

Introductory Preface

General Aspects

Biopolymers include broad families of biosynthesized materials. Living organisms are able to synthesize an overwhelming variety of polymers which can be classified as members of one of eight classes according to their chemical formulae: (1) polynucleotides or nucleic acids, e.g., DNA and RNA; (2) polyamides, e.g., protein and other poly(amino acids); (3) polysaccharides such as cellulose and starch; (4) polyesters, i.e., aliphatic polyoxoesters, better known as polyhydroxyalkanoates (PHA); (5) polythioesters such as poly(3-mercaptopropionate); (6) polyanhydrides, with polyphosphate as the only known example; (7) polyisoprenoids, principally rubber-like polymers; and (8) polyphenols, with lignin as the most abundant example. Within each category the chemistry of the repeating units, which are covalently linked, the type of linkage between the repeating units, and their structural arrangement (i.e., linear, cyclic, branched) distinguish the members. The study of these characteristics is ongoing, and some organic materials such as lignin do not have well-defined structures. Today's analytical tools have allowed rapid progress in identifying moieties. Furthermore, the physical organization (such as double-helical, or the complex three-dimensional arrangement of folded proteins) is readily available by x-ray diffraction. The polymorphism in a glycan such as cellulose or starch is usually a function of the material origin.

One other important aspect should be emphasized: only the polynucleotides and the proteins among the polyamides are monodisperse, and each polymer species exhibits a well-defined molecular weight, because these biopolymers are synthesized by template-dependent biosynthesis processes. All other polymers mentioned above are more or less polydisperse, because biosynthesis is template-independent. This also provides an opportunity of directing the average molecular weight to a certain extent, e.g., by varying the enzyme-to-substrate ratio in the cells and thereby modulating various properties of the biopolymer.

Among the biopolymers produced are the many used for various applications in industry. Until recently, biopolymers were the product of a biosynthetic process. Microorganisms are capable of synthesizing biopolymers belonging to classes 1–6, whereas eukaryotes synthesize mainly biopolymers belonging to classes 1–3 and 6–8. Whether derived from natural sources such as plants, animals, or algae by extraction processes, by controlled microbial fermentations in stirred tank reactors yielding extracellular or intracellular biopolymers, or by enzymatic synthesis, biosynthesis was the producing method. Today,

chemical synthesis can be also used on a biopolymer as starting material leading to a monomer which is then again transformed to a biopolymer by a chemical polymerization process. Polylactide (PLA) as produced by Cargill-Dow Inc. is a well-known example. In this case starch is fermented to lactic acid which is then converted to dimeric lactide and polymerized by ring-opening. Thus, agriculture and fermentation combined with polymer science lead to large-scale production of model biopolymers. Recently, Dupont Inc., a major plastics producer, and Tate & Lyle Inc. announced the fermentative production of 1,3-propanediol which will be a component of the new aromatic polyester Sorona.

In this overview, we will concentrate on the “workhorse” biopolymers prominent in biomedical applications. Thus, a polysaccharide such as heparin is one of the most widely used drugs in surgical practice. Excipients, prostheses (sutures, stents, surgical screws) and tissue culture matrices are fields where biopolymer materials with their biocompatible/biodegradable properties are major contributors. Biomedical uses of biopolymers often involve neutralization of toxic products from some physiological malfunction, e.g., bilirubin in babies suffering from jaundice. Wound dressings can be chemically modified cellulose or antimicrobial chitosan. Iron oxide-filled gutta-percha, a natural rubber with malleability, is used in dentistry to fill the void of a root canal. Because none of the buccal enzymes attack gutta-percha, it offers lifelong protection, and the iron oxide provides x-ray visibility. Important vaccines depend on biopolymers as the antigen to produce antibodies.

Drug Delivery

This field is highly innovative in terms of materials to assist delivery, excipients, and technology which allows fast or slow release of drugs. Analgesics, which often involve as much as five or six tablets a day, can be reduced to a single dose by using appropriate excipients, which are frequently based on carbohydrate polymers.

The most widely used excipient in the pharmaceutical industry is an HCl-hydrolyzed high-purity wood pulp (2.5 *N* HCl, 15 min reflux at the boiling point). This excipient, invented half a century ago, was originally intended as a low-calorie food additive. However, its properties as a tablet and the high-speed tableting process it enabled led to general adoption. The actual tablets are about 40% Avicel and 40% lactose, while the remaining components are adjuvants to aid the tableting and release processes. When compression-molded, the fine white powder AVICEL forms a marble-like tablet which can resist an oxyacetylene torch. In water, the tablet disperses in a few minutes, thereby releasing the drug. Large pharmaceutical companies dedicate a major development effort to understanding and controlling this valuable material.

Polysaccharide excipients are also based on starch, frequently the high-amylose hybrid with 70% amylose and 30% amylopectin, which consist of linear or branched chains of glucose, respectively. Unlike AVICEL, the starch-based excipient maintains its tablet shape in water but swells to an elastomeric hydrogel over a period of about 20–25 h at 37 °C. During this period the gel slowly releases its drug dose.

Many other polysaccharides are used in drug delivery. The water-soluble cellulose ether derivatives hydroxypropyl and carboxymethyl cellulose are adjuvants in this health-related technology. Polyelectrolyte biopolymers often form complexes with each other, i.e., they form coacervates by the interaction of their cationic and anionic functionalities, leading to molecular encapsulation. Ink, for example was locked in the familiar gelatin–gum Arabic capsular coating for paper, thereby providing a pressure-sensitive writing process.

Prostheses

A surgical suture is a classic example of a bioabsorbable/biocompatible prosthesis. The development of polyglycolide (PGA) sutures some 25 years ago by Davis and Geck Inc. in the United States was a major breakthrough. For centuries the familiar “catgut,” a collagenous suture, was the only compatible/bioabsorbable material available to surgeons. Made from animal intestines, it was not uniform in diameter and strength. Surgeons yearned for a continuous filament suitable for the fine threads needed for eye surgery. PGA is a synthetic bioabsorbable polymerization product which is melt-spun to uniform strength-oriented fibers, ideal for surgery. Sold under the trade name Dexon, it was soon in competition with Ethicon Inc.’s Vicryl. The copolymeric composition of the latter (70% glycolide/30% lactide) has a 30–40 °C lower melting temperature, which eliminates thermodegradation during melt/spinning. Other companies produce similar polymers. Ironically, the claimed biodegradation *in vivo* is in fact an aqueous hydrolysis. In similar trial applications, the bacterial polyesters poly(3-hydroxybutyrate), PHB, and the copolymer poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) proved to be much slower to bioabsorb, requiring several months compared to a few weeks for surgical use. It was soon appreciated that the polyhydroxyalkanoate (PHA) backbone compared to PGA or PLA slowed the hydrolysis due to an inductive effect. PHAs are therefore recommended as surgical pins where long life is desirable. Several other biocompatible/bioabsorbable synthetic sutures are now marketed.

Both synthetic and biosynthetic aliphatic polyesters have niches in orthopedic usage. The ability to use conventional polymer synthesis, plastic molding, and machining methods for thermoplastic biopolymers are the key properties. The hydrophobic character of these polyesters and the nontoxic byproducts of degradation *in vivo* favor polyesters over polysaccharides in these applications. When greater permanence is required, aromatic polyesters such as Dacron are used, e.g., in artery repair.

Tissue culture is the growth of cells (tissue) separated from the organism. Cells in living tissue provide a platform for motility, differentiation, and proliferation. Tissue replacement efforts require a biopolymer matrix that mimics the developing living tissue, especially biodegradability. Culture studies using osteoblastic and epithelial cell lines have revealed the excellent biocompatibility of the PHB matrix. Similar studies with mouse fibroblast cells revealed that irradiation (UV or plasma) post-treatments on PHB films and fibers could reduce cell adherence problems. The obvious use of the aliphatic biopolyesters (PHAs) in numerous applications such as organ replacement, e.g., heart valves, biocompatible bone and bone cement implants for osteoporosis, etc., has encouraged biomedical replacement studies. The ongoing advances in fundamental microbiology, chemistry, and mechanics of biopolymer materials, both synthetic and biosynthetic, have set the stage for progress and understanding of regeneration of functional living tissue.

Supramolecular Polymers

A fast developing field of chemistry involving synthetic and natural polymers goes under the name of supramolecular. Prime examples are the “host–guest” complexes of small molecules with the glucan called cyclodextrin, α -CD. The latter is the product of starch dextrins acted on by glucosyl transferase. These complexes are major players in drug delivery and enzyme mimicry. Recently, a supramolecular version of α -CD, called polyrotaxane, has been synthesized. It is the simple threading of α -CD rings onto a linear polymer such as

polyethylene glycol. Multiple α -DCs on the polymeric template lead to a molecular shish kebab, and when the α -CDs are cross-linked, a molecular tube is obtained. This kind of manipulation where noncovalent forces lead to self-assembly, as in the well-known surfactant “micelles,” is the “stuff” of supramolecular chemistry.

Not since Staudinger and Carothers convincingly established macromolecular chemistry has there been such a concerted effort toward a new giant molecule concept. It is the chemistry of the intermolecular bond based on noncovalent forces, as distinct from molecular chemistry. At first it was small molecules in host–guest complexes with descriptive family names such as kryptands, calixarenes, sarcophagines, etc. However, supramolecular polymers very soon were recognized by their numerous examples in existing fields such as liquid crystals or biological helicoids, all deserving the supramolecular label. Supramolecular hydrogen-bonded polymers occur when repeating units are joined into linear chains by hydrogen bonds. Columnar assemblies stabilized by supramolecular bonds perpendicular to the monomer surface could be shown to form nematic organizations similar to rod-like colloids. However, conformational variations add flexibility features at the repeating unit level, thereby allowing a wide variety of supramolecular shapes.

Double-helical DNA is supramolecular with hydrogen bonding and π stacking as the intermolecular bonds. Besides the double helix with its nanoscale distance for the intermolecular bonds, DNA teaches that the value of the hydrogen bond pairing between bases is essential for self-assembly. Thus, building blocks chosen at will offer an inexhaustible range of supramolecular design choices.

Scope of This Book

Taking the importance of biopolymers for biomedical and pharmaceutical applications into account, we carefully selected 32 chapters from the recently published ten-volume *Biopolymers*. These chapters have been collected in two volumes. This two-volume spin-off product contains in Volume 1: three chapters focusing on polyphenols and natural rubber, four chapters dealing with various polyesters including the polyanhydride polyphosphate, and 14 chapters focusing on the various polysaccharides; Volume 2 contains eight chapters focusing on polyamides and complex proteinaceous materials and three chapters dealing with special aspects of biopolymers. The polymers from these selected chapters are either already being successfully used for biomedical and pharmaceutical applications or have the potential to be used in the future for such applications, or else the contents of the chapters are in other respects relevant to the subject.

In compiling this handbook, it has been our intention to provide the scientific and industrial community with a comprehensive view of the current state of knowledge on biopolymers and their derivatives in medicine and pharmacy. This handbook attempts to review what is currently known about these fascinating biopolymers in terms of their discovery, occurrence, chemical and physical properties, analysis, biosynthesis, molecular genetics, physiological role, fermentative production, isolation, purification, and applications. With the title more focused and at a price more affordable than that of the complete *Biopolymers* series, this two-volume handbook will be of interest in particular to medium-sized laboratories that are interested or active in this area, and to libraries. We are convinced that each chapter is in some way appropriate to the overall topic. We will feel it has been

successful if some of these chapters stimulate readers to become interested in and solve specific problems, or make the field more accessible to newcomers.

Acknowledgments

Whatever is accomplished with these books is of course the achievement of the authors. We are most grateful to all of them for devoting so much of their valuable time to this endeavor and for sharing their knowledge and insights so generously. We are also particularly grateful to the authors of the selected chapters for allowing the contents of their *Biopolymers* contributions to be included in this new title.

Last but not least, we would like to thank Wiley-VCH for publishing this new handbook with their customary professionalism and excellence, and for their outstanding help throughout the gestation and birth of this handbook. Special thanks are due to Mrs. Karin Dembowski, who initiated the *Biopolymers* series, to Dr. Andreas Sendtko, who continued and finalized it, and to many others at Wiley-VCH for their initiative, constant efforts, helpful suggestions, constructive criticism, and wonderful ideas.

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