

# Nanodiamond for Structural Biomimetic Scaffolds

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## Abstract

Bio-mechanically active scaffolds for tissue engineering combining hydrophilic polymeric matrix and nano-diamond fillers properties are presented and discussed in this paper. The resulting scaffolding materials revealed remarkable mechanical and biological properties to be exploited in advanced biomedical applications. The novel hybrid material is based on 2 and 5 volume % of detonation nano-diamond particles in a hydrophilic poly-(hydroxyl-ethyl-methacrylate) matrix. According to its mechanical and biological properties, the nanocomposite shows a hybrid nature. The base analytical procedures for the preparation of the hybrid nano-composites and some preliminary mechanical characteristics are presented. The proposed hybrid system has been considered for potential biomimetic, osteoconductive and osteoinductive scaffolds application in bio-mechanically active bone scaffolds for osteoblast, and stem cell differentiation and growth. These more rigid hybrid nano-composites are predicted to possess improved mechanical strength overcoming the mechanical weaknesses of traditional hydrogels clinically utilized for bone regeneration.

## Keywords

Hybrid Nano-Composites, Biomaterials, Bioactive Scaffolds, Bioengineering

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## 1. Introduction

Traditional orthopaedic prostheses are mainly made of metals and ceramics materials with outstanding strength and rigidity properties but with a high physiological invasiveness. These systems, while guarantying mechanical functional tenure, they often strongly physiologically and mechanically interfere with hu-

man bone. This unwanted behaviour derives from the fact that bones are complex functional and structural entities composed both by less rigid open-cell trabecular and more dense and rigid materials that are combined, at medullar and cortical bone levels, to achieve specific rigidities and strength. Failures and long-term unreliability follow from a not full integration with the bone local physiology and with patient personal characteristics. In particular, the traditional prosthetic systems, which are not able to completely mimic all the healthy bone functions, become particularly not adequate for younger patients who have higher life expectations and then high prostheses requirements in terms of duration, biomechanical osseointegration and low invasiveness. Bone-prosthesis interferences have been recognized to occur at two dimensional levels, namely, at micro and macro scale. The first (at a micro-scale) accounts for the biological and micromechanical interactions of the synthetic biomaterial with the bone forming cells and their adaptive properties, while the second (at a macro scale) determines the prosthesis full biomechanical functionality and ability to restore the biological stress state distribution in the prothesized bone.

New bio-mechanically active materials with mechanical properties able to withstand loads without mechanically interfere with the healthy bone physiology are then needed. The bone orthotropy and complex structure should be accounted and preserved in order to recreate the same stresses and strains distribution. The use of micro-trabecular metallic prostheses and scaffolds simulating the behavior of cancellous and cortical bone has been proposed to recreate the macro distribution of stresses and deformations in the bone, however, a suitable biomimetic interface is needed at micro level where osteon and osteoblast cell interact. The development of polymeric hybrid nano-composites has been proposed in recent studies. These hybrid materials have shown to possess the necessary mechanical and biological properties to favor local healthy bone generations. Therefore, specific and tunable properties simulating the bone tissues are required at micro level of the interface to guide bone-forming cells to growth and successfully integrate with the bone-grafting material in the host tissue. The main reasons for using bone scaffolds are thus to provide an environment for bone formation, maintain space, and provide mechanical support to the bone skeleton during the repair process. Biomaterials science today is a highly interdisciplinary field playing a central role in the development of regenerative tissue engineering applications. Tight cooperation among biologists, chemists, material engineers, physicists, and clinician based research in this area to a level that is favoring the development of new biomaterials successfully fronting the different request of different tissue-engineering specifications. Even if more investigation have to be implemented, many biomaterials applications are near to clinical application, and regenerative medicine has greatly improved and it will guarantee for near future more applications from bench-to-the-bedside [1]-[6].

Graphite, which is one of the allotropic forms of Carbon, is thermodynamically more stable at ambient temperatures and pressures, conversely, the diamond allotropic form is more stable at high pressures and temperature and it

can exist only in its metastable state at ambient conditions. The differences in stability of allotropic forms are a consequence of the high-energy barrier that separated the graphitic  $Sp_2$  (Left in **Figure 1**) and the diamond  $Sp_3$  configuration (Right in **Figure 1**).

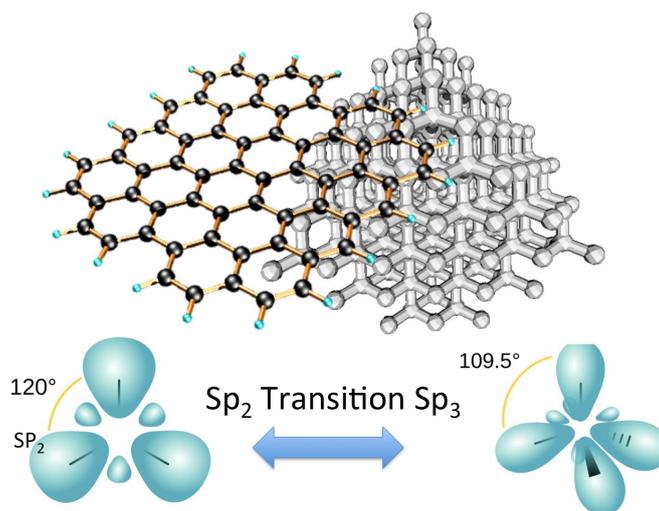
Therefore, the transformation of graphite in diamond requires high temperatures and pressures in presence of catalysts. However, at nano-size level, a third equilibrium parameter related to the surface area becomes crucial and relevant in the system equilibrium energy distribution: Gibbs free energy is significantly influenced by the contribution of the surface energy, leading to changes in the thermodynamic equilibrium phase diagram [7] [8] [9] [10]. Atomistic models demonstrated that nano-diamonds of 3 nm with tetrahedral hydrocarbons are more stable than graphite in its poly-aromatics form [7].

It is interesting and it opens interesting technological application the fact that a more complex structure is generated at the nano-diamond interface. Cubooctahedral clusters presenting a transition from  $Sp_3$  to  $Sp_2$  carbons at their surfaces in the case of atom cluster of 1.0 - 3.0 nm have been reported by Barnard and Sternberg [9].

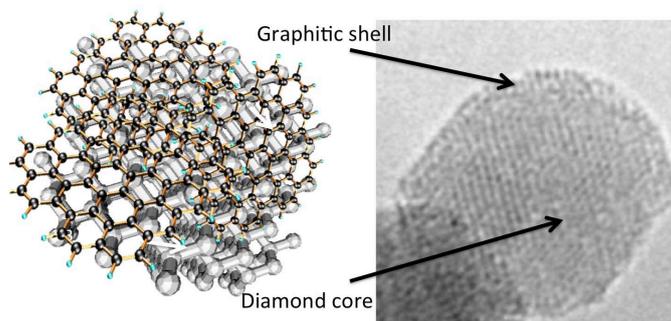
Reversible nanodiamond-graphitic carbon onion like phase transformation has been observed by Xiao *et al.* [11] to occur in this morphological transition interface even at room temperature and pressure leading to the formation of bucky-diamond characterized by diamond cores with graphitic shells (**Figure 2**) [9].

According to these findings, nano-diamond surfaces can be modified to form functionalised cyclohexene systems using the well-assessed chemistry of graphitic carbon, *i.e.* the Diels–Alder cycloaddition reactions between conjugated diene and dienophile, [12].

New perspectives open to these materials based on nano-crystalline  $Sp_2$  and  $Sp_3$  Carbon structures for future nano-technological development in biomedical



**Figure 1.** Left) Graphite ( $Sp_2$  hybridization) and Right) Diamond ( $Sp_3$  hybridization) Carbon allotropic forms.



**Figure 2.** Nano-diamond core with external graphitic shell (left side) and (TEM of a detonation nano-diamond atomic structure (right side).

structural applications. Such nano-crystalline particles are produced by detonation of carbon explosive materials [13] [14] [15] [16] and, hence, are reported as detonation nano-diamond with characteristic sizes of 3 - 5 nm. Simple applications in lubricants, galvanic coatings, polymer nano-composites, polishing systems, have been initially exploited for detonation nano-diamond, however, new and more valuable niche applications have recently arisen in the area of electronics, diamond ceramics production, emission devices, catalysts and fuel cells as proton-conducting nanocomposite membranes. Preliminary clinical and biochemical investigation have shown that these detonation nano-diamonds are biocompatible and non-toxic, opening for new bio-medical applications both considering its easy controllable variety of possible surface chemistry and their intrinsic high mechanical characteristics.

Detonation nano-diamonds, which surface is characterized by different levels of purity and presence of undesired functional groups/elements, may not be directly suitable for biomedical applications where high surface chemical purity and surfaces chemical uniformity are needed [17] [18]. After rough production, these materials undergo several purification procedures. A simple method utilizes surface oxidation and different levels of purities and surface properties can be obtained. Oxidation carried out at high temperatures in air/Ozone atmosphere can yield to purification of Carbon fraction not present as diamond up to 95 per cent by weight [19] [20].

Oxidation of the nano-diamond surfaces other than removing undesired processing functional compounds, it forms oxygen-containing groups (red dots in **Figure 2**), such as anhydrides and carboxylic acids [20], that are suitable for hydrogen or polar secondary bonding with suitable species.

By air/ozone purification, then, we can functionalize the surface obtaining carboxylated nano-diamond with highly reactive and hydrophilic surface OH terminations, which are highly appropriate for biomedical applications [21] [22].

However, the toxicity of nano-diamonds remains controversial and it is a real concern [23]. *In vitro* and *in vivo* further investigation are then needed to evaluate characteristics such as *in vivo* mechanical and physiological behaviors [23]-[28], cell viability, and undesired gene modification activity. Although bio-

compatibility and adverse effect were also described in literature for the use of nanosilica particles, our published investigations have shown that nano-composite and hybrid materials made combining amorphous silica nanoparticles reached high level of biocompatibility and bioactivity that were not reached by pure nano and micro silica, and by the p-HEMA matrix. These hydrogel hybrid nano-composites have been tested for water sorption, swelling in water and in iso-tonic saline solution, and for the fibroblasts and osteoblasts as cell response with assays of adhesion, distribution, and morphology. The presence of the polymer-linked 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.

Nanotechnology applied to micro and nano-materials bioengineering is being gradually accepted in emerging applications where coatings or three-dimensional scaffolds are needed [29]-[33]. The creation of ideal bone scaffolds is a growing argument of research. Such ideal scaffold has to provide a rigid and resilient network to temporarily substitute the damaged bone function while creating a bioactive substrate for bone regeneration. At the same time it should be able to fully integrate with it [1] [4] [6] [34].

These self assembled nanostructured composite were also micro-foamed and tested as peri-implantar scaffold to host osteoblast grow factors or stem cells for osteoblasts differentiation [35].

These new hybrid materials have been show to be able to biomechanically stimulate bone growth in the range of physiological strains that permit the healthy growth permitting an early and organized full integration of the implant in the receiving bone. This effect was primarily due to the micromechanical stress and strain states that generate at level of the bone/implant interface.

## 2. Materials and Methods

Raw detonation nanodiamonds (Aldrich,  $\geq 97\%$ ) with a mean diameter of 3 - 5 nm and specific surface area of  $400 \text{ m}^2 \cdot \text{g}^{-1}$  were utilized as bioactive filler. First detonation nanodiamond hydrophilization has been carried out according to Shenderova technique [29]. Surface graphitization with subsequent functionalization allows dispersion into  $\sim 20\text{-nm}$  aggregates. High-temperature hydrogen treatment resulted in stable single-particle aqueous nanodiamond colloids from which a fraction of 2 - 4-nm nanodiamonds was isolated by centrifugation at  $>10,000 \text{ rpm}$  [20].

The resulting nanodispersion was then mixed with 2-hydroxyethyl methacrylate (HEMA) (Sigma-Aldrich Chemicals Co., St. Louis, MO, USA). HEMA monomers-nanodiamond suspension (**Figure 2**) has been then radical polymerized in presence of the  $\alpha\text{-}\alpha'$  azoisobutyronitrile (AIBN, Fluka Milan, Italy) thermal initiator.

Nanocarbon contents at 2% and 5% by volume have been prepared.

The degassed reactive suspension was first transferred into 2.0 mm thick planar moulds and then polymerized at  $60^\circ\text{C}$  for 24 h. A post-cure of 1 h at  $90^\circ\text{C}$

was finally carried out.

Preliminary Dynamic Mechanical Tests have been run according to ref [29] for samples at 2% and 4% volume fractions.

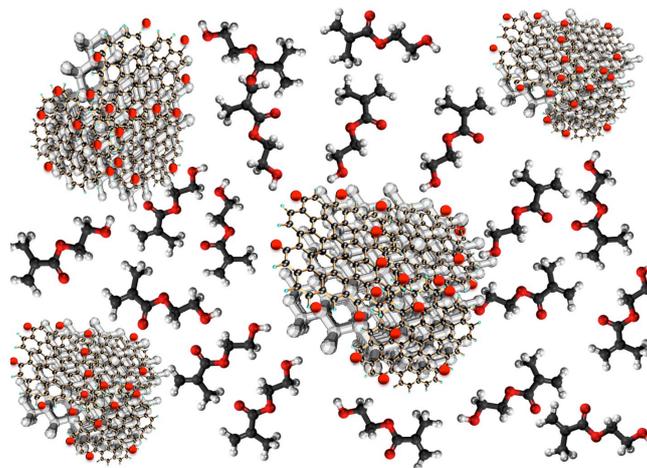
### 3. Results and Discussion

The presence of functionalised oxidized Detonation nano-diamonds in the monomer reacting mixture favour the self orientation of HEMA polar monomers. The nanoparticles, in fact, are characterized by the presence of oxygen-containing groups that leads to a preferential orientation and self assembly of the HEMA monomer hydroxyl groups toward the nano-filler surface (**Figure 3**).

Similar self-assembly mechanisms leading to the formation of nanostructured hybrid nano-composites have been described in a previous work [29]. In particular, amorphous nanosilica particles characterized by a disordered structure containing not regular silica rings and not bridging Oxygen atoms (red in **Figure 3**) and the HEMA monomer functional hydroxyl groups may create the condition for the creation of more ordered and hybrid ceramo-monomeric suspensions. The polymerization of these HEMA/amorphous nanosilica suspensions leads to the formation of a hybrid nanostructured material presenting specific and peculiar properties such as improved mechanical rigidity and biocompatibility [29].

Applying this nano-structure formation model to the nonodiamond/HEMA suspension polymerization, similar improvement of the mechanical properties and biocompatibility should be expected. Nevertheless, the mechanical properties enhancements are expected to be much more relevant due to diamond high Elastic modulus and strength (Azo tech spech).

The rigidity of synthetic diamond may rise up to 15 times higher than that of Silica, namely from about 450 GPa shear moduli Vs about 30 GPa (Azo). Acting



**Figure 3.** Selfassembly of HEMA monomers in presence of Detonation Nano-diamond: monomer and functionalised Nano-diamonds.

as a reinforcing filler or hybrid material forming component the detonation nano-diamond could generate, and accounting for the mechanical behaviour of the similar nano-silica based hybrid materials [29], 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.

As described by Aversa *et al.* [29], plasticization follows equilibration of the hybrid pHEMA-nanosilica in physiological solutions. The water molecules binding by the polymer hydrophilic groups induces a significant plasticization of the nanocomposite (in our case a 16% by volume nanocomposite) leading the initially dry sample shear modulus to drop from 8 - 9 GPa to 0.01 - 0.1 GPa when in the rubbery swollen state.

Compositional dependence of shear moduli of differently filled pHEMA-Nanosilica nano-composites is not described by the classical Halpin-Tsai [36] equation valid for particulate composites but a linear dependency was observed instead. These findings confirmed the hybrid nature of the nanosilica pHEMA composites.

On the other hand, the same rigidities can be obtained at much lower volumetric loading by using nanodiamond, namely values ranging from 1% to and 4% in the dry state. **Figure 4** presents the hypothesized nanodiamonds pHEMA self assembled structure, while **Figure 5** shows the comparison for the elastic moduli that can be obtained using nano-silica and nano-diamond fillers. The red dots represent the two explorative mechanical tests run on the detonation nano-diamond. Although more experimental tests are needed, these preliminary tests seem to confirm our expected theoretical values calculated for a hybrid configuration.

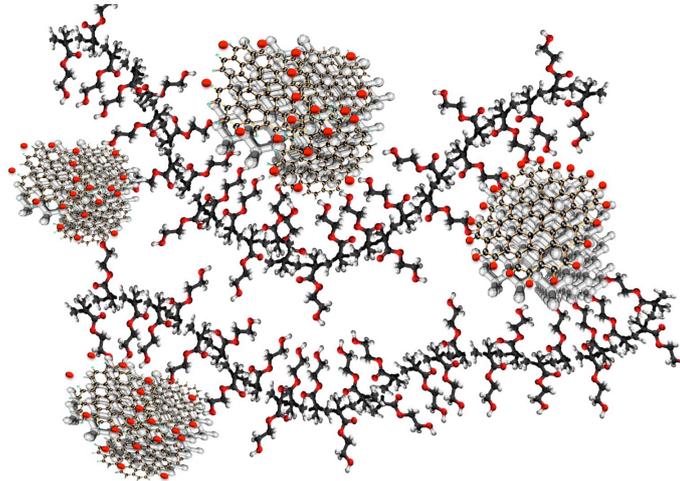
#### 4. Conclusions

The biomimetic approach [37]-[54] has been applied in the definition of new new bioactive hybrid nanodiamond-polymeric nano-composites to be used as biomechanical active materials for bone mineralization and regeneration.

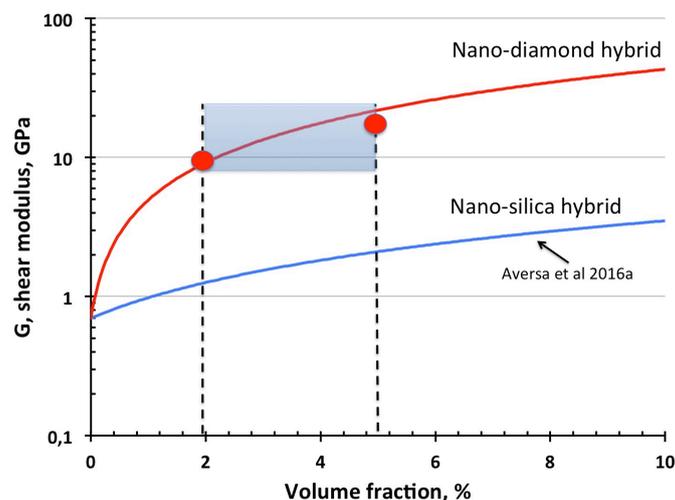
The biomimetic approach [37]-[54] has been applied in the definition of new new bioactive hybrid nanodiamond-polymeric nano-composites to be used as biomechanical active materials for bone mineralization and regeneration.

The new hybrid nano-composites is prepared by polymerizing Hydroxyl-Ethyl-Methacrylate monomers filled with detonation nanodiamond particles (up to 5% by volume). This material sorbs water and swells in aqueous physiological solutions (up to 40% - 45% by weight) turning from glassy and rubber states. Low levels of nonodiamond loadings are able to improve the mechanical properties of the hybrid materials.

Bio-mechanically compatible hybrid hydrogels may be used as scaffolding materials to increase micro and macro prosthesis stress adaptation mechanisms. The introduction of biomechanically active interfaces will improve implant biomimetics while reproducing cartilage and ligaments biomechanical functions [37]-[49]. The adaptive properties of the bone are expected to have positive effects



**Figure 4.** Hypothesized Nano-diamonds pHEMA self assembled hybrid nano-composite.



**Figure 5.** Preliminary mechanical test results and Hypothesized Nano-diamonds pHEMA hybrid nano-composite compared with analogous nano-silica composites.

in the use of biomechanically compatible and bioactive scaffold coupled with new designed prostheses [50] [51].

The use of micro-trabecular metallic [50] [51] prostheses coated with hybrid ceramo-polymeric scaffolds [54] has been proposed to recreate the macro and micro distribution of stresses and deformations in the bone. The development of polymeric hybrid nano-composites has been proposed in recent studies [52] [53]. These hybrid materials may induce the necessary mechanical and biological properties to favor local healthy bone generations.

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