Theory and Applications of Intelligent Biomaterials

Nicholas A Peppas
Department of Chemical Engineering, The University of Texas at Austin,
1 University Station, Code C0400
Austin, TX 78712

Introduction

In the rapidly changing scientific world, contributions of scientists and engineers are leading to major new solutions of significant medical problems. No longer is the treatment of diabetes, osteoporosis, asthma, cardiac problems, cancer and other diseases based only on conventional pharmaceutical formulations. Biology and medicine are beginning to reduce the problems of disease to problems of molecular science, and are creating new opportunities for treating and curing disease. Such advances are coupled closely with advances in biomaterials and are leading to a variety of approaches for relieving suffering and prolonging life.

Of particular interest is the central position that materials (especially polymers, ceramics and metals) have taken in the development of novel treatments over the last 30 years. Biomaterials are generally substances other than food or drugs contained in therapeutic or diagnostic systems that are in contact with tissue or biological fluids. They are used in many biomedical and pharmaceutical preparations, they play a central role in extracorporeal devices, from contact lenses to kidney dialyzers, and are essential components of implants, from vascular grafts to cardiac pacemakers. There are many current biomaterials applications, found in about 8,000 different kinds of medical devices, 2,500 separate diagnostic products, and 40,000 different pharmaceutical preparations. Although biomaterials already contribute greatly to the improvement of health, the need exists for better polymer, ceramic, and metal systems and improved methods of characterizing them.

Polymeric Materials as Biomaterials

The development of biomaterials has been an evolving process. Many biomaterials in clinical use were not originally designed as such but were off-the-shelf materials that clinicians found useful in solving a problem. In the last few years, novel synthetic techniques have been used to impart desirable chemical, physical, and biological properties to biomaterials. Materials have either been synthesized directly, so that desirable chain segments or functional groups are built into the material, or indirectly, by chemical modification of existing structures to add desirable segments or functional groups.

Polymeric biomaterials can be produced by copolymerizations of conventional monomers to achieve nearly monodisperse polymers. It is possible to produce polymers containing specific hydrophilic or hydrophobic entities, biodegradable repeating units, or multifunctional structures that can become points for three-dimensional expansion of networks. Advanced computer techniques allow researchers to follow the kinetics of formation of three-dimensional structures of these biomaterials.

Another synthetic approach involves genetic engineering for the preparation of artificial proteins of uniform structure. This enables the synthesis of periodic polypeptides that form well-defined lamellar crystals, polypeptides containing non-natural amino acids, and monodisperse helical rods. Important issues to be addressed include immunogenicity and purification from contaminants during large-scale production. If techniques were developed to produce polymers with the use of non-amide backbones, the versatility of this approach would be extended.

Efforts have also been made toward chemical modification of polymer surface or bulk properties, by treatments such as plasma modification. One surface treatment of biomaterials involves grafting inert substances such as PEO segments onto or within existing polymers such as polyurethanes to enhance biocompatibility or reduce protein adsorption. In addition, polymers

have been synthesized that promote a desirable interaction between themselves and surrounding cells. Thus peptide sequences, such as Arg-Glu-Asp-Val, that promote endothelial cell seeding have been synthesized into polymers for potential use as artificial blood vessels (vascular grafts) and copolymers of lactic acid and lysine have been synthesized, to which specific amino acid sequences that promote adhesion of hepatocytes or other cells can be attached for potential use in tissue engineering.

Other synthetic approaches have been used to develop environmentally responsive biomaterials (to surrounding pH, ionic strength, or temperature). For example, poly(acrylic acid) with ionizable side groups responds to changes in pH or ionic strength

Hydrogels Hydrogels are water-swollen networks (crosslinked structures) composed of hydrophilic homopolymers or copolymers. They are rendered insoluble due to the presence of chemical (covalent or ionic) or physical crosslinks. The latter can be entanglements, crystallites or hydrogen-bonded structures. Hydrogels may exhibit swelling behavior dependent on the external environment. Thus, in the last thirty years there has been a major interest in the development and analysis of environmentally or physiologically responsive hydrogels. These hydrogels show drastic changes in their swelling ratio due to changes in their external pH, temperature, ionic strength, nature of the swelling agent, and electromagnetic radiation. Hydrogels which exhibit pH-dependent swelling behavior contain either acidic or basic pendant groups. In aqueous media of appropriate pH and ionic strength, the pendent groups can ionize, developing fixed charges on the gel. Some advantages to using ionic materials, as they exhibit pH and ionic strength sensitivity, are relevant in drug delivery applications.

An additional advantage of hydrogels, which is only now being realized, is that they may provide desirable protection of drugs, peptides, and especially proteins from the potentially harsh environment in the vicinity of the release site. Thus, such carriers may be used in the future for the oral delivery of proteins or peptides. Finally, hydrogels may be excellent candidates as biorecognizable biomaterials. As such, they can be used as targetable carriers of bioactive agents, as bioadhesive systems or as conjugates with desirable biological properties.

Hydrophobic carriers and Molecular Design Initial studies focused on materials that were commercially available and had some useful properties such as being reasonably biocompatible, although the properties may not have always been optimal for a particular application. Ethylene-vinyl acetate copolymer was a polymer that was particularly useful. It had already been approved in certain medical devices; even though it's original applications were in commodity objects such as coatings.

In the 1980's, it became increasingly clear that polymers should be more rationally designed for medical purposes. A particular example are polyanhydrides. Biomaterials could be chemically synthesized from first principles to possess precisely the correct chemical, engineering, and biological properties for the exact medical application.

Most recently high throughput polymer synthesis has been employed to rapidly synthesize new polymers and screen them for different applications.

Environmentally Responsive Biomaterials Several factors affect the swelling/deswelling of environmentally responsive hydrogels. They include the degree of ionization in the network, the ionization equilibrium and the nature of the counterions. As the ionic content of a hydrogel is increased in response to an environmental stimulus, increased repulsive forces develop and the network becomes more hydrophilic. Because of Donnan equilibrium, the chemical potential of the ions inside the gel must be equal to the chemical potential of the ions in the solvent outside of the gel. An ionization equilibrium is established in the form of a double layer of fixed charges on the pendant groups and counterions in the gel. The nature of counterions in the dissolution medium also affects the swelling of the gel. Work on environmentally responsive hydrogels has taken several directions over the past several years, concentrating predominantly on ingeniously designed systems that utilize the pH- and temperature-sensitivity characteristics of certain hydrogel structures.

For example, various types of poly(N-isopropyl acrylamide) have been used both as expanding (swelling) and squeezing hydrogels. Such systems have been shown to exhibit an "on/off" mechanism of control of the drug or protein release/delivery rate. The physicochemical understanding of such hydrogels under the conditions of application is neither simple nor well developed. Considering that all these carriers are ionic hydrogels, and that several ionic and macromolecular components are involved, with associated thermodynamically non-ideal interactions, it is evident that analysis and prediction of the swelling and drug delivery behavior is rather complex.

Certain hydrogels may exhibit environmental sensitivity due to the formation of interpolymer complexes. These complexes, which have been shown in homo- and copolymer networks, are formed by non-covalent association between two or more complimentary polymers. The stability of the associations is dependent on such factors as the nature of the swelling agent, temperature, type of dissolution medium, pH and ionic strength, network composition and structure, and length of the interacting polymer chains. The incorporation of poly(ethylene glycol) (PEG) in pH- or temperature-sensitive materials seems to provide desirable characteristics of protein stability and biological stealth behavior. Hydrogen- bonded, complexation networks of poly(methacrylic acid-g-ethylene glycol) hydrogels exhibit abrupt expansion and contraction which is based on hydrogen bonding between the carboxyl group of MAA and the etheric group of EG. There is a rather abrupt change in the gel swelling ratio and mesh size due to pH changes.

Conclusions

The design of novel biomaterials requires careful consideration of their function and thermodynamic response to surrounding fluids. Using combinatorial method and other design techniques, we can achieve superior properties and long term stability.