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Detonation Nanodiamonds: Opportunity for Pharmaceutical and Medical Application

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Abstract

Detonation nanodiamonds have 4-5 nm size primary particles, stable inert core, high surface area and tunable surface structures. They are very attractive from pharmaceutical point of view as a drug delivery vehicle. Nitrogen impurity like defect in detonation nanodiamonds structure are absorbed light at wavelengths of visible, infrared or ultraviolet spectral region, and emit bright fluorescence. This allows their use as agent for imaging biological processes and tracking treatment approaches.

Keywords: Nanodiamonds; Detonation; Drug Delivery; Fluorescence

Introduction

For nanodiamonds were produced for first time in 1962 in Russia. The researchers started to produce them from outdated military explosives trotyl and hexogen with the sole purpose to increase the life of their tanks. The second half of the 20th century, after number of important studies started a broader interest to these particles. Detonation nanodiamonds (DNDs) present a new class of carbon family nanoparticles [1].

Based to their primary particle size, NDs are classified into nanocrystalline particles (1 to≥150 nm), ultrananocrystalline particles (2 to 10nm) and diamondoids (1 to 2nm) [2]. Diamond particles with a primary particle size of 4 to 5 nanometers are of interest for biomedical applications, as research has focused on detonation nano diamonds (DNDs) [3].

Synthesis and Purification

NDs were first produced by detonation technique. Oxygen-deficient explosive mixture of trinitrotoluene (TNT)/hexogen (in the proportion 60:40) is detonated in a closed chamber in an atmosphere of inert gases and H_2O or ice. To prevent diamond transformation into graphite at the high temperature generated by the detonation, the cooling rate of the reaction products should be no less than 3000 K/min [4]. DNDs are formed at the front of detonation wave in a fraction of a micro second. They consist of carbon predominantly in diamond phase to an extent of 80-88% [5]. An important feature of the DNDs structure is the presence of various functional groups such as carboxyl, hydroxyl, lactone, anhydride, ketone and ether on the surface of the particles (often called "a coat of functional groups") [6]. These groups are formed during detonation synthesis, when in the too short time (microsecond) during the explosion and non-stationary regime DNDs failed to stabilize their electron shell [7]. The yield of the obtained DNDs depends on the heat capacity of the cooling medium in detonation chamber. The diamonds are extracted from the soot by the use of liquid oxidants such as HNO_3, a mixture of H_2SO_4 and HNO_3, $K_2Cr_2O_7$ in H_2SO_4, or HC_lO_4. To remove non-carbon impurities, the product is subjected to HCl. Non-diamond

carbon can be oxidized by ozone-enriched air at elevated temperatures, like cheapest and more ecological alternative method. Ozone-purified DNDs have a smaller aggregate size in aqueous dispersions, higher content of single particles compared to this purified with a help of liquid oxidants [8].

Single DND particles have diameters of 4–5 nm. Firstly aggregates are formed from single DND particles with coherent and non-coherent boundaries with C-C bonds (directly under explosion conditions). The aggregation continues as a result of realized bonds between functional groups on the surface of DND particles and due to Vander Waals forces [7]. Another theory is the aggregation mediated through graphitic soot [9]. Graphitic soot embryos which are obtained after lowering of the temperature and the pressure start to coagulate and are arranged like an irregular graphitic shell around the particle before formed a core aggregate of DNDs.

Other methods of synthesis of ND are: laser ablation, plasma assisted chemical vapour deposition (CVD), autoclave synthesis from supercritical fluids, chlorination of carbides, ion irradiation of graphite, electron irradiation of carbon 'onions' and ultrasound cavitation [10-16].

De-Aggregation and Surface Modification

Formation and maintenance of de-aggregated DNDs formulation is very important for possible biomedical application. They are physical, chemical and combination methods for de-aggregation of NDs. Physical approaches are chosen when NDs aggregation is mediated through graphitic layering, while chemical methods are based on the functionalization of the surface. Chemical approaches use the conjugation of various organic or inorganic molecules on the surface of NDs to control aggregation and to impart them specific properties.

De-aggregation of ND in suspensions is obtained by milling with ceramic micro beads (ZrO_2, SiO_2) or ultrasonic disintegration with micro beads, dry milling with sodium chloride or coarse sucrose, high-temperature hydrogen treatment, ultrasonic treatment in borane presence [17-20]. There was data that purification and oxidation in air allow to isolate a stable hydrosol of particles 4-5 nm in diameter by centrifugation [21]. By the first method are yielding colloidal solutions of individual NDs 4-5 nm in diameter, but during the bead milling graphitic layer are formed around primary particles. Liquid oxidants are used to remove it following of the formation of new aggregates. The second method is cheap and allows particles and small aggregates of 5-20nm to be achieved without additional contamination. Obtained by high-temperature hydrogen treatment NDs have size 2-4 nm. Ultrasonic treatment in borane presence, reduce aggregates size to ~20-nm. The possible re-aggregation of ND particles is prevented by ultrasound-assisted treatment in the presence of sodium chloride. It is assumed that Na^+ repels each other when they are attached to the surface of the individual particles [18].

Functionalization of the surface can also assist the reduction of the size of the aggregates. The above-mentioned method with borane, lice combined method showed the greatest reduction of aggregates after functionalization [22].

Functionalization was often use from biomedical and pharmaceutical utilization, thus allows loading of drug substances. Modification of NDs surface can be achieved through physical adsorption or through chemical interaction. Physical adsorption of NDs has been widely accomplished using proteins, drugs, and nucleic acids [23-27].

An important step before chemical functionalization of NDs is the unification of the surface groups of the NDs, in order to ensure similar behavior conjugating from the entire surface. Oxidation or reduction of NDs is selected based on the terminal functional groups required on the surface. Different oxidative agents give variable functional group distribution on the surface after oxidation. For example nitric acid and sulphuric acid result in carboxylate (COO-) rich surface, potassium permanganate and sulphuric acid result in SO_3- or O- derivatives of phenol [28,29]. Reduction converted most of the functional groups into hydrogen or hydroxyl groups [6]. Therefore, reduction of NDs can create either positive surface through hydrogenation or negative surface through hydroxylation of ND surfaces.

There are three different types of surface chemistries: wet chemistry, gas phase methods or atmospheric plasma treatments.

Wet chemistry treatment use of suitable solvent systems to introduce functional groups. Depending of functional groups to be attached on the surface oxidized carboxylated NDs or reduced hydroxylated NDs can be used. Carboxylate functionalized NDs can be reacted with thionyl chloride to form acyl chloride functionalities which can be further attached to amine containing chemical moieties [1].

The treatment of NDs in gas or a vapor reactive medium is different approach. The gas phases used can include hydrogen, ammonia, carbon tetrachloride or argon. NDs treated with ammonia yield carbonyl, amine or cyano groups on the ND surface, while treatment with chlorine results in the formation of chloro-NDs or acyl-chloride functionalized NDs. Functionalized with amino acids and alkyl chains via covalent bonding or alkyl-, amino-, and amino acid-functionalized diamonds have been created by chemical modification of fluorinated NDs with alkyl lithium, ethylenediamine, or glycine ethyl ester hydrochloride, respectively [30-32].

Another approach for modifying the surface is atom transfers radical polymerization, when radical initiators (benzoyl peroxides, hydroxyethyl-2-bromoisobutyrate or 2, 2, 2-trichloroethanol) which are attached covalently to oxidized NDs through esterification. Chemical groups are then introduced in the system which polymerize and arrange as brush arrays on the surface [33,34]. This process create hydrophilic or hydrophobic surface depending of the nature of polymer. Radical generation mechanism is used for successful grafting of carboxylic groups onto NDs [35,36].

Different functional groups on the surface of NDs give possibilities for their conjugation with different moieties without compromising the useful properties of the diamond core [37]. As well as systems for drug delivery, DNDs can be used as bioimaging agents.

Photoluminescence Properties

Fluorescence is often used interchangeably with photoluminescence to define spectroscopic properties of NDs. Nitrogen impurity is common defect that exist in the diamond structure as a result of detonation. The nearest-neighbor pair of nitrogen atom, substitutes carbon atom and forms a vacancy in the diamond latticez [38].

Fluorescent nitrogen vacancies $(N\text{-}V)^0$ and (N-V)-in ND core are formed during synthesis and are responsible for photoluminescence properties of NDs. They absorb light at wavelengths of visible, infrared or ultraviolet spectral region, and emit bright fluorescence at 550-800 nm [39,40]. To enhance the fluorescence centers in NDs are used techniques with irradiation of NDs with helium ions (He^+) at 40 keV followed by thermal annealing at 800°C, also hydrogen ions (H^+) at 3 MeV to create vacancy centers in ND core. Directly incorporate nitrogen atoms as native nitrogen 14N, its isotope 15N or as cyanide (CN^-) ions in the core is another method to create nitrogen vacancies. To preserve fluorescence NDs are encapsulated by bulky groups like phenols, which reduce the non-radioactive decay pathways of colored centers [41-46]. Fluorescence can also be produced through surface conjugation. NDs can be functionalized with a hydrophobic molecule octadecylamine producing bright blue fluorescence and can be useful for imaging hydrophobic components [47].

Conclusion

Nanodiamonds possess unique properties that make them attractive for medical and pharmaceutical technology. The possibility for amino-, carboxyl –and other functionalization of their surface is often used from biomedical utilization, thus allows loading of larger number of drugs, proteins, small molecules. Changes in pH with respect to pKa can cause variations in the charge of the surface functional groups which make possible interactions with other molecules. Combination of roles of drug vehicle with imaging effect is an important opportunity for monitoring of the delivery of cargo into the target cells, organs or systems. Major disadvantage of nanodiamond suspensions and powders is their tendency to aggregates. The storage of de-aggregated by different techniques particles form again aggregates with time. Therefore, the search continues in order to obtain single nanodiamond particles well dispersed and stable for a long period.

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