

Polymer Nanocomposites for Biomedical Applications

Rohan A. Hule and Darrin J. Pochan

Abstract

Bionanocomposites have established themselves as a promising class of hybrid materials derived from natural and synthetic biodegradable polymers and organic/inorganic fillers. Different chemistries and compositions can lead to applications from tissue engineering to load-bearing composites for bone reconstruction. A critical factor underlying biomedical nanocomposite properties is interaction between the chosen matrix and the filler. This article discusses current efforts and key research challenges in the development of these materials for use in potential biomedical applications.

Introduction and Challenges

Bionanocomposites form a fascinating interdisciplinary area that brings together biology, materials science, and nanotechnology. New bionanocomposites are impacting diverse areas, in particular, biomedical science. Generally, polymer nanocomposites are the result of the combination of polymers and inorganic/organic fillers at the nanometer scale. The extraordinary versatility of these new materials springs from the large selection of biopolymers and fillers available to researchers. Existing biopolymers include, but are not limited to, polysaccharides, aliphatic polyesters, polypeptides and proteins, and polynucleic acids, whereas fillers include clays, hydroxyapatite, and metal nanoparticles.¹

The interaction between filler components of nanocomposites at the nanometer scale enables them to act as molecular bridges in the polymer matrix. This is the basis for enhanced mechanical properties of the nanocomposite as compared to conventional microcomposites.² Bionanocomposites add a new dimension to these enhanced properties in that they are biocompatible and/or biodegradable materials.

For the sake of this review, biodegradable materials can be described as materials degraded and gradually absorbed and/or eliminated by the body, whether

degradation is caused mainly by hydrolysis or mediated by metabolic processes.³ Therefore, these nanocomposites are of immense interest to biomedical technologies such as tissue engineering, bone replacement/repair, dental applications, and controlled drug delivery. Table I lists some biopolymers commonly used in biomedical applications.

Current opportunities for polymer nanocomposites in the biomedical arena arise from the multitude of applications and the vastly different functional requirements for each of these applications. For example, the screws and rods that are used for internal bone fixation bring the bone surfaces in close proximity to promote healing. This stabilization must persist for weeks to months without loosening or breaking.³ The modulus of the implant must be close to that of the bone for efficient load transfer.^{4,5} The screws and rods must be non-corrosive, nontoxic, and easy to remove if necessary.⁶ Thus, a polymer nanocomposite implant must meet certain design and functional criteria, including biocompatibility, biodegradability, mechanical properties, and, in some cases, aesthetic demands. The underlying solution to the use of polymer nanocomposites in vastly differing applications is the correct choice of

matrix polymer chemistry, filler type, and matrix-filler interaction. This article discusses current efforts and focuses on key research challenges in the emerging usage of polymer nanocomposites for potential biomedical applications.

Hydroxyapatite-Polymer Nanocomposites

Producing bionanocomposites based on biomimetic approaches has been a recent focus of researchers. Among these materials, hydroxyapatite (HAP)-polymer nanocomposites have been used as a biocompatible and osteoconductive substitute for bone repair and implantation.^{7,8} As the main inorganic component of hard tissue, HAP [$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$] has long been used in orthopedic surgery. However, HAP is difficult to shape because of its brittleness and lack of flexibility. HAP powders can migrate from implanted sites, thus making them inappropriate for use. Moreover, these powders do not disperse well and agglomerate easily.⁹ Therefore, the incorporation of HAP in polymeric nanocomposites to overcome processing and dispersion challenges is of great interest to the biomedical community. Consequently, a desirable material for use in clinical orthopedics would be a biodegradable structure that induces and promotes new bone formation at the required site.

To date, primarily polysaccharide and polypeptidic matrices have been used with HAP nanoparticles for composite formation. Yamaguchi and co-workers have synthesized and studied flexible chitosan-HAP nanocomposites.⁹ The matrix used for this study, chitosan (a cationic, biodegradable polysaccharide), is flexible and has a high resistance upon heating because of intramolecular hydrogen bonds formed between the hydroxyl and amino groups.^{10,11} The resulting nanocomposite, prepared by the coprecipitation method, is mechanically flexible and can be formed into any desired shape.⁹

Nanocomposites formed from gelatin and HAP nanocrystals are conducive to the attachment, growth, and proliferation of human osteoblast cells.¹² Collagen-based, polypeptidic gelatin has a high number of functional groups and is currently being used in wound dressings and pharmaceutical adhesives in clinics.¹³ The flexibility and cost-effectiveness of gelatin can be combined with the bioactivity and osteoconductivity of HAP to generate potential engineering biomaterials. The traditional problem of HAP aggregation was overcome by precipitation of the apatite crystals within a polymer solution.^{14,15} The porous scaffold generated by this method exhibited well-developed structural features

Table I: Biopolymers Commonly Used in Biomedical Applications.

Biopolymer	Structure
Chitosan	
Collagen	
Poly(lactic acid) (PLA)	
Poly(epsilon-caprolactone) (PCL)	
Poly(L-lysine) (PLL)	

and pore configuration to induce blood circulation and cell ingrowth. Such nanocomposites have high potential for use as hard-tissue scaffolds.¹²

Three-dimensional porous scaffolds from biomimetic HAP/chitosan-gelatin network composites with microscale porosity have shown adhesion, proliferation, and expression of osteoblasts.¹⁶ A low-magnification scanning electron micrograph of such a scaffold showing uniform pore sizes and walls is shown in Figure 1. Porosity is critical for tissue-engineering applications because it enables the diffusion of cellular nutrients and waste, and provides for cell movement.¹⁷

Polysaccharides, such as alginate, provide a natural polymeric sponge structure that has been used in tissue-engineering scaffold design. The weak, soft alginate scaffolds can be strengthened with HAP and have widespread applications.¹⁸ Composite membranes from HAP nanoparticles and chitosan/collagen sols have also been synthesized to study connective-tissue reactions.^{19,20}

Studies that target the nucleation of calcium phosphates and bone cell signaling within the matrix have used acidic macromolecules as the nanocomposite matrix.²¹ Specifically, amino acids like aspartic acid and glutamic acid have been used as the

matrix protein. Both of these amino acids are known to play an important role in intercellular communication and osteoblast differentiation that increases extracellular mineralization. Related studies have also highlighted the significance of aspartic acid in the treatment of osteoporosis and other bone dysfunctions.²²

Aliphatic Polyester Nanocomposites

Aliphatic polyesters have been the predominant choice for materials in degradable drug delivery systems. Homopolymers and copolymers derived from glycolic acid or glycolide, lactic acid or lactide, and

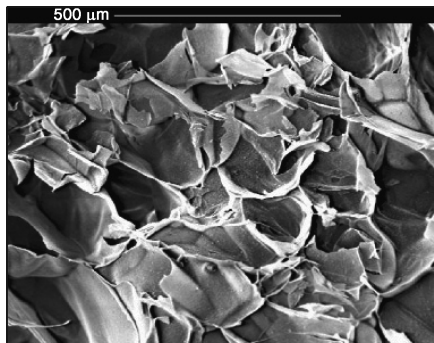


Figure 1. Low-magnification scanning electron micrograph of a hydroxyapatite (HAP)-polymer/chitosan-gelatin scaffold prepared from HAP/chitosan-gelatin/ acetic acid mixture. The uniform porosity observed in the micrograph is advantageous for tissue-engineering applications. The chitosan-gelatin concentration used was 2.5 wt%; HAP/chitosan-gelatin, 30/70 parts by weight. (Reproduced from Reference 16.)

ϵ -caprolactone form the bulk of this research. Most of these polymers degrade by acid- or base-catalyzed hydrolytic cleavage of the backbone or by enzymatic activity.²³

Of the polyesters that show promise in biomedical fields, poly(L-lactic acid) (PLLA) is the most prevalent. Although reports of the use of PLLA can be found in the 1960s, a phenomenal amount of work has been performed recently. PLLA has widespread applications in sutures, drug delivery devices, prosthetics, scaffolds, vascular grafts, bone screws, pins, and plates for temporary internal fixation.²⁴ Good mechanical properties and degradation into nontoxic products²⁵ are the main reasons for such an array of applications. Additionally, PLLA is U.S. Food and Drug Administration-approved and available commercially in a variety of grades. As a material, PLLA is relatively hard and crystalline with a melting point between 170°C–180°C and a glass-transition temperature T_g of ~60°C–67°C. Another factor contributing to the use of PLLA in biomedical applications is its ability to be copolymerized and blended to obtain a nanocomposite-like product with desirable properties. The racemic version of the polymer, poly(D,L-lactide) (PDLLA), sometimes simply called PLA, is amorphous with a T_g of around 50°C–60°C.

Studies also have been done to evaluate the potential of PLLA as a bone reinforcement material. The mechanical properties of neat PLLA might be inadequate for high load-bearing applications.²⁶ This necessitates the incorporation of reinforcements

like oriented fibers, HAP, or clays to form nanocomposites. Such studies report an increase in the flexural modulus, strength, and moduli values commensurate with bone replacement implants.²⁷

“Self-reinforced” composites have also been synthesized by incorporation of oriented PLA fibers in a matrix of the same material.²⁸ Past work in our group²⁹ involved the synthesis of PLLA-organoclay nanocomposites via the exfoliation adsorption film-casting technique, in which both the matrix and the filler are sonicated separately in a common solvent. The two solutions are then mixed and cast on a substrate under controlled evaporation conditions, resulting in a film.

Exfoliation in the case of Cloisite 30B clay was ascribed to favorable enthalpic interactions between the diols of the organic modifier and carbonyl bonds of the PLLA backbone with polymer crystallinity being suppressed at complete exfoliation.²⁹ This unusual phenomenon necessitated in-depth studies that revealed lower crystallinity and crystallization rates and higher radial spherulitic growth rates resulting from the addition of highly miscible organoclay in PLLA.³⁰ Subsequent time-lapsed Fourier transform infrared (FTIR) studies attributed this behavior to the precedence of intrachain interactions, specifically, PLA 10₃ helix formation and backbone reorientation, over interchain interactions, as opposed to neat PLLA.^{31–33}

Poly(glycolic acid) (PGA) is another aliphatic polyester with applicability for biomedical use. However, unlike PLLA, PGA is readily soluble in water. Mechanical properties of self-reinforced PGA have been investigated and are found to worsen on exposure to distilled water.²³ Thus, water solubility and its high melting point limit the use of PGA in bionanocomposites.

Another biodegradable and nontoxic aliphatic polyester discussed in the biomedical nanocomposite literature is poly(ϵ -caprolactone) (PCL). Synthesized by the ring-opening polymerization of ϵ -caprolactone, it has a melting temperature of 61°C and a T_g of –60°C. The rubbery state permits the diffusion of low-molecular-weight species at body temperature, thus making PCL a promising candidate for controlled release and soft-tissue engineering. The range of properties can be furthered by copolymerization with other lactones such as glycolide, lactide, and poly(ethylene oxide) (PEO) or by nanofiller incorporation. Both techniques have been adopted and have shown great potential for biomedical applications.²³ Nanocomposite polymer-clay hydrogels have also been studied extensively by microscopy and scattering techniques.³⁴

Recently, electrospinning has been used as an alternative scaffold fabrication technique in soft-tissue transplantation and hard-tissue regeneration. This method provides woven mats with individual fiber diameters ranging from 50 nm to a few microns. The interconnected, porous network so formed is desirable for drug delivery as well as biomedical substrates for tissue regeneration, wound dressing, artificial blood vessels, and other uses. Electrospinning helps tailor the mechanical, biological, and kinetic properties of the scaffolds by varying parameters such as polymer solution properties and processing conditions (e.g., electrical force, the distance between the electrospinning needle and the oppositely charged surface acting as ground, spinneret geometry, and solution flow rate).³⁵ However, some of the restrictions of this method, like controlling the pore size and softness of the electrospun mat, currently prevents it from being used for hard-tissue applications. Studies incorporating montmorillonite clay³⁶ (MMT) in a PLLA solution that was subsequently electrospun into a mat found improved mechanical and biodegradation characteristics and ideal pore sizes (microns) for cell growth, blood vessel invasion, and nano-sized pores for nutrient/waste transfer.³⁷

Polypeptide-Based Nanocomposites

Polypeptides as matrices provide an additional array of opportunities in materials design and application in terms of a unique ability to adopt specific secondary, tertiary, and quaternary structures, a feature not available with synthetic polymers. Functionality can also be incorporated by the use of natural and non-natural amino acids with desired activity at specific sites along the polypeptide backbone. Our group has been investigating the incorporation of polypeptides, particularly, poly(L-lysine) (PLL), as the matrix polypeptide and MMT as the filler.³⁸ Initial work³⁹ produced nanocomposites from PLL and MMT that exhibited enhanced mechanical properties and thermal properties comparable to other widely explored biomaterials and engineering thermoplastics. A transmission electron micrograph showing the intercalated MMT layers in a PLL-MMT nanocomposite is shown in Figure 2.

The potential applicability of these materials was further investigated by studying the effect of the molecular weight of the polypeptide on the secondary conformation of the final nanocomposite matrix. PLL is a good choice for such a study because it can display a variety of secondary structures: the random coil, α -helix, or β -sheet in aqueous solution. Moreover, transitions

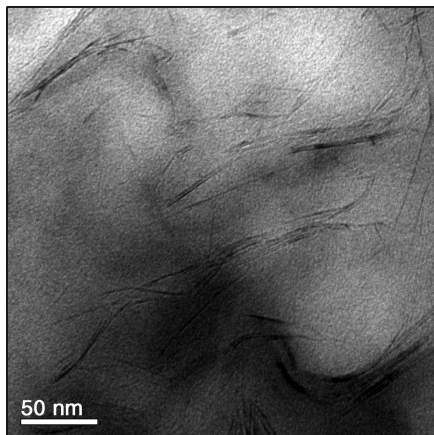


Figure 2. Bright-field transmission electron micrograph of a 5 wt% poly(L-lysine)-montmorillonite clay nanocomposite film, showing intercalated regions. The image was obtained on a microtomed film (<80 nm) at 200 kV. (Reproduced from Reference 38.)

between conformations can be easily achieved using pH, temperature, salt concentration, or alcohol content as an environmental stimulus. The secondary structure transitions in the liquid as well as the solid state and related thermodynamics have been accurately mapped using circular dichroism (CD), FTIR, and Raman spectroscopy. PLL folds preferentially in the β -sheet structure at the high concentrations relevant to nanocomposite film formation regardless of solution conformation from which films were cast. The transition from α -helix to β -sheet is directly dependent on molecular weight, with high-molecular-weight films showing a consistent β -sheet conformation and exhibiting a kinetic dependence on temperature. We hope this insight into the mechanism of secondary structural control in polypeptides will foster the design of new peptidic nanomaterials for specific desired applications in the biomedical arena.³⁸

Efforts in our group⁴⁰ have also been directed at responsive hydrogels constructed via self-assembly of short 20-residue peptides. These synthetic peptides are designed to intramolecularly fold under desired aqueous conditions and subsequently intermolecularly self-assemble into supramolecular networks.⁴⁰ The network scaffold is comprised of stiff, fibrillar structures that exhibit varied morphology, including twisted or untwisted single fibrils and fibril laminates.

Materials like these, in addition to proteins, introduce the possibility of fibril incorporation into nanocomposites as reinforcement with biodegradable matrices.

Such unique nanocomposites combine the degradability and strength of the gel matrix with control over functionality and morphology of the fibrillar fillers. Potential applications of such nanomaterials include drug delivery matrices, tissue-engineering scaffolds, and bioengineering materials, to name a few.

Nanocomposites from Other Polymers and Fillers

Nanocomposites from bioactive molecules and clays have also been reported. One such example is smectite nanocomposites that use the ability of smectites to induce specific cointercalation of purines and pyrimidines. Thus, thymine and uracil are absorbed on MMT appreciably if solutions also contain coabsorbed adenine.⁴¹

Layered double hydroxides (LDHs) present a layered structure comprised of di- and trivalent metal cations [M(II) and M(III)] coordinated by six oxygen anions. The substitution of M(III) cations induces an overall positive charge that is counterbalanced by exchangeable interlayer anions. Thus, LDHs can serve as hosts for polymeric intercalation. An attractive, potential application of LDHs is controlled drug release carriers. Several bioactive compounds like DNA and pharmaceuticals have been incorporated within LDH hosts.⁴²

Poly(urethane urea) (PUU) segmented block copolymers are common in ventricular assist devices and total artificial hearts as blood sacs. One of the main disadvantages of PUUs in these devices is their relatively high permeability to air and water vapor, a result of the diffusion through the poly(tetramethylene oxide) soft segments that are present as the majority component of the copolymer. The use of organically modified layered silicates seems particularly attractive among the variety of approaches taken to reduce permeability while maintaining desired biocompatibility and mechanical properties. This can be ascribed to the dramatic increase of barrier properties because of intercalated or exfoliated high-aspect-ratio (~1000) clay layers in the polymer matrix. Studies on the PUU-clay system have shown increases in the modulus and strength of the nanocomposite. However, in contrast to conventional composite systems, this enhancement does not come at the expense of ductility. In fact, it is reported that the ductility increases with clay loading.⁴³ A convincing explanation for this remarkable behavior has not yet emerged. Nonetheless, a significant reduction in gas permeability with an increase in mechanical properties has been shown.

Just as nanocomposites used for various biomedical applications have different requirements, nanocomposites used for dental

applications have unique necessities. Thermoset methacrylate-based composites are used commonly as dental restorative materials, because of a relatively high cure efficiency by free-radical polymerization and excellent aesthetic qualities. However, the demands of the oral environment and the masticatory loads encountered by dental restoratives require further property improvements in these materials. Specifically, nanocomposites with improved modulus, better efficiency of the free-radical polymerization, low water sorption, improved processability, and low shrinkage are needed. Selective functionalization of the filler can lead to better interactions at the filler-matrix interphase and has been used in studies in which silica nanoparticles were silanized to varying extents using two different modifiers and then mixed with a dimethacrylate resin. A few practical advantages of the dual silanization are improved workability of the composite paste, higher filler loadings leading to better modulus values, and nanocomposites with lower polymer shrinkage.⁴⁴

The design of cardiovascular interfaces necessitates a combination of amphiphilicity and antithrombogenicity. Amphiphilicity ensures optimal endothelial cell response at the vascular interface. Thrombogenicity refers to blood clot formation and can lead to early graft occlusion. Using reports of polyhedral oligomeric silsesquioxanes (POSS) acting as an amphiphile at the water-air interface, researchers have studied the possibility of using POSS at the vascular interface. The strong intermolecular forces between constituent molecules and neighbors and the robust framework of shorter bond lengths make POSS nanocomposites more resistant to degradation. Initial work has shown that POSS nanocomposites are cytocompatible, making them potentially suitable for tissue engineering.⁴⁵ Future efforts in this field are directed at assessing the thrombogenic potential of these nanocomposites, which would be critical in their application as cardiovascular interfaces.

Concluding Remarks

We have discussed an emerging group of hybrid materials based on various polymers and nanofillers that are either used extensively or show promise in the area of biomedical materials. These novel materials vary from inorganic/ceramic-reinforced nanocomposites for mechanical enhancement to peptide-based nanomaterials in which peptides are both the filler and the matrix, with the chemistry designed to render the entire material biocompatible. Interest in these nanocomposites varies from application-oriented design to understanding a multitude of structure-property

relations. Requisite functional criteria include mechanical strength, biocompatibility, biodegradability, morphology, and a host of other parameters, depending on end use. However, at the basis of the performance of these nanocomposites are interactions between the biopolymer or synthetic polymer and the filler, which can be tuned and perfected to suit specific needs. We hope that further research into these interactions will prove valuable in contemplating the design of novel bionanocomposites for biomedical applications.

Acknowledgments

This work was partially funded by the National Science Foundation Career Award DMR-0348147 and the DuPont Young Faculty Award.

References

1. E. Ruiz-Hitzky, M. Darder, P. Aranda, *J. Mater. Chem.* **15**, 3650 (2005).
2. A.P. Alivisatos, *Science* **271**, 933 (1996).
3. A.U. Daniels, M.K.O. Chang, K.P. Andriano, *J. Appl. Biomater.* **1** (1), 57 (1990).
4. G.W. Bradley et al., *J. Bone Joint Surg.* **61** (6), 866 (1979).
5. T. Terjesen, K. Apalset, *J. Orthop. Res.* **6**, 293 (1988).
6. N. Gillett, S.A. Brown, J.H. Dumbleton, R.P. Pool, *Biomaterials* **6** (2), 113 (1985).
7. A. Uchida et al., *J. Bone Joint Surg. Br.* **72-B** (2), 298 (1990).
8. F.W. Cooke, *Clin. Orthop. Relat. Res.* **276**, 135 (1992).
9. I. Yamaguchi et al., *J. Biomed. Mater. Res.* **55** (1), 20 (2001).
10. K. Ogawa et al., *Macromolecules* **17**, 973 (1984).
11. K. Okuyama et al., *Int. J. Biol. Macromol.* **26** (4), 285 (1999).
12. H.-W. Kim, H.-E. Kim, V. Salih, *Biomaterials* **26** (25), 5221 (2005).
13. E. Cenni et al., *J. Biomater. Sci. Polym. Ed.* **11**, 685 (2000).
14. S. Mann, G.A. Ozin, *Nature* **382**, 313 (1996).
15. J.E. Zerwekh et al., *J. Orthop. Res.* **10** (4), 562 (1992).
16. F. Zhao et al., *Biomaterials* **23** (15), 3227 (2002).
17. J.L. Drury, D.J. Mooney, *Biomaterials* **24** (24), 4337 (2003).
18. H.-R. Lin, Y.-J. Yeh, *J. Biomed. Mater. Res. Part B: Appl. Biomater.* **71B** (1), 52 (2004).
19. M. Ito, Y. Hidaka, M. Nakajima, H. Yagasaki, A.H. Kafrawy, *J. Biomed. Mater. Res.* **45** (3), 204 (1999).
20. C. Du et al., *J. Biomed. Mater. Res.* **42** (4), 540 (1998).
21. C.M. Müller-Mai, S.I. Stupp, C. Voigt, U. Gross, *J. Biomed. Mater. Res.* **29** (1), 9 (1995).
22. E. Boanini et al., *Biomaterials* **27** (25), 4428 (2006).
23. U. Edlund, A.-C. Albertsson, *Adv. Polym. Sci.* **157**, 67 (2002).
24. R.L. Kronenthal, *Polymer Medicine and Surgery* (Plenum Press, New York, 1975) p. 119.
25. H. Tsuji, Y. Ikada, *Polym. Degrad. Stab.* **67**, 179 (2000).
26. N.C. Bleach et al., *Biomaterials* **23** (7), 1579 (2002).
27. H. Alexander, N. Langrana, J. Massengill, A. Weiss, *J. Biomech.* **14** (6), 377 (1981).
28. A. Majola et al., *J. Mater. Sci. Mater. Med.* **3** (1), 43 (1991).
29. V. Krikorian, D.J. Pochan, *Chem. Mater.* **15** (22), 4317 (2003).
30. V. Krikorian, D.J. Pochan, *Macromolecules* **37** (17), 6480 (2004).
31. V. Krikorian, D.J. Pochan, *Macromolecules* **38** (15), 6520 (2005).
32. J. Zhang, H. Tsuji, I. Noda, Y. Ozaki, *Macromolecules* **37** (17), 6433 (2004).
33. J. Zhang, H. Tsuji, I. Noda, Y.J. Ozaki, *Phys. Chem. B* **108** (31), 11514 (2004).
34. E. Loizou et al., *Macromolecules* **38** (6), 2047 (2005).
35. X. Zong et al., *Polymer* **43** (16), 4403 (2002).
36. M. Alexandre, P. Dubois, *Mater. Sci. Eng. R* **28**, 1 (2000).
37. Y.H. Lee et al., *Biomaterials* **26** (16), 3165 (2005).
38. R.A. Hule, D.J. Pochan, *J. Polym. Sci. Part B: Polym. Phys.* **45**, 239 (2007).
39. V. Krikorian et al., *J. Polym. Sci. Part B: Polym. Phys.* **40**, 2579 (2002).
40. B. Ozbas et al., *Macromolecules* **37** (19), 7331 (2004).
41. G.E. Lailach, G.W. Brindley, *Clays Clay Miner.* **17**, 95 (1969).
42. M. Wei et al., *J. Mater. Chem.* **15**, 1197 (2005).
43. R. Xu, E. Manias, A.J. Snyder, J. Runt, *Macromolecules* **34** (2), 337 (2001).
44. K.S. Wilson, K. Zhang, J.M. Antonucci, *Biomaterials* **26** (25), 5095 (2005).
45. R.Y. Kannan, H.J. Salacinski, P.E. Butler, A.M. Seifalian, *Acc. Chem. Res.* **38** (11), 879 (2005). □