INTRODUCTION

Materials that can be applied in bionanotechnology and biomedicine are a subject of current research. Bio- or multifunctional polymeric materials might help solving many of today’s medical problems and allow, for example, a safer use of medicinal products and implants, a more targeted and specific drug administration, and finally even in vivo tissue engineering for effective regenerative medicine. Furthermore, specially designed functional materials provide new perspectives in diagnosis and fundamental studies of biological processes as well as significantly increase the number of controllable targets in medical treatments.

The aim of this book is to outline why and how synthetic bio- and/or multifunctional polymers are particularly promising in this context. Therefore, chemical and physical tools that are available to custom-make polymers and to control specific biointeractions will be introduced. Combining up-to-date polymer synthesis knowledge with a fundamental understanding of the bio-system and ways to control specific biological interaction has led to highly promising advances in the design of specific polymers for biomedical applications, which has been recently successfully demonstrated.

1.1 WHAT MAKES POLYMERS SO INTERESTING?

Various types of materials like metals and alloys, ceramics, different inorganic scaffolds, and low and high molar mass organic molecules are proven instrumental for the broad variety and the specific needs of bionanotechnology as
well as biomedicine applications. Synthetic polymers play a very special role in this context because they are organic in nature and can be tailor-made in many forms to mimic the complexity of the natural biomacromolecules that define and control life. Thus, polymer scientists have taken up the challenge of identifying important design rules that come from nature and at least partially implemented them, essentially reduced, into synthetic polymer structures. Biomacromolecules in the form of polynucleotides and polypeptides contain a large complexity of information in a single molecule that is the base for tertiary structure formation, recognition, bioactions, and biointeractions. This is achieved in biology by a full sequence and molar mass control during the synthesis of the biomacromolecules as well as by an amazing control of the interplay of noncovalent interactions such as found in hydrophobic or electrostatic interactions and hydrogen bonding.

Synthetic macromolecules have similar basic structural features as biomacromolecules, which has given rise to many different kinds of polymers that can seamlessly interface with biosystems and provide particular advantages for new biomedical applications. The first of these features are that they are formed by a large number of repeating units (monomers). Secondly, they can be prepared in different molar masses. Constitution (composition) and connectivity (linear, branched) of the repeating units are already two important parameters that can be varied in synthetic macromolecules. In addition, the characteristics of polymers can be significantly broadened by combining several comonomers in one polymer chain. These can be randomly distributed within a linear polymer chain or added in a special sequence and in a specific topology (see polymer architectures), which results in block, star, and graft copolymers, for example.

Since the variety of monomer structures is nearly unlimited synthetic polymers offer many more variation possibilities with regard to introduction of specific chemical units and functions than, for example, proteins where a limited number of amino acids is found in nature. Similarly, there is theoretically also no limit to the number of different monomer units that can be combined in one polymer chain. However, so far, the exact sequence of the monomers has not been controllable by common synthetic approaches since polymerization is usually a statistical process.

A specific feature of polymers and the major difference to naturally occurring proteins and polynucleic acids is their dispersity. This can account on the one hand for the chemical composition in copolymers, whereby each individual chain may have a different sequence of the comonomers (= isomers). However, it is especially prominent when one looks at the molar mass. The statistic nature of the polymerization process always results in a mixture of macromolecules of different lengths with a specific distribution in molar mass.
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In analogy to proteins, however, one can further define a “primary structure” in synthetic polymers, which describes not only the constitution but also the configuration of the monomer units within the polymer chain. Although monomer units are usually introduced head-to-tail, sometimes, head-to-head or tail-to-tail connections are observed that reduce the potential order in the chain. Similarly, cis- and trans-configuration within individual monomer units may have to be considered that can significantly change the material’s properties as can be seen in the comparison of poly(cis-1,4-isoprene) (natural rubber) to poly(trans-1,4-isoprene) (a brittle material without commercial use). A specific feature in polymers is tacticity, which describes the arrangement of the substituent in a repeating unit and can be isotactic (always in the same direction), syndiotactic (controlled alternating), or atactic (random) (Fig. 1.1). Isotactic polypropylene is a million-ton-scale technical thermoplastic material that is used widely in packaging, whereas atactic polypropylene is a viscous oil with no practical use (see Chapter 2).

In further analogy to proteins, macromolecules can also have a secondary structure, which is the arrangement of the chain in a coil, wormlike, or rigid structure, which is mainly defined by the rigidity of the repeating units and specific physical interactions with the solvent or nearby polymer chains. Finally, a tertiary structure can also be assigned, which describes the arrangement of the polymer chains toward each other in the bulk state. Today, one

![Random coil](image1)

![Worm like](image2)

![Rigid rod](image3)

![Highly crystalline polymers](image4)

![Partial crystalline polymers](image5)

![Liquid crystalline polymers](image6)

**FIGURE 1.1** Structure and form of polymer chains in solution and melt (top) and possible ordered bulk structures (bottom).
could stretch the term “tertiary structure” in polymers even further to include their self-assembly and aggregation status in solution, which can lead to very complex and rather well-defined nanostructures.

The statistical synthesis process and the many parameters determining a polymer product tend to make it a complex and often rather ill-defined material. However, new methods in polymer synthesis have recently evolved and existing methods have been further developed that allow much higher control of a polymer’s constitution, connectivity, molar mass, configuration, and even its “tertiary structure” formation and self-assembly. So, the ultimate goal to prepare synthetic macromolecules with the same precision found in nature but with precisely adjusted combinations of functionality—even beyond nature—may come within reach.

1.2 MACROMOLECULAR ENGINEERING AND NANOSTRUCTURE FORMATION

For many years, synthetic processes for polymers have been optimized with regard to reducing costs, increasing production output, and allowing high reproducibility. In addition, methods have been developed to control the configuration of polymers so that the thermal and mechanical properties of structural polymers and their order in bulk can be defined.

However, with the focus in research shifting from large-scale structural polymers to tailor-made functional polymers, polymerization methods have evolved, which allow macromolecular engineering of synthetic macromolecules mainly involving controlled polymerization techniques (see Section 3.2) and efficient polymer analogous reactions (see Section 3.3). For biomedical applications, bioconjugation and self-assembly processes have obtained an even more prominent role. Polymer chemists are presently taking lessons from nature by attempting to essentially simplify and generalize in order to use this knowledge to produce something that is even better for a very specific target.

As a result, polymers with narrow dispersity can be now prepared that have well-defined block structures and in some cases even star and dendritic topologies. Control of the end functionality and effective organic polymer analogous reactions allow highly efficient bioconjugation. In addition, due to a much higher understanding of the behavior of macromolecules in solution, self-assembly strategies can be used to prepare complex multifunctional nanostructures in solution as ideal carrier structures for targeted and controlled drug delivery such as core–multishell nanocarriers (Fig. 1.2; see also Chapter 6).
For any material that is meant to eventually be applied in contact with a biosystem, specific needs arise that increase with the complexity of the application. This is certainly also true for polymers. Besides a high level of control over and knowledge of the chemical structure, architecture, and molar mass, which are essential prerequisites for admission in biomedical applications, one also has to be able to control the biointeractions. Polymers can be fully bioinert or may have various aspects of biocompatibility like low cell toxicity and low unspecific protein adsorption, or may exhibit specific bioactivity. Furthermore, they can be biostable, which is a major prerequisite for most conventional implants. But stable materials have to be excreted completely from a human body when used as a carrier system, or they may degrade in a biological system, which leads to the need to consider the fate of the degradation products. Some polymers are already very well established in biomedical applications. For example, poly(ethylene glycol) (PEG) is used in particular to introduce water solubility into drugs and carrier systems and to reduce any unspecific biointeractions due to its property to cause negligible protein adsorption, but the biointeractions have to be elucidated with extreme care for any new polymer.

Applications of polymers can vary broadly from short-term peripheral like a simple coating that lubricates a surface of a catheter to enhance comfort and biocompatibility up to permanent implants and finally active and responsive systems that actively interfere with biological processes. In their role as carriers for diagnostics and treatment, polymers can either just be a “neutral” material acting as a reservoir or they can carry targeting functions or actively respond to stimuli for inducing delivery. Increasing complexity of the macromolecular
architectures and use of bioactive conjugates results in similar regulatory requirements as necessary for pharmaceuticals and complicates market introduction in many cases.

Therefore, more interdisciplinary research work is needed between polymer chemistry, biology, and medicine, and specific characterization tools have to be developed, to meet these new challenges.

Still, huge progress is being made due to synthetic tools and specific characterization methods now available and the first promising structures have already evolved. Even in vivo tissue engineering is no longer a vision of the future, because there are now bioconjugate scaffolds that not only act as simple base for cell adhesion but also recapitulate and modulate functional features of biological microenvironments to direct cellular fate decision and tissue regeneration (Fig. 1.3).

REFERENCE