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Combinatorial nanodiamond in pharmaceutical and biomedical applications

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ABSTRACT

One of the newly emerging carbon materials, nanodiamond (ND), has been exploited for use in traditional electric materials and this has extended into biomedical and pharmaceutical applications. Recently, NDs have attained significant interests as a multifunctional and combinational drug delivery system. ND studies have provided insights into granting new potentials with their wide ranging surface chemistry, complex formation with biopolymers, and combination with biomolecules. The studies that have proved ND inertness, biocompatibility, and low toxicity have made NDs much more feasible for use in real *in vivo* applications. This review gives an understanding of NDs in biomedical engineering and pharmaceuticals, focusing on the classified introduction of ND/drug complexes. In addition, the diverse potential applications that can be obtained with chemical modification are presented.

1. Introduction

Nanodiamonds (NDs) have been developed as electric materials since they have promising properties such as energy absorbance, thermal diffusivity, and high capacity (Branson et al., 2013; Lim et al., 2013; Sundar et al., 2014). NDs also have applications in lubricants, composites, electromagnetic shielding, and special catalysts similar to other carbon materials (Mochalin et al., 2012). Recently, NDs have emerged as a new platform for nano/biomaterials due to their interfacial integration with a variety of biomolecules, including proteins, polymers, chemical drugs, and genes. In detail, exploring the biomedical applications of versatile potential ND via chemical modification or physical absorption has been proposed for many different applications including photo-acoustic imaging agents, polymer composites as a dental resin (Mochalin et al., 2011), gene carrier (Bertrand et al., 2015; Zhang et al., 2009), drug reservoir (Chen et al., 2009), and fluorescence marker (Schrand et al., 2011). The easy access of NDs to biomedical applications relies on the moderate condition of the surface modifying capability in charges and other functional groups on the ND substrate. Moreover, it has been observed that ND particles uptaken by cells are minimally cytotoxic and biocompatible, which means they do not affect mitochondrial function or ATP production at the cellular level (Schrand et al., 2007a); however, the biocompatibility of ND varies depending on its material properties.

The nature of promising NDs depends mainly on their chemical production and purification procedures. NDs can be produced via detonation method (Mochalin et al., 2012), chemical vapor deposition (Liu and Dandy, 1995), high-energy ion irradiation of graphite (Daulton et al., 2001), and high-energy ball milling of diamond microcrystals (Boudou et al., 2009). Different production methods, treatment conditions, and processing techniques result in diverse types of NDs that vary in size, shape, structure, and even surface chemistry (Kulakova, 2004; Paci et al., 2013; Sabirov and Ōsawa, 2015). This creates distinct surface properties making it possible to use as an extensively good platform for other potential discoveries (Paci et al., 2013). However, this is also why identifying the physical and chemical properties of NDs and carrying out quantitative analysis of its surrounding chemistries remain a challenge (Mochalin et al., 2012).

NDs contain a core diamond crystalline structure and possess a unique surface structure. They have a large specific surface area, high adsorption capacity, and chemical inertness (Kulakova, 2004; Mochalin et al., 2012). Various functional groups in the ND surface

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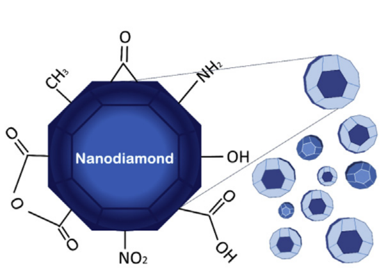

Fig. 1. Summary of the functional groups present on the nanodiamond surface.

have been revealed saturation of the reactive surface of carbon atoms (Kulakova, 2004) and existence of dangling bonds for various covalent bonding (Krueger, 2008). These dangling bonds react with the surrounding media to trigger the functionalization of the ND particles (Krueger, 2008).

The ND surface is covered with amorphous carbon and mainly oxygen-containing functional groups [6]. These functional groups are analyzed using Fourier Transform Infrared Spectroscopy (FT-IR), which can detect functional groups and changes in the surface chemistry of functionalized NDs (Chen et al., 2009; Mochalin et al., 2012). Measurements confirm that there is significant presence of oxygen-containing groups on the ND surface (Chen et al., 2009). Small amounts of nitrogen-containing groups, methyl and methylene groups, sulfone, and other groups are also present (Kulakova, 2004). Fig. 1 shows a summary of the functional groups present on the ND surface.

The ND retains amorphous carbon, graphitic shells, and the sp3 phase of carbon on the diamond surface (Gaebel et al., 2012), which is available for surface functionalization. The physicochemical properties of the ND may be altered via surface modification (Sabirov and Ōsawa, 2015). Functional groups can be replaced by other groups, but they always remain attached within the surface of the ND (Kulakova, 2004). They can also be the binding site for the covalent integration of ND into polymer structures and help improve the dispersibility of ND powders in common solvents (Liu et al., 2004). Various groups are compatible with ND surface chemistries, allowing for radical surface functionalization, and thus present a distinct characteristic of ND compared to other nanoparticles (Mochalin et al., 2012; Wahab et al., 2015); ND also exhibits high surface reactivity compared to other carbon nanostructures. ND is chemically functionalized in many ways, but the outcome depends on the purity and uniformity of their surface chemistry (Fig. 2) (Mochalin et al., 2012; Sabirov and Ōsawa, 2015; Wahab et al., 2015). Surface functionalization was also said to affect the stability of ND surfaces (Mochalin et al., 2012). The functionality of the ND surface is responsible for its drug binding ability and imaging, and is also a determining factor for its other applications (Paci et al., 2013).

With these specific potentials and capabilities, ND complexes that are formed either by physical adsorption or chemical conjugation have the benefits of reducing the multidrug resistance of anticancer drugs, enhancing delivery efficacy with convective diffusion. This property of ND complexes may possibly be useful for diverse smart designs (Wang et al., 2014). Small ND of 5 nm diameter can perform as a carrier platform by holding drug molecules within an intracellular compartment due to their large surface area. Moreover, ambiguous surface functional groups and their density on the ND have dependence on versatile sources. This review summarized the versatile chemical modifications of NDs required to develop its desirable properties, the potentials of ND as a drug delivery carrier platform, and the fate of ND within cells and other *in vivo* applications. Future applications of ND were also discussed with the objective of creating pharmaceutical applications.

2. Molecular dynamics

Possible concepts of versatile and novel ND applications have been disclosed in several recent studies, which have made a strong driving force towards analogous goals. However, different commercial sources of NDs provide ambiguous and veiled surface characteristics that require fundamental understanding and methodology standardization in ND experiments (Lai and Barnard, 2014). Understanding the faceted ND surface is a critical step in taking advantage of the high surface area to volume ratio for biomedical and pharmaceutical applications. Furthermore,

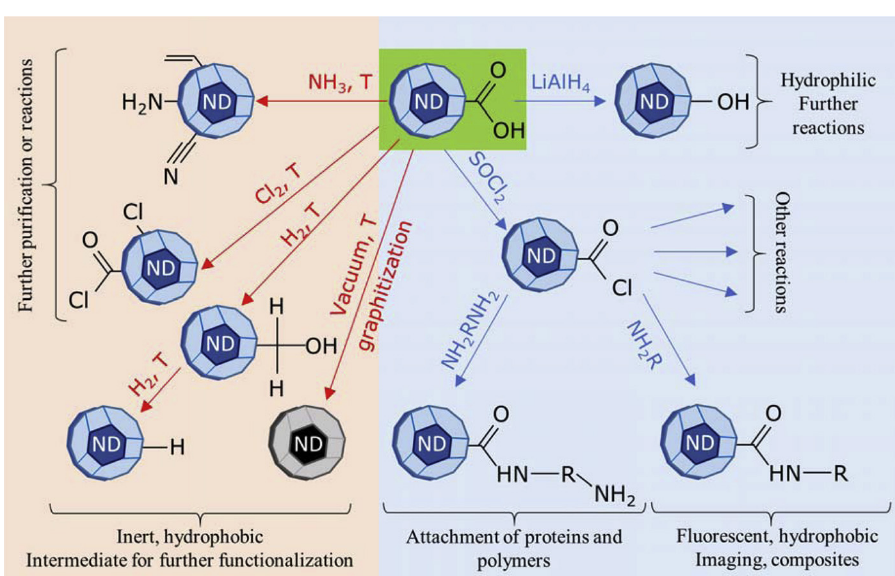

Fig. 2. Schematic description of ND surface modification. Carboxylated ND (ND–COOH) is a common starting material. The surface of ND–COOH can be modified by reaction with gas at high-temperature condition (red area) or wet chemistry modification at ambient-temperature condition (blue area). (Adapted by permission from Mochalin et al., Copyright 2012 Macmillan Publishers Ltd.). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)