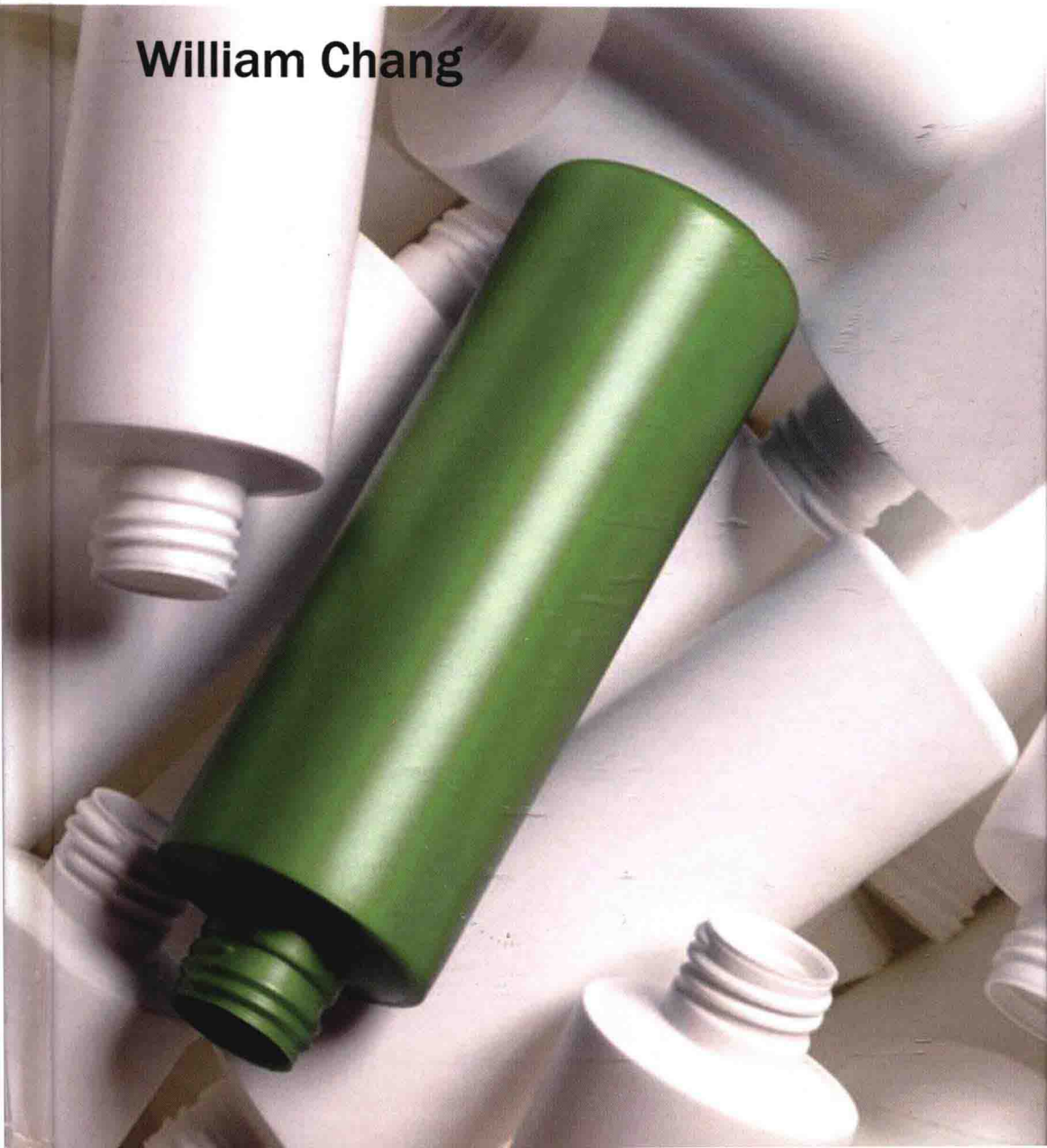
BIODEGRADATION HANDBOOK

William Chang



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Edited by **William Chang**

New York

Published by Callisto Reference,
106 Park Avenue, Suite 200,
New York, NY 10016, USA
www.callistoreference.com

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International Standard Book Number: 978-1-63239-088-2 (Hardback)

Printed in China.

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Preface

This book, written for readers with interest in the process of biodegradation, serves as a good source of information. It is a compilation of various biodegradation research procedures which lead to various biological processes. It deals with biodegradation with respect to polymers and surfactants and also takes into account the microbial behavior.

This book is the end result of constructive efforts and intensive research done by experts in this field. The aim of this book is to enlighten the readers with recent information in this area of research. The information provided in this profound book would serve as a valuable reference to students and researchers in this field.

At the end, I would like to thank all the authors for devoting their precious time and providing their valuable contribution to this book. I would also like to express my gratitude to my fellow colleagues who encouraged me throughout the process.

Editor

Contents

Section 1

Biodegradation of Polymers and Surfactants

Chapter 1

Biodegradation of Medical Purpose Polymeric Materials and Their Impact on Biocompatibility

Elisa Tamariz and Ariadna Rios-Ramírez

Additional information is available at the end of the chapter

1. Introduction

The use of polymeric materials in medical devices and pharmaceutical applications has been extended in the last decades. Biodegradable implantable polymers for tissue engineering and drug release have the advantage to avoid a permanent and chronic immune response, and to avoid removal surgery; moreover the versatility of polymeric materials aloud the design of specific biodegradable characteristics to control drug release, to develop resorbable devices, and to improve cell integration.

Biodegradation is a term used to describe the process of break down a material by nature; however in the case of medical purpose biomaterials, biodegradation is focus in the biological processes inside the body that cause a gradual breakdown of the material.

Biomaterials degradation is a very important aspect to consider when they are used for medical purpose, since their ability to function for a certain application depends on the length of time that it is necessary to keep them in the body.

Polymers biodegradation process and rate within an organism is related to the polymer characteristics and the place in the body where will be exposed. This chapter intended to offer an overview of the mechanisms that influences the biodegradation of polymeric materials used for medical purposes, with special emphasis in the immunological mechanisms that modulates biodegradation rates and biocompatibility, and in the features that implies their use in the central nervous system (CNS). It will be also focused in the importance of modulate the biodegradation for some biomedical application, and how the on purpose control of biodegradation could be a relevant aspect to design biomaterials with a more interactive and efficient role in medicine.

2. Polymeric material for biomedical applications

The use of polymers in biomedical applications is now widely accepted and they are termed with the generic name of polymeric biomaterials. A biomaterial can be defined by their function as a material in contact with living tissue, used to the treatment of disease or injury, and to improve human health by restoring the function of tissue and organs in the body [1]. The 1982 Consensus Development Conference Statement of the National Institute of Health (NIH) defines a biomaterial as any substance (other than drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments or replaces any tissue, organ or function in the body [2]. Polymeric biomaterials in medicine include surgical sutures, drug delivery vectors, orthopedic devices and implants, and scaffolds for tissue engineering.

After decades of research many polymeric biomaterials have been developed from synthetic or natural origin. All the polymeric biomaterials have to be evaluated in terms of their biocompatibility, mechanical properties and biodegradation to determine if they are suitable for specific medical applications.

Biocompatibility refers to several characteristics of the biomaterial which leads to the acceptance of the material in the body, such as being non toxic, non carcinogenic, non allergenic, non immunogenic. The materials for in vivo use have to be exposed to hemocompatibility, citotoxicity, mutagenicity, and pyrogenicity test [1].

Mechanical properties like elastic modulus, compression modulus, fatigue, and viscoelasticity are important characteristics to determined their use in the body, for example for bone implants and prosthesis; however micrometric or nanometric characterization is also important in the case of biomaterials for tissue replacement and cell scaffolds, since micro and nano-characteristics are important to manipulate cell proliferation, differentiation, and function to mimic the tissue to be replaced [3].

Biodegradation refers to the rate of breakdown mediated by biological activity, and is an important property for biomaterials used as non permanent scaffolds, implants, drug delivery vectors, and sutures [1].

The most commercial and earliest developed polymers for biomedical applications were the synthetic polymers developed from linear aliphatic polyesters. Synthetic polymers are made by linking small molecules (mers) through primary covalent binding in the main molecular chain backbone, and have a close resemble with natural occurring tissue components like proteins, polysaccharides and deoxyribonucleic acids. Besides synthetic polymers, natural occurring polymers are also used as biomaterials. Many of the natural polymers are synthesized by condensation reactions and the condensing molecule is always the water [4]. Natural polymers and their chemical and mechanical properties specifically provide functions to each of them in the organisms, for example collagen in the dermis, fibrin in the clot, chitin in the exoskeleton of insects and crustaceans [5, 6].

Either synthetic and natural polymers, or bonds among both has been studied and used as materials for medical application; below we shortly describe some examples of the main

natural and synthetic polymers and some of their proposed uses in medicine, particularly in the nervous system.

2.1. Natural polymers

Natural polymers are used in clinical applications such as dermal fillers, lubricants, wound sealants and surgical sponges. Other naturally derived polymers have readily available functional groups which facilitate chemical modification.

Agarose is a polysaccharide of D-galactose and 3,6- anhydro-L-galactopyranose derived from the cell walls of red algae. Agarose is biologically inert and is attractive for drug delivery because it has soft, tissue-like mechanical properties, and can form porous gels at low temperatures. Agarose is heated to solubilize the powder in aqueous solutions and then gels through hydrogen bonding upon cooling [7]. Agarose decrease potential immune rejection when inserted into the brain, for example, Brain-derived neurotrophic factor (BDNF) delivered in this way was found to reduce the reactivity of the astrocytes and the production of chondroitin sulfate proteoglycans (CSPGs), and to enhance the number of regenerating fibers that entered the hydrogel into the injured spinal cord in rats [7, 8].

Fibrin is a promising material because of its natural role in wound healing and its current application as a tissue sealant. Obtained from pooled human plasma, fibrin presents an advantage since it could be an autologous source avoiding risk of immune rejection. The most used gel is the fibrin glue and consist of fibrinogen and thrombin enzymatically crosslinked; however it has also used in conjugation with other polymers such as hyaluronic acid [1, 9]. This polymer has the advantage to be injected and polymerized in situ and has been tested for controlled delivery of Nerve growth factor (NGF), Neurotrophin -3 (NT-3) and BDNF in the CNS [7].

Collagen is the main component of connective tissue and is the most abundant protein in mammals, there are at least 19 different types of collagen, for example type I collagen is a fibril forming collagen and is present in the skin and fibrocartilage, type II collagen is found in articular cartilage[10, 11]. Collagen can be isolated from tissue like skin, bone or tendon. Collagen gels alone are quite weak, and are often crosslinked to improve durability. While many applications use unmodified collagen, chemical crosslinkers can be used to inhibit in vivo absorption in applications which require slow degrading constructs, such as drug delivery [7, 12]. Although collagen is abundant in many tissues, is not the main component in the CNS extracellular matrix, therefore some concern is present about their use as CNS cells scaffolds [12], however their use for stably releasing of growth factors like ciliary neurotrophic factor (CNTF), has shown to improve the survival, growth and proliferation of neural stem/progenitor cells (NSPCs) [1].

Alginate is a linear block copolymer of D-mannuronic acid (M) and L-guluronic acid (G) residues. Commercially available, alginate is extracted from brown seaweed algae. Alginate has a high biocompatibility since their hydrophobic nature; however, cannot be enzimatically broken down and has poorly regulated degradation. Partial oxidation of alginate with sodium periodate makes the chains more susceptible to be degraded by hydrolysis [13]. Mammalian

cells cannot adhere to alginate unless it is modified with cellular adhesion molecules like laminin, fibronectin, collagen, and RGD sequences, which allow more specific interactions [9]. Covalently modified gels of alginate containing different ration of RGD peptides have been used to encapsulate cells and to induce their differentiation [14].

Hyaluronic acid (HA) is a glycosamine glycane made of residues of N-acetylglucosamine and D-glucuronic. HA is normally presented at high levels in the extracellular matrix of connective, epithelial and neural tissues, and is known to play roles in cellular processes like cell proliferation, morphogenesis, inflammation, and wound repair. However, HA alone does not gel and is rapidly degraded through the action of the enzyme hyaluronidase into smaller oligosacharides, HA can also be degraded by reactive oxygen species at the site of inflammation [15], and is readily cleared due to its high solubility [1]. HA is fabricated into hydrogels using chemical crosslinkers such as glutaraldehyde or carbodiimide, and has also been widely derivatized to form photocrosslinkable and injectable hydrogels. Its polyanionic and hydrophilic characteristics made it highly biocompatible and suitable for applications with minimal cell invasion [9].

Poly(β-1,4-D-glucosamine) or Chitosan is a natural polymer that can be prepared by de-N-acetylation of chitin from crustacean shells, the degree of chitosan deacetylation affects the charge density of the polysaccharide, more deacetylation increase the positive-charge character of the chitosan chains. It can form gels by covalent crosslinking with aldehydes such as glutaraldehyde or ionic crosslinking by polyanions such as sodium citrate or sodium tripolyphosphate [6]. The limited solubility of chitosan in neutral pH provides a unique opportunity to form nanoparticulate drug/gene delivery platforms, but it is also an obstacle if one intends to apply chitosan as a solution in the physiological condition [5]. Chitosan can be easily conjugated with organic materials as well as biomolecules, a number of studies have reported controlled drug delivery using chitosan nanoparticles that incorporate biologically active ingredients such as DNA, proteins, anticancer drugs, and insulin [16]. Chitosan has been extensively investigated as a potential biomaterial in a variety of applications, including drug carriers, wound-healing agents, and in tissue engineering. Chitosan scaffolds have been used to transplant viable peripheral nerve grafts, neural stem cells, and neural progenitor cells into rat spinal cords, resulting in increased axonal regeneration [17].

Methylcellulose (MC) is a chemically modified cellulose derivative in which there is a partial substitution of OH groups with methoxy moieties forming a non-toxic material. MC is a water-soluble polymer at low temperature with thermo reversible gelation at a particular temperature. Thermoreversible characteristics are related to the association of MC hydrophobic groups, and the gelation temperature can be manipulated by salts or ions [18]. MC is widely accepted as a highly compatible material and has been used in traumatic CNS lesion like a scaffold for tissue regeneration [19].

2.2. Synthetic polymers

Synthetic polymers offer exceptional control over polymer composition, architecture, and physical properties not fully accessible with natural polymers. After many years of research

in this field numerous polymers have developed like polyesters, polyurethanes, polyanhydrides, polyacrylates, polyphosphoesters, and polydiaxanone. One of the first and now most common uses of polymers in medicine is for resorbable sutures, pins and screws. An extensive review of synthetic polymers is out of this chapter and we will only mention some examples and their main characteristics.

2.2.1. *Polyesters*

Polyglycolide or polyglycolic acid (PGA) is polymerized from glycolic acid and many of the most important polymer for biomedical use are derived from PGA either through copolymerization or modified glicolide monomers. PGA is one of the most successful and commercially available polymers and is widely used as biodegradable biomaterial in surgery [20].

Poly(lactide-co-glycolide) acid (PLGA) is a PGA derived polymer, is a polyesters obtainable by linear polycondensation of hydroxyacids, or by ring opening of the corresponding lactones. It is the most commonly used biomaterial in medicine. This polymeric agent has been implanted into the brain and has shown good biocompatibility and sustainable drug delivery [8]. In normal untreated animals, polymer microspheres implanted into the brain did not produce gross behavioral or neurological symptoms, and it has been approved for the FDA for repair of human peripheral nerves [5]. Various drugs, especially therapeutic proteins like neurotrophic factors have been encapsulated in this type of brain delivery system, however, the in vivo hydrolysis of PLGA produce and acidic environment that result in a transient pH decline that can compromise the proteins action and stability, and consequently the process of encapsulation and release from biodegradable microspheres must be carefully monitored [5, 21].

Polyethylene glycol (PEG)- based polymers are hydrophilic and water-swellable cross-linked polymers with a high level of elasticity, making them ideal candidates for tissue engineering; more importantly, the degradation rate of the implant can be controlled by simply altering the chemistry of the cross-links within the polymer network [9]. PEG has a variety of applications in drug delivery and tissue engineering, their hydrophilic and non ionic characteristics made it relatively resistant to protein adsorption and highly biocompatible. *In vitro,* they can support the survival of PC12 cells, fetal ventral mesencephalic neural cells, and human neural progenitor cells. Furthermore, in culture, neural cells encapsulated into PEG-based hydrogels survive, maintain phenotype, and extend processes indicating that the hydrogels are not themselves cytotoxic [22, 23]. A recent study in primates found that PEG was completely degraded and the neuroimmune response was less than that found in sham penetrated brains [22, 23].

2.2.2. *Polyacrylates*

Poly(2-hydroxethyl methacrylate) PHEMA, is one of the earliest polymer used as implantable material. Polymerized from 2-hydroxyethyl methacrylate using free radical precipitation, PHEMA forms a hydrogel biologically inert. One of the main concerns about PHEMA is its low biodegradability, their biodegradation however can be manipulated by modifying the porosity by photopatterning [24]. One of the earliest uses of PHEMA was as an artificial cornea, or keratoprosthesis [25]. Methacrylic-acid- and acrylic-acid-based hydrogels have a high

affinity for calcium and other alkaline earth metals, making them more prone to calcification, thereby some calcification episodes has been found after in vivo implantation [9].

Poly(N-isopropylacrylamide) (PNIPAAm) has been widely studied as a temperature responsive drug delivery system. It has the particular ability to undergo a thermally induced phase transition at 32 °C that induces swelling in the polymer network. The phase transition temperature can be tuned via copolymerization of more hydrophilic or hydrophobic co-monomers to achieve desired transitions in relevant *in vivo* environments. At physiological temperatures, PNIPAAm homopolymer gels hold little water and show poor elastic recovery [7, 26].

2.2.3. Poly(ω-hydroxyl acids)

The poly(ω-caprolactone) contains five (CH)2 units in the repeating unit, making the chains much more flexible than PGA, which has one. Therefore, thermal and mechanical properties decreased considerably compared to PGA. However, the rate of biodegradation is slow, making it better suited to slow drug release applications such as one-year implantable contraceptives, biodegradable wound closure staples, etc [27].

2.2.4. Poly(ortho esters)

Poly(ortho esters) (POE) undergo surface degradation, making them ideal as a drug-delivery vehicle. Erosion process is confined predominantly to the surface layers; therefore controlled drug release is possible as well as maintenance of an essentially neutral pH in the interior of the matrix because acidic hydrolysis products diffuse away from the device. The rate of degradation can be controlled by incorporating acidic or basic excipients into the polymer matrix since the orthoester link is less stable in an acid than in a base [27]. The polymer is stable at room temperature when stored under anhydrous conditions. Either solid or injectable materials can be fabricated into different shapes such as wafers, strands, or microspheres that allow drug incorporation by a simple mixing at room temperature and without the use of solvents [28].

2.2.5. Poly(ester-amides)

Poly(ester-amides) (PEAs) combine the high degradability of polyesters with high thermal stability and high modulus and tensil strength of polyamides [29], are non-toxic building blocks and had excellent film forming properties. These polymers were mostly amorphous materials, combine the well-known absorbability and biocompatibility of linear aliphatic polyesters with the high performance and the flexibility of potential chemical reactive sites of amide of polyamides [20]. PEAs can be functionalized to conjugated different drug, peptides or molecules for cells signaling and had been used for microspheres and hydrogels formation [29].