is often added to control molecular weight during synthesis.

As with most polymerizations, monomer purity is highly critical in the synthesis of polylactides. Differential scanning calorimetry (DSC) purity of 99.9% or greater is usually required with the starting lactide and glycolide materials. Low monomer acidity is also a critical parameter. Free acid of 0.05% or less is normally required for achieving a high molecular weight polymer. Of equal importance, however, are the environmental conditions, particularly humidity levels, in the processing areas. Most failed glycolide polymerizations can be traced to high levels of humidity or high monomer acidity.

III. POLYMER CHARACTERISTICS

A well-proven advantage of the lactide/glycolide polymers is no doubt the available versatility in polymer properties and performance characteristics. For wide applications in controlled drug delivery, it is imperative that a range of rates and durations of drug release be achievable. A broad spectrum of performance characteristics with the polylactides can be obtained by careful manipulation of four key variables: monomer stereochemistry, comonomer ratio, polymer chain linearity, and polymer molecular weight. Because the mechanism of biodegradation is simple hydrolysis of the ester linkages, it is apparent how each of these factors plays an important role in the in vivo performance of the lactide/glycolide materials. Crystallinity and water uptake are key factors in determining the rates of in vivo degradation.

The racemic poly(DL-lactide) DL-PLA is less crystalline and lower melting than the two stereoregular polymers, D-PLA and L-PLA. Further, the copolymers of lactide and glycolide are less crystalline than the two homopolymers of the two monomers. In addition, the lactic acid polymer, because of the methyl group, is more hydrophobic than the glycolide polymer.

Table 1 provides a summary of the glass transition temperatures of several lactide/glycolide polymers. Tg values range from about 40 to 65°C. Poly(L-lactide) has the highest Tg at about 65°C.

Rate of hydration of the polymeric materials has been shown to be an important consideration in regard to drug release. Gilding and Reed (24) demonstrated that water uptake increases as the glycolide ratio in the copolymer increases. The extent of block or random structure in the copolymer can also affect the rate of hydration and the rate of degradation (25). Careful control of the polymerization conditions is required in order to afford reproducible drug release behavior in a finished product. Kissel (26) showed drastic differences in water uptake between various homopolymers and copolymers of caprolactone, lactide, and glycolide.

Siemann (27) recently determined the solubility parameters and densities of a group of biodegradable polyesters. Solubility parameters