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A review on recent developments in bio-nanocomposites for bio-medical applications

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ABSTRACT

Bio-nanocomposites form a unique class of a research area that integrates biology, chemistry, materials science, engineering and nanotechnology to present an interdisciplinary approach for solving of problems. In today's world, bio-nanocomposites are becoming increasingly prevalent due to the extraordinary properties that they possess. Scientists learn to select suitable matrices (e.g. aliphatic polyesters, polypeptides and proteins, polysaccharides, and polynucleic acids) and fillers (e.g. nanotubes, nanofibers, clay nanoparticles, hydroxyapetite and metal nanoparticles) and alter their chemistry and structure to suit the target field. This paper provides the most recent research made in the field of bio-nanocomposites as applied to biomedical fields including drug-delivery, biosensors, cancer diagnosis, and tissue engineering. Emerging trends in bio-technological and biomedical nanocomposites are highlighted and potential new fields of applications are examined.

KEYWORDS

Bio-Nanocomposites;
Biosensors;
Biopolymers;
Biomedical;
Nanomaterials.

INTRODUCTION

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 micro composites[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 noncorrosive, 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 $[Ca_{10}(PO_4)_6(OH)_2]$ 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. 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 and pore configuration to induce blood circulation and cell ingrowth. Such nanocomposites have high potential for use as hard-tissue scaffolds. Three-di-

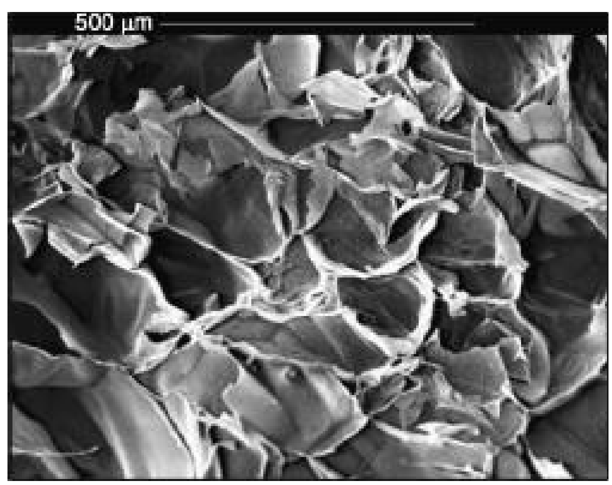

Figure 1 : Low-magnification scanning electron micrograph of a hydroxyapatite (HAP)–polymer/chitosan–gelatin scaffold prepared from HAP/chitosan–gelatin/ acetic acid mixture. (Reproduced from Reference 16.)

mensional 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].

MULTI-FUNCTIONAL NANOMATERIALS

Magnetic and fluorescent inorganic nanoparticles are of particular importance due to their broad range of potential applications. It is expected that the combination of magnetic and fluorescent properties in one nanocomposite would enable the engineering of unique multifunctional nanoscale devices, which could be manipulated using external magnetic fields. An overview of bimodal ''two-in-one'' magnetic-fluorescent nanocomposite materials which combine both magnetic and fluorescent properties in one entity, in particular those with potential applications in biotechnology and nanomedicine were discussed by Serena A. Corr et.al[18]. Multi-functional nanomaterials possessing fluorescent and magnetic properties may be used in a number of biomedical applications in nanobiotechnology, such as bioimaging, bio- and chemo-sensing, cell tracking and sorting, bioseparation, drug delivery and therapy systems in nanomedicine.

Bioimaging probes

Fluorescence microscopy and nuclear MRI are two main imaging techniques which have had a tremendous impact upon biomedical science in recent years. Unlike previous approaches which may have required the processing of fixed tissue samples, these techniques allow for the imaging of live and intact organisms both in vivo and in vitro, resulting in a more realistic picture of the processes occurring in live biological species. Frequently, these imaging techniques are complimentary to each other and could be used for parallel detection to have a clearer picture and provide a correct diagnosis. In this case, fluorescent-magnetic nanocomposites serve as new dual function contrast agents, which can be used simultaneously in confocal fluorescent microscopy and in MRI. In addition, fluorescent-magnetic nanocomposites allow us to perform optical tracking of biological entities and processes in combination with magnetophoretic manipulation. There are several reports on the utilization of multifunctional fluorescent-magnetic nanocomposites as contrast agents. These multi-functional materials are of particular importance as probes and biological labels for cellular imaging. Intracellular uptake and imaging using magnetic fluorescent nanoparticles prepared by M_enager and co-workers[19] have shown that, after cellular uptake, these nanoparticles were confined inside endosomes which are submicrometric vesicles of the endocytotic pathway. The authors have shown the possibility of magnetic manipulation of these internalised nanocomposites, resulting in the formation of spectacular fluorescent chains aligned in the direction of the applied magnetic field (Figure 2.)

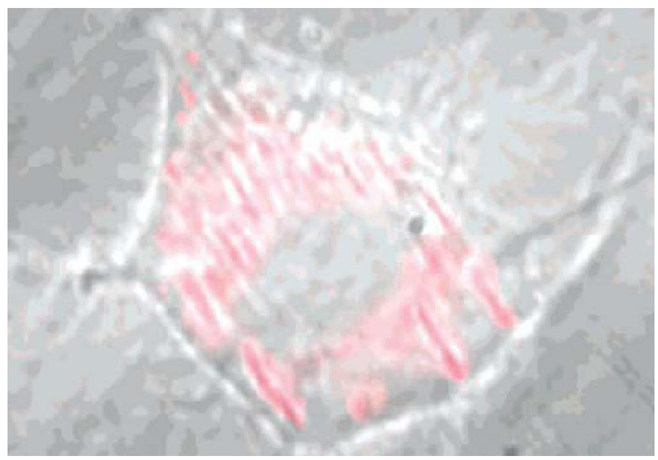

Figure 2 : The overlay image of endosomes forming chains within the cell cytoplasm in the direction of the applied magnetic field (Bar 10 lm; magnification 1009). From[19]

In another study, biocompatible PEG-modified, phospholipid- coated iron oxide nanoparticles have been conjugated to a fluorescent dye and the Tat-peptide and used for the imaging of primary human dermal fibroblast cells and Madin–Darby bovine kidney derived cells. These micelle-coated iron oxide nanocomposites demonstrate great potential for conjugation of a variety of moieties for specific intracellular and tissue imaging[20]. The rhodamine- labelled citric acid capped magnetite nanoparticles have been used as fluorescent biological markers. Confocal fluorescence microscopy demonstrated that these nanocomposites respond to an applied magnetic field and are taken up by KB cells in vitro. These materials can serve as biocompatible fluorescent ferrofluids, which enable optical tracking of processes at the cellular level combined with magnetophoretic manipulation[21]. Strong luminescence and high relaxivity at low field were demonstrated by a new type of "two-in-one" fluorescent- magnetic nanocomposites based on magnetite nanoparticles, a polyhedral octaaminopropylsilsesquioxane and a porphyrin derivative confocal imaging found that the incubation of macrophage and bone osteoblast cells at the presence of these nanocomposites resulted in their fast intercellular localization. The nanocomposites also exhibited a distinctive subcellular distribution corresponding to the location of the mitochondria, endoplasmic reticulum and nuclei (Figure - 3). It was suggested that there is a dissociation of the ionic components of the magneticfluorescent nanocomposites inside cells resulting in release of porphyrin species, which can penetrate various intracellular compartments. Such intracellular fragmentation of the nanocomposites allows potential utilization of these new nanocomposites both as subcellular imaging contrast agents and targeted drug delivery systems[22].

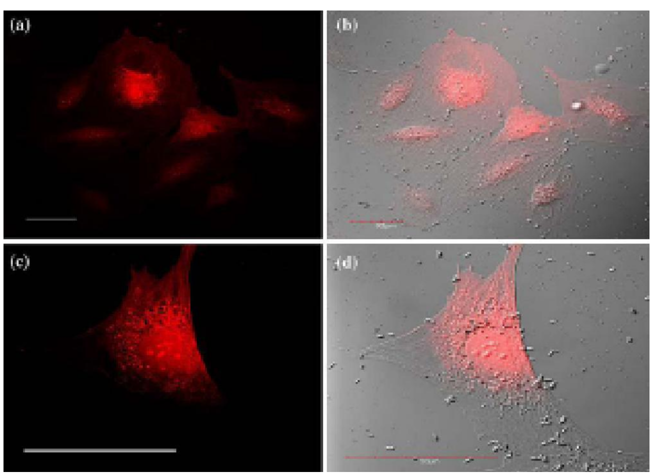

Figure 3 : Osteoblast cells uptake of particles. Population imaging (a) confocal image and (b) overlay with phase contrast (magnification 409, Scale bar = 50 lm). Single cell imaging. (c) confocal image and (d) with combined phase contrast (magnification 609, Scale bar = 50 lm). From[21]

Nanomedicine applications

The term "nanoclinics" was initially introduced by Prasad and co-workers[23], when their report on hierarchically built nanoparticles for targeted diagnostics and therapy appeared in 2002. These nanocomposites consist of a thin functionalized silica shell encapsulating magnetic (Fe_2O_3) nanoparticles and two-photon fluorescent dyes. The silica surface of these core-shell structures was functionalized with aluteinising hormone-releasing hormone for specific targeting of cancer cells. These nanocomposites have potential applications as MRI contrast agents, optical imaging diagnostic tools and as magnetic-induced cancer therapy devices. Xu et al.[24] have reported porphyrin—iron oxide nanoparticles conjugates, which can be utilized as bimodal anticancer agents for combined PDT and hyperthermia therapy. These conjugates can be effectively taken up by cancer HeLa cancer cells. The exposure of the cells containing the nanocomposites to yellow light resulted in a significant change of their morphology due to the cell apoptosis. These results demonstrate a potential of these nanoparticles for cancer therapy. An interesting experiment was performed using magnetic-fluorescent polymer capsules, which were simultaneously functionalized with magnetic nanoparticles and fluorescent CdTe nanocrystals. These nanocomposites have been used for modeling the bloodstream in a flow channel system under a magnetic field gradient, which allowed for the specific trapping of polymer capsules. In the regions where the capsules were trapped by the magnetic field, an increased uptake of the capsules by breast cancer cells was observed due to the high local concentration of the composites. The process was monitored by fluorescence microscopy. These results demonstrate the potential use the multi-modal fluorescent-magnetic polymer capsules loaded with pharmaceutical agents for targeted drug delivery and cancer therapy[25].

Polymer nanocomposite

A review on design and development of polymer-silicate nanocomposites (including clay based silicate nanoparticles and bioactive glass nanoparticles) ranging from diagnostic and therapeutic devices, tissue regeneration and drug delivery matrixes to various biotechnologies were summarized by Chia-Jung Wu, Akhilesh K. Gaharwar[26]. A variety of polymeric bionanocomposite materials are generated by the combination of inorganic nanoparticles with polymers of synthetic or natural origin (Figure 4). Nanocomposites made from biomedical polymers and silicate nanoparticles are reviewed while highlighting their potential and shortcomings in the biomedical and bio-technological arenas.

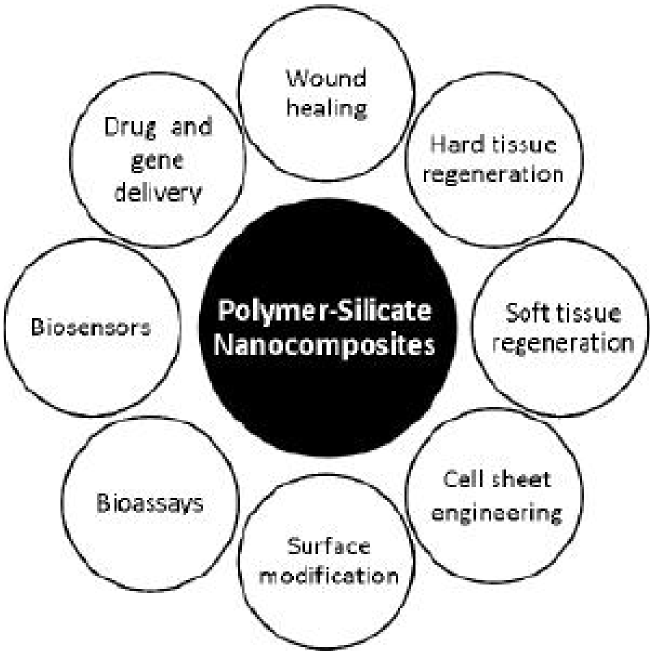

Figure 4 : Polymer-silicate nanocomposites have been developed to address a multitude of biomedical applications

CONCLUSIONS

In this review, we have discussed an emerging group of nano-materials based on various polymers and nanofillers that are either used extensively or show promise in the area of biomedical materials developed over recent years. There is a great need and demand for these materials. However, despite of all recent progress made, some of the nanocomposite areas are still in the infant stage and significant efforts are needed for further development of these materials and their utilization. We hope that further research into these interactions will prove valuable in contemplating the design of novel Bionanocomposites for biomedical applications.

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