ISSN : 2350-0743

www.ijramr.com

International Journal of Recent Advances in Multidisciplinary Research
Vol. 05, Issue 07, pp.3980-3982, July, 2018

RESEARCH ARTICLE

NANODIAMOND: INNOVATIVE CLASS OF MULTIFUNCTIONAL NANOSYSTEMS

[1,*]Spera, R., [2]Nobile, S. and [3]Di Trapani, L.

[1]Department of Drug Chemistry and Technologies, "Sapienza" University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy
[2]Department of Drug Chemistry and Technologies, University of Perugia, Via del Liceo 1, 06123 Perugia, Italy
[3]School of Medicinal Sciences and Health Products, University of Camerino, Via S. Agostino 1, 62032 Camerino, Italy

ARTICLE INFO

Article History:
Received 18th April, 2018
Received in revised form
20th May, 2018
Accepted 27th June, 2018
Published online 30th July, 2018

Keywords:
Nanodiamonds, Drug delivery, Targeted delivery, Imaging.

ABSTRACT

The continued search for the optimization of a versatile and efficient drug carrier is catalyzing multidisciplinary efforts that integrate diagnosis and delivery of therapeutic agents. Nanodiamonds (NDs) are versatile nanocomposite which exhibit excellent mechanical and optical properties, high surface areas, tunable surface structures and low toxicity. These advantageous properties make them well suited to a wide range of potential applications in tribology, drug delivery, bioimaging, tissue engineering, and also as protein mimics and a filler material for nanocomposites. This review provides an overview of the synthesis technique and surface functionalization of NDs. Advanced research on NDs as platform for a host of biomedical applications are also described.

INTRODUCTION

Recent advances in nanomedicine are focused on the study and developing of multifunctional systems for diagnosis and delivery of therapeutic agents. In this scenario, liposomes and polymeric nanoparticles can be considered milestone. Other carriers such as metal nanoparticles and nanotubes represent attractive alternative. Recently, there has been a growing interest in the use of carbon-based nanomaterials, including fullerenes, nanotubes and graphene for biotechnological and biomedical applications. Nanocrystalline diamonds, often simply referred to as nanodiamonds (NDs), has gaining rapidly growing attention due to their unique features including biocompatibility, functional versatility, and advantages surface properties. These nanoscale approximately spherical diamond particles with diameter size of about 5 nm and a narrow particle size distribution feature chemically inert cores with superior mechanical properties characteristic of bulk diamond, and fully accessible external reactive surfaces terminated by a large number of tailorable functional groups. In order for nanomaterials to be a clinically viable option, several issues must be addressed. First, in order for any material to be considered, it must be easily mass produced. Due to the unique characteristics and the availability of several, relatively simple processes for its synthesis, ND has become one of only few nanomaterials produced on an industrial scale.

***Corresponding author:* Spera, R.,**
Department of Drug Chemistry and Technologies, "Sapienza" University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy.

In addition to this, it has been suggested that NDs colloidal stability and dispersibility within solutions significantly influences their biocompatibility. Steady progressions in creating stable suspensions of NDs within aqueous media have thus steadily improved and could be ready for translation to biomedical applications. ND–drug conjugates have demonstrated promise results both in improving current therapeutic efficacies and delivering therapeutic agents difficult to formulate. For localized treatments, ND-based films constructed for a variety of treatments and afflictions, including chemotherapy, cardio-thoracic medicine and wound-healing, are reported in literature. Further milestones of importance would also include the pursuit of combining targeting, imaging and drug release capabilities of NDs into a single platform with the preservation of the aforementioned biocompatibility in an *in vivo* setting. In fact, for *in vivo* application NDs would be able of fluorescing in a medically relevant range of wavelengths (i.e., infrared, PET/CT/MRI) in addition to coupling with therapeutics. The advantages of such a diamond marker, in addition to its favorable emission wavelength, are the high stability of the emission and the biocompatibility of the material. It is important to point out that the NDs biocompatibility has thus far proved extremely promising but it must continue to be evaluated *in vivo*.

Synthesis and surface modifications of NDs

Since their discovery and inception 45 years ago, NDs have been synthesized by various established techniques. Methods

exist for the synthesis of single-crystalline and polycrystalline diamond films, as well as the production of nano- to microscopic diamond particles. Depending on the chosen synthetic method, diamond materials exhibit significantly different surface properties. Besides the shock-wave transformation of graphite into sintered nanodiamond, nanoscale diamond can be obtained by the detonation of explosives such as TNT–hexogene mixtures. This so-called detonation diamond consists of tiny diamond crystallites of about 5 nm in size. They are covered with some graphitic and amorphous carbon and interconnected by soot-like structures.
A major drawback of the detonation method, is the limited control over structural uniformity and composition of the produced nanomaterial. Due to the lack of oxygen, the combustion of the explosive is incomplete and the detonation process yields a powder containing up to 80 % of non-diamond species. Thus, the resulting detonation soot is primarily composed of amorphous and graphitic carbon, which prevents a direct use of the as-produced powders and makes purification one of the most crucial steps in NDs production. In order to overcome the well-known challenges associated with liquid-phase purification methods, researchers have explored a variety of gas-phase methods. In particular, oxidation in air was found to be an economically feasible alternative to currently-employed methods as it provides a simple and efficient route to selectively remove non-diamond carbon and other impurities from the as-produced material

Depending on the purification history of the sample, diamond contents range from 25% to more than 80%. It is also important to note that the presence of different amounts of metal catalyst and large variations in surface chemistry further complicate the oxidation kinetics and must be taken into consideration when determining the oxidation conditions of commercial ND powders. Finally, it should be considered the surface chemistry of the various samples as it directly affects ND properties such as wetting behavior, surface charge, agglomeration, adsorption, and chemical reactivity. The quantity and type of functional groups formed vary depending on the oxidation conditions and the reacting species. Acid oxidation tends to yield more carboxylic groups, while gas phase oxidation result in a high concentration of carbonyl groups, which exhibit higher thermal stability. This explains the higher oxidation resistance of ND powders that were treated by both acid- and air-oxidation, which contain similar amounts of Fe as compared to samples purified solely in acid. Smaller crystals etch faster than bigger crystals which seem to be more resilient to the air-oxidation process, which may be explained by the rapidly increasing surface-to-volume ratio at the lower end of the nanoscale. After synthesis, chemical treatment of NDs is often necessary to create homogenized reactive surfaces that enable further surface modifications. Since the ratio of polar to non-polar functional groups on the surface of NDs defines several important properties, such as their hydrophobicity or hydrophilicity, it is essential to establish reproducible methods to ensure uniformity or homogeneity of their surface chemistry. Methods such as detonation synthesis introduce a highly diverse surface chemistry to NDs, with functional groups including hydroxyl, carbonyl, ether and carboxyl groups. For localized delivery systems, NDs could become key contributors in providing sustained release and improving biocompatibility as a coating or standalone drug release device owing to their flexibility and ease of manufacture. The covalent surface modification of diamond films has recently become an active field of research. Different strategies for the covalent grafting of complex structures as well as for the tuning of hydrophobicity have been reported. One method includes the photochemical reaction of hydrogen-terminated diamond films with organic compounds possessing a terminal vinyl group leading to stable C-C bonds at the diamond surface. When bifunctional molecules are used, further functionalisation leads to ever more complex conjugates. On the other hand, the covalent surface modification of nanoscale diamond particles has proven to be a challenging task. Although the surface is covered with a variety of initial surface groups (from production and purification treatment), there have not been too many reports on the selective grafting of bigger entities. Once the correct functionality has been homogeneously introduced on the surface of NDs further chemical modifications are possible to covalently link biomolecules, drugs, antibodies or fluorescent probes. The type of bond and its stability in an aqueous environment are critical parameters to consider for a successful therapy. NDs represent a platform which enables a great variety of chemical modifications based on the functional groups introduced with chemical homogenization. For example, purified COOH-terminated NDs can be used to generate ester or amide bonds although a previous activation of the carboxyl group is required. Proven to be a versatile platform, NDs have also been conjugated and attached to several types of biologically relevant agent, including amino acids and peptides through silane linkage, and cytochrome c and lysozymes adsorbed by means of surface–protein electrostatic interactions. In addition, NDs have been functionalized to capture glycoproteins within protein mixtures, a promising precursor for extraction in proteomics. Future conjugations are very plausible, as diamond surfaces have been conjugated with a variety of extra agents. It is important to underline that every modification described can have a profound impact not only on the reactivity of the surface but also on the general biocompatibility of NDs.

Biomedical applications

Several crucial factors have been historically considered when selecting a drug delivery platform. Mounting evidence has indicated that drug efficacy is determined through a combination of factors, including, among others, the timing of drug administration, dosages and drug release patterns. A variety of methods have used NDs as biological imaging agents. Nitrogen-vacancy center defects created through various types of irradiation on 35 and 100 nm NDs have generated photostable fluorescence excitation and emission at ~ 560 and ~ 680 – 700 nm, capable of high spatial and temporal resolution within cells. Advances in defect generation have made mass-production of these fluorescent particles possible. An added benefit in this method of production is that the fluorescence originates from point defects within the lattice, and therefore is uninhibited by surface functionalization. A preliminary study demonstrated that DNA could nonspecifically attach onto carboxylated NDs without any loss in fluorescence. Another contrasting method in using NDs as biolabeling agents is through Raman spectroscopy. Diamond materials have a strong Raman intensity signal at 1332 cm^{-1} due to its sp^3 carbon bonds, a wavelength that is typically independent of surface functionalization and biomolecules. Furthermore, Raman spectroscopy is performed at ambient conditions and does not invasively harm the cell. 100 nm-diameter carboxylated NDs conjugated with growth hormones were used to label growth hormone receptors within epithelial cells and identified through its unique Raman signature.

Potential future work manipulating the NDs may demonstrate further their application as both a simultaneous imaging and drug release platform with preclinical and clinical relevance. For systemic treatments, NDs are visualized as a nanoparticle drug carrier that addresses a multitude of diseases, in particular late stage malignant cancers. Owing to their small size and biologically amenable surface, penetration of leaky vasculature for thorough therapeutic exposure is possible. As opposed to localized implants, the nanoparticles would provide a non-surgical method of introduction. To realize the potential in using NDs for systemic delivery, the mechanisms of cellular uptake and intracellular trafficking must be investigated. The interplay between cellular response and size has shown that particle properties have a crucial role in mediating cellular response. NDs can be used also to formulate a biocompatible, thermo sensitive and multifunctional hydrogel platform that can function both as a filling agent to modulate hydrogel properties, as well as a delivery platform for the controlled release of bioactive molecules and growth factors. One of the major drawbacks associated with the use of conventional hydrogels as carriers of growth factors is their inability to control the release kinetics of the loaded molecules. In fact, in most cases, a burst release is inevitable leading to diminished therapeutic effects and unsuccessful therapies. As a potential solution to this issue, a strategy of incorporating ND complexes within an injectable hydrogel matrix was proposed.

Conclusion

In recent years NDs have emerged as promising platform for biological imaging and drug delivery system. Over other drug carriers, NDs exhibit excellent mechanical and optical properties. Their high biocompatibility is of paramount importance in order to make them suited for biomedical applications. However *in vivo* behavior should be better defined in order to take full advantage from these interesting nanocomposites.

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