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Nano-Diamond Hybrid Materials for Structural Biomedical Application

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Abstract: The development of new diamond based bio-mechanically active hybrid nano-structured scaffolds for cartilage cells tissue engineering are proposed in this study. Innovative tissue engineering biomimetic materials based on hydrogel have shown attractive physical, biological and mechanical properties in several biomedical applications. A highly biocompatible novel hybrid material based on nanodiamonds and hydrophilic poly-(hydroxyl-ethyl-methacrylate) (pHEMA) is proposed. The aim of this paper is to describe the chemical and analytical procedures for the preparation of nanofilled hybrid composites possessing biomimetic, osteoconductive and osteoinductivity properties that can be useful in the design of bio-mechanically active innovative bone scaffolding systems for stem cell differentiation and growth. A more rigid and rubber transparent hybrid nano-composites are predicted to posses improved mechanical strength overwhelming one of the major weaknesses of hydrogels, which is due their poor mechanical characteristics, for applications in biomedical structural application.

Keywords: Biomaterials, Bioactive Scaffolds, Bioengineering, Biomedical

Introduction

Biomaterials are today playing a central role in tissue engineering and regenerative medicine applications. The collaboration between engineers, chemists, physicists, biologists and physicians speeded up research in this field, allowing a faster development of new biomaterials and technologies to overcome the challenges and to front the various needs of each specific tissue-engineering field. Although many biomaterials applications are far from clinical translation, regenerative medicine has greatly advanced during the last years and it bodes well for future translation of research discoveries from bench-to-the-bedside, in order to gain in life expectancy and life quality (Montheard *et al*., 1992; Filmon *et al*., 2002; Davis *et al*., 1991; Kabra *et al*., 1991; Apicella *et al*., 1993; Peluso *et al*., 1997; Petrescu *et al*., 2016a; 2016b; 2016c; 2016d; 2016e).

Among the different allotropic forms of Carbon, graphite is the more thermodynamically stable at ambient temperatures and pressures, while diamond, in these conditions, may exist only in its metastable state. In fact, due to the high-energy barrier that separated the graphitic sp_2 and diamond sp_3 configurations (Fig. 1A and B), high temperatures and pressures in presence of catalysts are needed to transform graphite in diamond.

Nevertheless, a third parameter (surface area) becomes crucial at the nanoscale level and it become relevant in the definition of the system equilibrium energy levels: At this nano-dimensions, the Gibbs free energy becomes dependent on the contribution of the surface energy, leading to changes in the thermodynamic equilibrium phase diagram (Barnard *et al*., 2003; Barnard and Sternberg, 2007; Viecelli *et al*., 2001). Tetrahedral hydrocarbons in the form of nano-diamonds of 3 nm have been demonstrated by atomistic models to be more stable than poly-aromatics graphite (Fig. 1C).

In addition, a more complex morphological structure is generated at the nanodiamond interface; Barnard and Sternberg (2007) reported that cuboctahedral clusters presented a transition from Sp_3 to Sp_2 carbons at the surfaces of aggregations of 1.0-3.0 nm.

On this morphological transition at the interface, it has been recently demonstrated by Xiao *et al*. (2014) that reversible nanodiamond-graphitic carbon onion like phase transformation can occur even at room temperature and pressure leading to the formation of diamond cores with graphitic shells (*bucky-diamond*) (Fig. 1C) (Barnard and Sternberg, 2007).

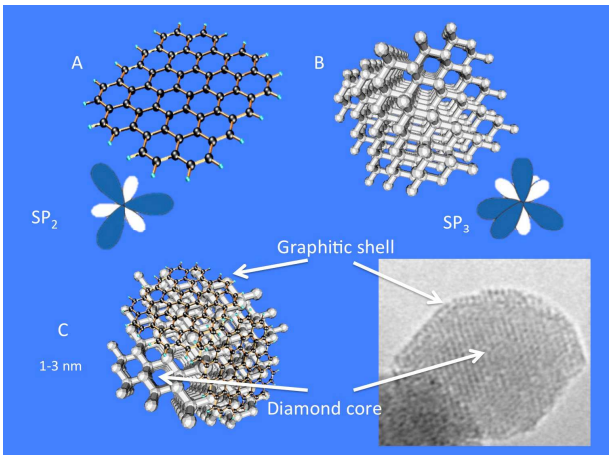

Fig. 1. (A) Graphite (SP_2 hybridization) and (B) Diamond (SP_3 hybridization) Carbon allotropic forms. (C) Nanodiamond core with external graphitic shell (TEM of a nanodiamond atom structure, right side)

These findings allowed us to understand that the nanodiamond surfaces can be then easily modified through the chemistry of graphitic carbon in many different chemical methods, such are the Diels–Alder cycloaddition reactions between conjugated diene and dienophile, to form functionalised cyclohexene systems (Jarre *et al*., 2011).

This new class of materials based on Carbon Sp_2 and Sp_3 nanocrystalline structures is very attractive for future nanotechnological development in biomedical structural applications. Nanocrystalline particles, which are often named detonation nanodiamond and characterized by sizes of 3-6 nm, are produced by detonation of carbon explosive materials (Danilenko, 2004; Greiner *et al*., 1988; Ozawa *et al*., 2007; Chang *et al*., 2008).

Detonation nanodiamond have been initially utilized in applications such as galvanic coatings, polishing systems, polymer nano-composities, lubricants. New niche applications, however, are recently developing; magnetic recording, adsorbents, diamond ceramics production, coatings in field emission devices, catalyzes of heterogeneous catalysts and in fuel cells as proton-conducting nanocomposite membranes. Preliminary investigation demonstrated that detonation nanodiamonds are non-toxic and biocompatible, making them very attractive for bio-medical applications considering its easy controllable rich surface chemistry.

However, it has been reported that detonation nanodiamonds may be characterized by different levels of purity and by the presence of several undesired functional groups/elements at the diamond particles surface, while high surface chemical purity and uniformity surfaces are needed for biomedical applications (Lai and Barnard, 2011a; 2011b). A simple purification method utilizes oxidation procedures. Depending on the type of procedure, the detonation powder of different levels of purities and specific surface characteristics can be obtained. The fraction of the Carbon that is not present as diamond can be purified up to 95% by weight by oxidation at high temperatures in air/Ozone atmosphere (Osswald *et al*., 2006; Shenderova *et al*., 2011).

Oxidation, while removing undesired processing functional compunds at nanodiamond surfaces, forms oxygen-containing groups, such are anhydrides and carboxylic acids (Shenderova *et al*., 2011).

The simple air/ozone purification, then, produces carboxylated nano-diamond with highly reactive and hydrophilic surface OH terminations appropriate in biomedical applications (Krueger *et al*., 2008; Kruger *et al*., 2006).

Diamond and glassy carbon has been recognized in literature, however, the toxicity of nano-diamonds remains a real concern (Schrand *et al*., 2009b). In vitro and in vivo studies are still needed to evaluate characteristics such as in vivo mechanical and physiological behaviours (Zhang *et al*., 2011; Schrand *et al*., 2009a; 2009b; Yuan *et al*., 2010; Mohan *et al*., 2010) as well as cell viability or undesired gene modification activity.

Previous investigations of our group have shown that high level of biocompatibility and bioactivity has been observed for nano-composite materials made combining amorphous silica nanoparticles of about 7 nm.

Bioengineering and nanotechnology applied to micro and nano-materials are being progressively adopted as emerging solutions in 2D (coatings) and 3D applicatons (scaffolds) (Sorrentino *et al*., 2007; Aversa *et al*., 2016a). Conclusively, such micro and nano-technologies have shown a high potential for usage in advanced manufacture models finalized to the growth of well-organized tissue engineered structures (Petrescu and Calautit, 2016a; 2016b).

Bone scaffolds have been always a relevant matter for research since they should provide sufficiently rigid but resilient network to be an ideal scaffold that momentarily substitute the damaged bone. Nevertheless, they should be able at the same time to readily biodegrade after the formation of the new tissue in order to fully integrate with it (Kabra *et al*., 1991; Montheard *et al*., 1992; Peluso *et al*., 1997; Schiraldi *et al*., 2004; Buzea *et al*., 2015; Aversa *et al*., 2016a; 2016b; 2016c; 2016d; 2016e; 2016f; 2016g; 2016h; 2016i; 2016j; 2016k; 2016l; 2016m; 2016n; 2016o).

Our research group have investigated hydrogel hybrid composites, based on the association of pHEMA with Amorphous Pyrogenic Silica that were tested for the intake of water, the balance of swelling in water and in saline solution and for the cell response with assays of adhesion, morphology, distribution, using fibroblasts and osteoblasts as cell-models. The presence of the silica makes this biomaterials excellent, with respect to the pHEMA alone. Good properties of

osteoinduction have been also observed for differentiation of dental pulp stem cells (Abdul-Razzak *et al*., 2012; Ajith *et al*., 2009; Ahmed *et al*., 2011; Apicella and Hopfenberg, 1982; Atasayar *et al*., 2009; Babaev *et al*., 2010; Chow *et al*., 2010; Comerun, 1986; Covic *et al*., 2007; Frost, 1964; 1990; 1994; 2004; Gramanzini *et al*., 2016; Holley *et al*., 1970; Krueger and Boedeker, 2008; Nicolais *et al*., 1984; Petrescu *et al*., 2015; Prashantha *et al*., 2001; Raffaella and Antonio, 2016; Raffaella *et al*., 2016; Sorrentino *et al*., 2009; Töyräsa *et al*., 2001; Wolff, 1892).

Silica nano-composites synthesized in our laboratory, which contained highly-bioactive amorphous fumed, have been found to represent a new class of hybrid polymeric-ceramic scaffolding materials able to mimic the mechanical behavior of the bone. Micro-foamed self assembled nanostructured composite have been tested as scaffold that showed osteoblast grow ability and stem cells differentiation (Marrelli *et al*., 2015).

Materials and Methods

Materials

The monomer 2-hydroxyethylmethacrylate (HEMA), obtained from Sigma-Aldrich Chemicals Co., St. Louis, MO, USA, has been used for the polymerization of a hydrophilic composite matrix. Raw detonation nanodiamonds (Aldrich, ≥ 97%), which mean diameter ranged between 3-5 nm and which specific surface area was of 400 $m^2 \cdot g^{-1}$, were utilized as bioactive filler. HEMA monomers (Fig. 2) have been thermally polymerized in presence of an initiator for radical polymerization, namely, the α-α' azoisobutyrronitrile (AIBN), obtained from Fluka Milan, Italy. In a preliminary test of nanocomposite preparation, the nanodiamond were mixed in the ratio of 5% by volume with the HEMA monomers and degassed. The mixture was then poured into 2.0 mm thick planar moulds before polymerization in the oven that was hold at the controlled temperature of 60°C for 24 h. The nano-composite plates were subjected to a final post-cure at 90°C for 1 h.

Results and Discussion

Nano-diamonds dispersion in the HEMA monomer resulted in a transparent and clear, light grey colour, solution. This behaviour testified the good dispersion and absence of nanofiller clusters. The good dispersion ability of the Oxidized Detonation nano-diamonds in the reacting mixture could be attributed to the strong interactions between the oxygen containing functional groups on the filler and the HEMA hydroxyl that led to the preferential self-assembly orientation of the monomers toward the nano-filler surface (Fig. 3 detail upper left). The successive polymerization of the HEMA resulted in a still clear and transparent glassy solid. The good dispersion of the nano-diamond was reasonably preserved after the polymerization (Abdul-Razzak *et al*., 2012; Ajith *et al*., 2009; Ahmed *et al*., 2011; Apicella and Hopfenberg, 1982; Atasayar *et al*., 2009; Babaev *et al*., 2010; Chow *et al*., 2010; Comerun, 1986; Covic *et al*., 2007; Frost, 1964; 1990; 1994; 2004; Gramanzini *et al*., 2016; Holley *et al*., 1970; Krueger and Boedeker, 2008; Nicolais *et al*., 1984; Petrescu *et al*., 2015; Prashantha *et al*., 2001; Raffaella and Antonio, 2016; Raffaella *et al*., 2016; Sorrentino *et al*., 2009; Töyräsa *et al*., 2001; Wolff, 1892).

A similar self assembly condition has been described by Aversa *et al*. (2016a; 2009) to occur between amorphous nanosilica particles, which are characterized by a disordered structure containing many not regular rings and not bridging Oxygen atoms (red in Fig. 4) and the same HEMA monomer.

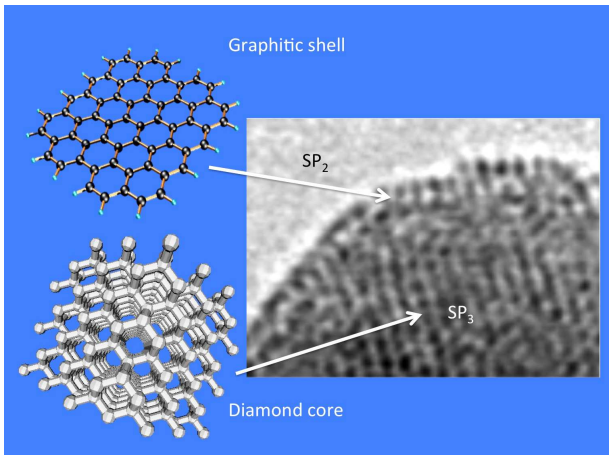

Fig. 2. *bucky-diamond*: A 2–3-nm diamond core surrounded by a fullerene-like carbon network right TEM of a diamond-graphene transition)

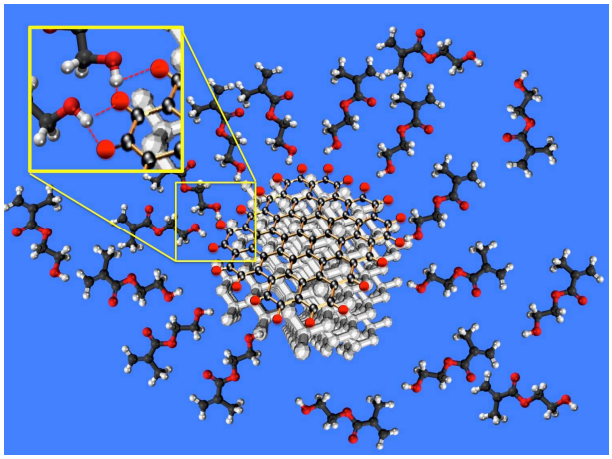

Fig. 3. Behaviour of HEMA monomers in presence of Detonation Nano_Diamond

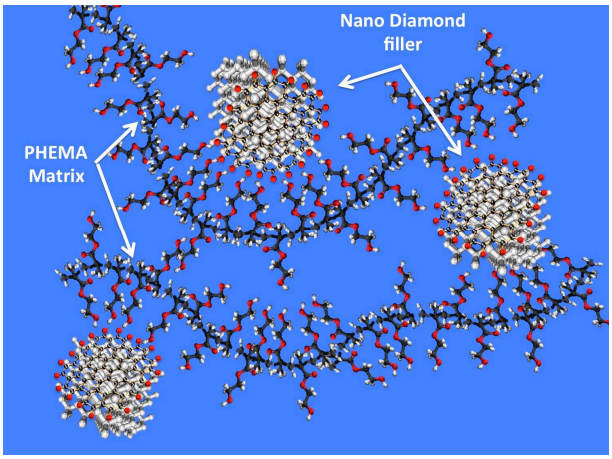

Fig. 4. Hypothesized Nano-Diamonds pHEMA self assembled structure

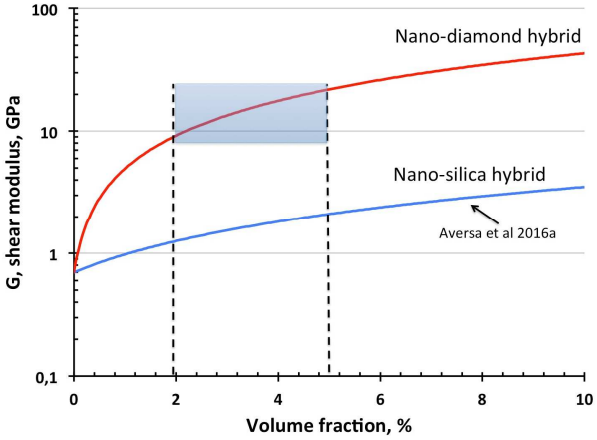

Fig. 5. Comparison between the elastic shear moduli of the experimentally measured Nanosilica-pHEMA hybrids (blue line) and the hypothesized Nano-Diamonds pHEMA self assembled Hybrid

The polymerization of HEMA/amorphous nanosilica mixtures leads to the formation of a hybrid nanostructured material with particularly peculiar and improved mechanical properties and biocompatibility (Aversa *et al*., 2016b).

In the case of nono-diamond filled pHEMA, the same improvement of the mechanical properties and biocompatibility could be then expected. However, the expected mechanical properties enhancements could be much more relevant due to diamond much higher rigidity and strength (Azo tech spech).

The shear Modulus of synthetic diamond, which ranges from 440 to 470 GPa (Azo tech information), is almost 15 times higher than that of Silica, which ranges from 27.9 to 32.3 (Azo tech spec.). According to this information and considering the mechanical shear behaviour of the analogous hybrid materials based on silica nanoparticles (Aversa *et al*., 2016c), the behaviour of the variation of the shear modulus as a function of the diamond nanoparticles volume fraction in the hybrid material could be evaluated Fig. 5.

According to Aversa *et al*. (2016e), strong plasticization is induced by the physiological solutions sorption in the hybrid pHEMA-nanosilica composite.

It has been described by Aversa *et al*. (2016f; 2009) that the measured shear modulus of the Nanosilica hybrid composites at different filler content was not described by the classical Halpin and Kardos (1976) equation that is commonly utilized for the particulate composites. The hybrid nano-composites showed a linear dependency at increasing contents of nanosilica filler. This occurrence confirmed the hybrid nature of the nanosilica filled pHEMA.

At nano-diamond volumetric fractions ranging from 2 to and 5%, the shear moduli were comparable to those of the cortical bone (10-20 GPa, reported as grey area in Fig. 5). Similar results have been described by Aversa *et al*. (2016g; 2009) to occur for nanosilica hybrids at higher loading ranging from 15 to 30% by volume.

Conclusion

New bioactive nanodiamond-polymeric hybrid materials to be used as biomechanical active scaffold materials showing potential improved bone scaffold mineralization and ossification properties have been developed by following a biomimetic approach.

The new nanocomposites based on poly-Hydroxyl-Ethyl-Methacrylate (pHEMA) filled with detonation nanodiamonds could be identified as a biomimetic biomaterial at filler concentration up to 5% by volume. Moreover, this glassy hybrid material swells to rubber in presence of aqueous physiological solution picking-up more than 40% of water. At very low levels of nano-diamond loading, the mechanical behaviour of the proposed hybrid materials could be comparable with that of bone when in the glassy state, or to that of cartilage and ligaments when in the rubbery state following water sorption.

The use as scaffolds of these mechanically compatible hybrid hydrogels is expected to improve the adaptation mechanisms of the bone by introducing an active interface that could ameliorate biomimetics by correctly reproducing cartilage and ligaments biomechanical functions (Schwartz-Dabney and Dechow, 2003; Perillo *et al*., 2010; Apicella *et al*., 2010; 2011; 2015; Aversa *et al*., 2016h; 2009).

Adaptive properties of bone could benefit of use of biomechanically compatible and bioactive scaffold biomaterials associated to new design odontostomatological prostheses.

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Author's Contributions

All the authors contributed equally to prepare, develop and carry out this manuscript.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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