Recent Advances of Biodegradable Polymers for Medical Applications

Jung-Suk Sung* and Yong Kiel Sung

1Department of Life Science, Dongguk University, Seoul 100-715, Korea
2Department of Chemistry, Dongguk University, Seoul 100-715, Korea
(Received December 5, 2005/Accepted July 21, 2006)

The recent advances of biodegradable polymers for medical applications have been reviewed on the basis of biodegradability, functionality, and biocompatibility. These include the functional biodegradable polymers developed for biomedical applications. The biodegradable polymers synthesized from Krebs cycle acid derivatives, injectable biodegradable block copolymers, biodegradable polymers for RNA interference and DNA matrix-based biopolymeric systems for tissue engineering have been also discussed briefly.

Key words: Biodegradable polymer, RNA, DNA, Krebs cycle acids, Biocompatibility, Biodegradability, Drug delivery systems, Gene carriers, Biomedical applications

INTRODUCTION

Functional biodegradable polymers have been recently developed to apply to tissue regeneration, gene carriers, and drug delivery systems for biomedical applications. The main reasons introducing the biodegradable polymers as biomaterials involve: non-toxicity and biodegradation. The first one is that the products of biodegradation in living body may be eliminated metabolically from the body, resulting in no need anymore for the procedure of post-surgical function after use as biomaterials. The other is that the biodegradation may be affected to the controlled drug releasing profiles using biodegradable polymeric biomaterials. The nature and behaviors of biodegradable polymeric matrices are contributed to the important roles in the construction and in determining the drug controlled release profile in living body. A number of biodegradable functional polymers have been developed for the purpose of reconstructive generation and drug delivery systems for biomedical applications. Among the polymeric systems, the important functional polymers are belong to mostly biocompatible, nontoxic natural and synthetic biodegradable polymers such as proteins, polysaccharides, celluloses, poly(α-amino acids), poly(esters), poly(ortho esters), poly(phoshazenes), poly(alkyl cyanoacrylates), poly(anhydrides), and so on. The useful biomedical polymers in this field should be biodegraded into nontoxic intermediate degraded monomers in living body. The biodegradation rate is very important in the medical applications of biodegradable polymeric systems. The degradation processes of biodegradable polymers should be examined both in vitro and in vivo examinations. The in vitro biodegradation tests can be carried out in pseudo extra cellular fluid, plasma solution, and enzymes buffer solutions. The in vivo biodegradation tests can be usually carried out by introducing the adjustably biodegradable biomaterials into the particular site of living body such as sub-dermal muscle peritoneal cavity, subcutaneous tissue, and blood tubes.

The medical applications of biodegradable polymers include the absorbable bone plates and other surgical fixation devices, artificial skin substitutes, and carrier systems for the controlled release of drugs. Especially, functional biodegradable polymers have been used in the development of polymeric matrices for the controlled and sustained release of low molecular weight therapeutic agents and short-term implants such as suture and surgical staple for biomedical applications. Such implants should maintain their functionality over a relatively short period of time. However, the efforts to develop the absorbable implants that will fulfill more demanding functions such as vascular prosthesis and osteoplastic devices (bone screws, plates, pins, etc) have been recently continued. Such implants must maintain chemical and mechanical stabilities in vivo over a sufficient period of time for the fulfillment of their primary function of allowing regeneration of the substituted organ or assuring adequate stability of bone fracture during healing. The scarcity of the polymers that meet these demanding requirements has prompted a continuous search for the improved functional biodegradable polymers.

There are many factors affecting the biodegradability of polymeric materials. They are related to primary structures...
(chemical composition, molecular weight, molecular weight distribution, etc.), higher-order structures (melting point, glass transition temperature, crystallinity, crystal structure, etc.), and surface conditions (surface area, hydrophilicity, hydrophobicity, etc.)

When these factors are interrelated in a complicated way, it is not easy to clarify the structure-biodegradability relationships for a wide range of polymers. In this review, the biodegradable functional polymers for medical applications have been briefly discussed on the basis of biodegradability, functionality, and biocompatibility.

**FUNCTIONAL BIODEGRADABLE POLYMERS FOR MEDICAL APPLICATIONS**

**Biodegradable Polymers from Krebs Cycle Acid Derivatives**

The efforts have been recently directed toward the synthesis of functional biodegradable polymers for the biomedical applications. The Krebs cycle acid derivatives are good candidates for the development of new polyesters for the medical application such as drug delivery systems. The tricarboxylic acid cycle or Krebs cycle is the process during which acetyl moiety in acetyl CoA is oxidized completely to carbon dioxide and water. It has been proven that the polyesters prepared from the Krebs cycle acid derivatives are biocompatible and biodegradable. Therefore, their degradation residues may be nontoxic. The monomers such as 1,4-butanediol dilactate and 2-acetoxy succinic acid were synthesized for the development of new biodegradable polymers. 1,4-Butanediol dilactate (BDLA) was synthesized using L-lactic acid and 1,4-butanediol diluted in cyclohexane. The synthesis of 2-acetoxy succinic acid (2-ASA) was also carried out using L-malic acid and acetic anhydride. Poly(1,4-butanediol-co-succinate) (PBS) was synthesized from 1,4-butanediol, succinic anhydride, and p-toluene-sulfonic acid. Poly(1,4-butanediol dilactate-co-succinate) (PBDS) was prepared from BDLA and succinic anhydride. Poly(1,4-butanediol dilactate-co-2-acetoxy succinate) (PBDDS) was polymerized using 2-acetoxy succinic acid with 1,4-butanediol as the same method of PBS polymerization. The crosslinked poly(1,4-butanediol-co-L-lactide) were also synthesized from L-lactic acid and 1,4-butanediol by varying functional group ratios.

The hydrolytic behaviors of the synthesized polymers in various pH buffer solutions and their biodegradation by microorganisms were studied. Thus far, the effects of crystallinity and molecular weights on the biodegradation have been also investigated. The swelling ratios of the crosslinked copolyesters were also measured in different pH solutions at 20, 30, and 37°C. The swelling degree of crosslinked poly(1,4-butanediol-co-L-lactide) was increased with decreasing crosslink density at pH 7.4. The hydrolysis of the copolyesters proceeded faster with increasing pH of solutions. The hydrolytic degradation of polylactic acid (PLA) and polyglycolic acid (PGA) is a good example.

**Injectable Biodegradable Block Copolymer Systems**

Injectable biodegradable polymers are of particular interest for tissue engineering and drug delivery systems. Several types of in situ forming biodegradable polymers have been synthe-
The aqueous poly(ethylene glycol)-block-poly(D, L-lactic acid-co-glycolic acid)-block-ethylene glycol (PEG-PLGA-PEG) triblock copolymer solutions are free flowing sols at room temperature, however, a gel of PEG-PLGA-PEG is formed at body temperature near 37 °C. These PEG-PLGA-PEG triblock copolymers were prepared by ring-opening polymerization of DL-lactide and glycolide onto monomethoxy poly(ethylene glycol) followed by coupling of the hydroxyl groups of resulting PEG-PLGA diblock copolymers using hexamethylene diisocyanate. The PEG-PLGA-PEG systems have been recently designed on the basis of the proven biocompatibility of PEG, lactic acid, and glycolic acid which are final degradation products of these polymers. The PEG-PLGA diblock copolymers with different length of PLGA may be formed during the degradation of these triblock copolymers.

RNA interference (RNAi) represents a naturally powerful method occurring biological strategy for inhibition of gene expression. It is mediated through small interfering RNAs (siRNAs), which trigger specific mRNA degradation. In mammalian systems, however, the application of siRNAs is severely limited by the instability and poor delivery of unmodified siRNA molecules into the cells in vivo. Similar strategy has been developed for the construction of a target-specific delivery system of green fluorescent protein (GFP) siRNA plasmid DNA by utilizing folate-modified cationic low molecular weight poly(ethylene imine) (PEI). The application of this system to folate receptor positive cells resulted in a marked reduction of GFP expression. The extent of GFP gene inhibition and cellular uptake behaviors appeared to be more effective with pSUPER-sGFP/PEI-PEG-folate complex than pSUPER-sGFP/PEI complex with no folate moieties, while such inhibition was largely dependent on the presence of folate receptors in the cells. This observation indicates the use of folate receptor-mediated endocytosis as a major pathway in the process of cellular uptake of siRNA-plasmid, suggesting that targeted delivery of siRNA vector could be achieved by cell-specific manners.

On the other hand, self-assembling nanoparticles with siRNA has been constructed with PEI that is PEGylated with an peptide ligand attached at the distal end of PEG. When the organic-inorganic hybrid nanoparticles entrapping oligodeoxynucleotide or siRNA were prepared through the self-associating phenomenon of the block copolymer, poly(ethylene glycol)-block-poly(aspartic acid) (PEG-b-PAA), with calcium phosphate, the calcium phosphate core dissociates in the intracellular environment with appreciably lowered calcium ion concentration compared to the exterior, allowing the release of the incorporated oligodeoxynucleotide and siRNA in a controlled manner. Utilizing functional biodegradable polymers in the development of better method for highly efficient delivery of siRNA in a controlled manner, they will provide powerful RNAi tools for biomedical applications in future.

### Biodegradable Polymeric DNA Matrix-based Systems

DNA-based tissue engineering for biomedical application has been investigated as a way to grow new tissues and organs. Ideally, the local delivery of plasmid DNA will allow appropriate levels of transgene expression for a prolonged period. For example, sustained release of plasmid DNA from biodegradable poly(D,L-lactic-co-glycolic acid) (PLGA) matrices can lead to the transfection of large number of cells at a localized site, leading to the production of therapeutic proteins needed for tissue regeneration. PLGA matrices containing plasmid DNA can be targeted physically, and can express protein for a prolonged period of time. It has been incorporated plasmid DNA encoding platelet-derived growth factor (PDGF) directly into PLGA three-dimensional matrices. Plasmid DNA was subsequently released from the matrices over a period ranging from days to month in vitro, and led to enhancement of matrix deposition and blood vessel formation in developing tissues in vivo. The inefficient delivery of growth factors locally in a transient but sustained manner is a major barrier to effective tissue regeneration. However, systems for localized and sustained delivery of plasmids should be suited for growth factor therapeutics. It has been investigated the possible use of polymer matrices containing pMai-1 plasmid DNA, which encodes a secreted peptide fragment of human parathyroid hormone, for bone regeneration in a beagle thia critical defect model. The implantation of polymer matrices with plasmid DNA at the site of bone injury was associated with retention and gene expression of the plasmid DNA for at least 6 week. Using biocompatible materials for local and sustained-controlled release of plasmid DNA carrying a PLGA/FGF-4 cDNA, the plasmid DNA delivery systems were developed for tissue engineering.

Poly [α-(4-aminobutyl)-L-glycolic acid] (PAGA) is a biodegradable analogue of PLL, which can rapidly degrade in aqueous solution to give L-oxylsine as a final product. To circumvent the cytotoxicity, non-biodegradability and low transfection efficiency of PLL, PAGA was synthesized. This water-soluble polymer efficiently condenses plasmids and demonstrates transfection efficiencies higher than those of PLL-based systems in cultured cells. PAGA is currently being investigated for cytokine gene delivery for the treatment of diabetes and cancer. The expression level of IL-10 in 293 T cells with PAGA/pmIL-10 was significantly higher than that attained with naked DNA. Systemic administration of PAGA / pmIL-10 into NOD mice markedly reduced insulitis compared to diabetic controls. However, systemic delivery of PAGA / pmIL-10 into diabetic NOD/SII mice was associated with the induction of autoimmune diabetes.
to the mice injection with naked DNA (15.79% vs 90.9%). Single injection of PAGA/pmIL-12 complexes to subcutaneous tumor bearing BALB/c mice significantly enhanced mIL-12 expression and reduced the tumor growth. PAGA/pluc or PAGA/pmIL-12 complexes are likely to degrade quickly after entering the cytosol due to autohydrolysis of ester linkages in PAGA, which could explain the relatively low DNA transfection efficiency.

The chemical modifications of PAGA aimed at slowing down the degradation rates are currently being studied. Another biodegradable cationic polymer, poly (4-hydroxy-L-proline ester) (PHP ester), has been also studied. PHP ester can be synthesized from CBZ-4-hydroxy-L-proline by melting-condensation polymerization of NCbz-4-hydroxy-L-proline followed by deprotection using palladium on activated carbon as a catalyst or by using dicyclohexylcarbodiimide/(dimethylamino)pyridine (DCC/DMAP)-activated polycodensation of N-carboxy-4-hydroxy-L-proline. PHP ester can condense DNA and it shows low cytotoxicity. Its transfection efficiency is similar to that of PLL. Poly(D,L-lactic acid-co-glycolic acid) (PLGA) is a commonly used biodegradable and biocompatible polymer. PLGA microspheres have been shown to protect DNA from degradation by nuclease. Using a water-in-oil-in-water (W/O/W) double-emulsion and solvent evaporation method, the nanospheres containing plasmid DNA was prepared. The microsphere size, release kinetics, and encapsulation efficiency of plasmid DNA were found to be dependent on the emulsification method, water/oil ratio, primary emulsion, and the surfactant concentration. Furthermore, DNA is nicked in the steps of microencapsulation and lyophilization. Therefore, prior to the preparation of microsphere, PLL is used to pre-condense the DNA.

Plasmid DNA was mixed with these nanoparticles and incubated for 1 hr at room temperature. The adsorption of DNA on the surface of the nanoparticle was dependent on the dextran contents in the graft copolymer. The adsorption of DNA on the surface of the nanoparticle was dependent on the dextran contents in the graft copolymer. It has been conjugated polysaccharide-grafted PLL and mixed this with poly(D,L-lactide) to prepare nanoparticles by either solvent evaporation or dialfiltration. The ionic interaction between DNA and PLL moieties on the nanoparticles is thought to be the main driving force for DNA absorption on the nanoparticles. For the nanoparticles prepared from PLL homopolymer/PLA, the majority of the amino groups in PLL might be interacting with PLA, leading to form adsorption of PLL on the nanoparticle surfaces.

On the other hand, dextran-graft chains partially disturb the ionic interaction between PLA and PLL segments. Therefore, PLL segments on the copolymer nanoparticles adopt the "loop" and "tail" forms. The majority of the amino groups in PLL backbone are free on the surface adsorption form, providing a higher capacity for DNA adsorption. PLL-graft-Dex/PLA nanoparticles with DNA complexes can be produced at a size of 250 nm in diameter, and which enhance the ability of complex formation by 3 times as compared to PLL/PLA systems. DNA-based tissue engineering is going to progress as a way in near future. The local delivery of plasmid DNA will also allow appropriate levels of transgene expression for a prolonged period. As compared to viral vectors, nonviral systems have a low or absent immunogenicity. These include low molecular weight linear poly(ethylene imine)-poly(ethylene glycol)-poly(ethylene glycol) triblock copolymers and biodegradable hyperbranched polyester amine. The impact that monoclonal antibodies have had in the clinical treatment of cancer has been also pronounced. The new linker technology such as monomethylauristatin F through monoclonal antibody delivery appears to be ideally suited for drugs that are both relatively cell-impermeable and tolerant of substitution with amino acids.

ACKNOWLEDGEMENTS

The research has been supported by Dongguk University and KOSEF. We would like to express their appreciutions to Prof. Jin Ho Lee, Editor-in-Chief, Prof. Jong-Chul Park, Associate Editor, and the other members of editorial board who have provided an opportunity to write an invited paper in the 10th anniversary journal of Biomaterials Research.

REFERENCES


Biomaterials Research 2006
54. Y. B. Lim, Y. H. Choi, and J. S. Park, “A Self-Destroying Polyca-}

61. Z. Y. Zhong, Y. Song, J. F. Engbersen, M. C. Lok, W. E. Hen-}}

63. S. O. Doronina, B. A. Mendelsohn, T. D. Bovée, C. G. Cer-}}