Critical Reviews™ in Therapeutic Drug Carrier Systems, 38(4):39–78 (2021)

Nanodiamonds: A Versatile Drug-Delivery System in the Recent Therapeutics Scenario

Awesh Kumar Yadav,* Rahul Shukla, & S.J.S. Flora

Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Uttar Pradesh 226301, India

*Address all correspondence to: Dr. Awesh Kumar Yadav, Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Raebareli (NIPER-R) Bijnor-Sisendi Road, Near CRPF Base Camp, Sarojini Nagar, Lucknow, Uttar Pradesh 226301, India; Tel.: +918226093943, E-mail: aweshyadav@gmail.com

ABSTRACT: Nanodiamonds (ND) belong to the nano-carbon family, which involves several synthesis, post-synthesis methods, and other modifications for ND preparation. NDs have played vital role both inside and outside of medicine in recent years. The study of NDs has stated in early 1960s, NDs are smaller particles with a size of about 4–5 nm with confined size distribution, large-scale synthesis at lower costs relying on the carbon explosives ignition, apparent surface functional design along with bio-conjugation and extreme biocompatibility. It has been predicted that the ND's magnetic characteristics will contribute to the up-growth of various therapeutic promoters for delivery vehicles, diagnostic probes, gene therapy, tissue scaffolds, anti-bacterial and anti-viral treatments, and devices like nano-robots. Furthermore, the wide applications of biotechnology have displayed the potential usage of NDs in certain bioanalytical needs like fluorescent bio labeling through fluorescent and protein purification of proteins. In this current review, the determination of ND's design, property, classes, constancy, organization, surface modification, biocompatibility, and its applications in the biomedical field have penned. The usage of ND as anti-neoplastic agents and in other health related formulations have displayed exceptional results for future growth. Additionally, NDs provide other functionalities such as production of biodegradable surgical devices of bone, the assassination of drug resistant microbes and viruses, tissue engineering scaffolds, and aids in the delivery of genetic matter into the nucleus of cells.

KEY WORDS: nanodiamond, surface modification, biomedical applications, biocompatibility, bio-sensing

I. INTRODUCTION

Nanodiamonds (NDs), or diamond nanoparticles, are diamond-like structures having particle size range less than 10 nm. Nano-scale-size diamond fragments are propitious components for research due to their comparably small size allocation, flexible surface complex and chemical dormancy altogether that constitute them as affirmative elements for various biological and electronic applications.[1–4] ND powder are processed through detonation as ultra-dispersed diamond displays exclusive surface characteristics. Homogeneous distribution of the particles composed with varied types of functional groups along with lactone, carboxyl, ketone, alkyl and hydroxyl groups are identified on the ND particles surface and their corresponding aggregates.[5–10] Any covalent or non-covalent alterations of these functional groups can modify the features of these ND materials.[11]

0743-4863/21/$35.00

It is foreseen that the properties of NDs will be utilized in an identical fashion to other quantum dots, carbon and metallic nanoparticles for the creation of curative agents for transmission vehicles, probes, anti-bacterial and anti-viral treatments, gene therapy, tissue scaffolds, and medical devices like nano-robots.[12–15] Especially, applications in biotechnology have displayed potential uses of NDs in various bioanalytical insights like bio-labeling and protein purification by making use of FND particles.[16] In bio-designing process, manufacturing of nano-scale materials like ceramic, metallic, composite and polymeric molecular level of interaction with greater specificity determines the exceptional probability of nanotechnology in life sciences.[15,17,18] Nevertheless, the adaptation of these improvements in clinical research and applications actually depend on a set of diversified techniques of nanofabrication, additionally downsizing devices like BioMEMS, along with augmentation of novel analytical processes.[17,19–21]

II. STRUCTURE OF NDS

In its ground state the electronic configuration of elemental carbon is $1s^2$, $2s^2$, $2p^2$. Two of the electrons in the 1S orbital are known to be core electrons and the rest 4 are valence electrons. The hybridization (sp^2) of C atoms possess into graphite that is a 2D hexagonal structure, whilst hybridization (sp^2) of C atoms results in a tetrahedral structure (diamond). The valence e- of diamond with nearby C atoms leads to the formation of σ-bond thus forming a layer of C atoms with a modified FCC (face-centered cubic structure). Absence of free electrons in diamond makes it a toughest solid with thermal conductance, and optical dispersion features. Gallium arsenide, silicon and germanium possess the similar structure like of diamond. ND structure is a complex made of (i) central core composed of C with sp^3 hybridization (ii) C shell with sp^2 hybridization that envelopes the core partly (iii) the outer surface of C atoms leads to the formation of functional groups which aids to cease the bonds and holds on H and O atoms (Fig. 1).

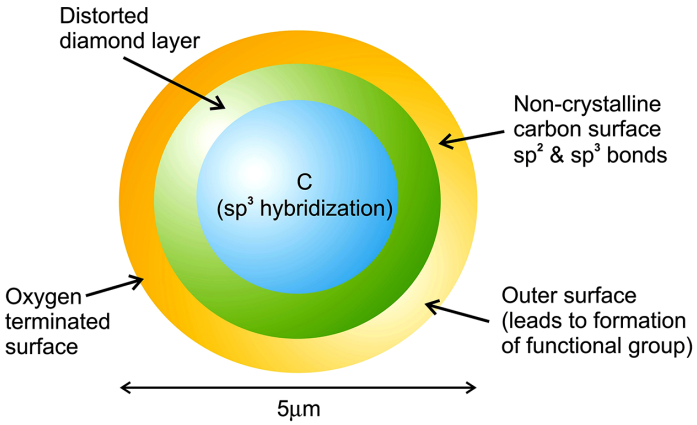

FIG. 1: Structure explaining the different layers of diamond (reprinted from Bera et al. with permission from Springer Nature, copyright 2019)[22]

Over the surface of pristine ND, varied groups such as CH moieties, CH_2, CH_3 are determined in distinct configurations ($O{=}CH_2$, $C{-}CH_2$, O–CH, O–H) along with O moiety such as carboxylic (–COOH) group, lactone (O–C=O), carbonyl groups (–C=O), and ether (–C–O–C–) (Fig. 2).[23,24]

Although diamond is known to be reliable when compared to graphite at atmospheric pressure, in the nano-scale-size range, the particles of diamond with smaller size of 5 nm are observed to be stable greater than graphite.[24,25] In a research carried out by Barnard et al.,[26] based on the density functional theory, the endurance of diamond, graphite and fullerene was evaluated and concluded that diamond is found to be one of the stable C clusters (size of 1.9–5.2 nm). Barnard, through computer simulation techniques, has documented the effect of polyhedral shape on the stability of NDs.[26,27] Three different shapes of ND particles like truncated octahedral (TO), octahedral (OC), and cubo-octahedral (CO), where OC consists of 8 {111} facets, TO of 8 {111} facets for which 2 adverse vertices are actually truncated in order to form (100) surface structures, CO contains 8 {111} and 6 {100} facets, respectively. The facets are trimmed down from the crystal with a lattice constant of 3.56 Å. Each one of them is at similar distance from that of the cluster center.

III. CATEGORIZATION OF NDS

Based on the particle size of primary forms, ND particles are classified into 3 group of particles such as ultra-nanocrystalline (nm), nano-crystalline (tens of micrometers), and diamondiods which are defined H terminated forms contains tens of C atoms.

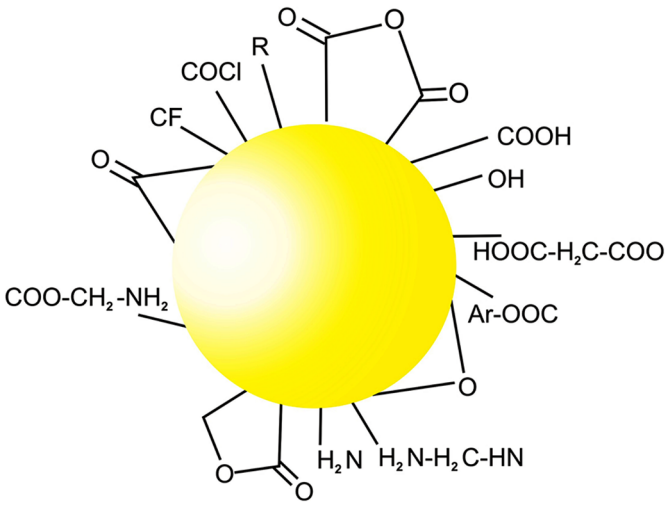

FIG. 2: Presence of various functional groups on surface of ND surface (outer surface leads to formation of functional group) (reprinted from Bera et al. with permission from Springer Nature, copyright 2019)[22]

A. Nanocrystalline Diamond Particles

Nanocrystalline particles of diamond with typical sizes (tens of nanometers) are found in isolated monocrystalline or polycrystals forms (Fig. 3). The monocrystalline forms are derived by processing monocrystalline (byproduct of natural form of diamond or HPHT synthesis) particles that are of micron size. Processing of these micron particles to lesser fractions usually include crushing, distillation, and branding of the powder. The monocrystalline forms are observed to be having sharper edges when distinguished with other ND forms. Monocrystalline ND powder is the absolute fine product among the class of ND products. Synthetic HPHT types consisting of 100 ppm N atoms with sizes of 25 nm, 35 nm, 100 nm were utilized to generate fluorescent structures by proton irradiation trailed by strengthening for applications in bio-labeling.[28–30] While the polycrystalline ND powder is produced by using micron scale-sized polycrystalline particles which are usually derived through shock synthesis (DuPont de Nemours's method).[30] The polycrystalline forms have nanometer scale-sized grains which are

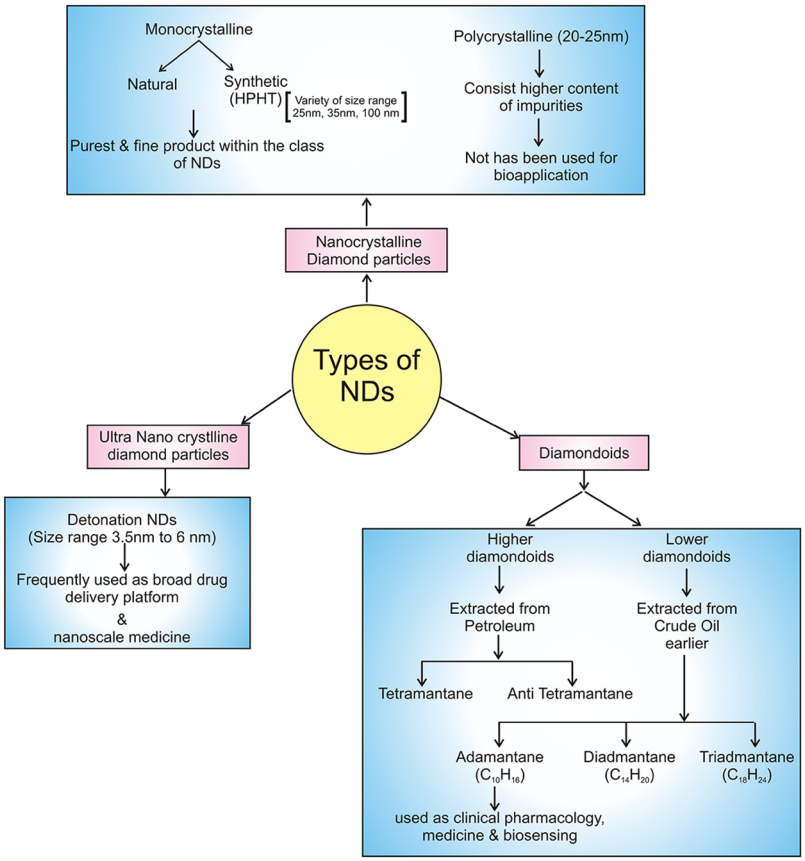

FIG. 3: Explanatory description of different types of NDs and their applications

about 20–25 nm. The fractions of diamond formed through micronizing and grading have the particle size of 25 nm. This kind of ND has impurities and is not used in any biological applications. The configuration of the primary matter is more like platelets than like a sphere.[31]

B. Ultrananocrystalline Diamond Particles

Among different types of ultra-nanocrystalline forms (Fig. 3), the detonation method is exclusive and mainly commercialized. The size range of the particles resulted through this detonation method rely upon the explosive charge weight and hence no specific size is in principle, though majority of the vendors develop the particles within 3.5–6.0 nm. These small NDs are useful for biological applications such as drug delivery (Nanoscale medicine)[32] adsorption of protein,[33,34] genetic material transporter,[35] gene gun ballistic transfer as enterosorbents.[36,37]

C. Family of Diamonds

A family of species with H-terminated forms consisting of 1–2 nm where been discovered in the recent past. These structures called as diamonds are found to be highly solid, well exemplified, and deducible,[38] and act as building mass for nanotechnology. The size of diamondoids is found to be in between the size of adamantine molecule which is the smallest of hydrogen terminated form and the size of ultra-nanocrystalline forms. These diamond molecules are derived from petrol as nanometric sized helices, rods, pyramids and discs.[39,40] Hitherto, the synthesis of diamondiod forms like tetramantane, and antitetramantane was only possible under the category of higher diamondoids.[41] Nevertheless, lower forms of diamondoids such as diadamantane, adamantane, and triadamantane have been extricated using crude oil much prior than the higher forms and are available in large quantities. These lower forms like the adamantane derivatives have wide applications across clinical medicine, pharmacology, and bio-sensing units.[42]

IV. SYNTHESIS AND AMALGAMATION OF NDS

A. Commercial Methods

The synthesis of NDs occurs in different methods with their commercialization.[43] One of the widely used is the Du Pont method where the precursors of carbon precursors like graphite, coal, and carbon black are converted to diamond within a capsule through the shock wave application (~ 140 GPa) which is produced external to the capsule. The precursors are fixed within the inner tube and outer tube looped through a driving tube. The free room within the tube is infused with certain explosive components. The shock waves usually are produced through the combustion of explosive compound at particular end of the equipment that actually condense the tube and converts the sp^2 C-component into nanoscale diamond particles. A combination of graphite 6% to 10% and metallic powder

either of Cu, Al, and Ni are utilized to avoid diamond re-graphitization. The final yield of ND is found to be almost 5% that of primary supplied matter within the capsule or about 60% of that of carbon phase. The final product of ND has bimodal size distribution of 1–4 nm and the other with 10–150 nm. Nevertheless, numerous modifications are made across this method.[44] The next procedure for the production of ND in large scale depends on the C detonation with explosives. In this particular process, ND synthesis occurs in both of the C material along with the explosive's C atoms condensation.[43] The cubic phase which is not higher than 20 nm is produced in an inert atmosphere however in atmospheric air the size is 8 nm only. The production rate of the final product is 3.4% of mass or 17% of the C at the primary stage. The last and third method is through the explosion process for the synthesis of diamond clusters produced from the explosives used as precursors. Currently numerous industrial reactors are processed for the production of ND particles.[5]

B. High-Pressure High-Temperature (HPHT) Method

In this particular process natural C form like (graphite/coke) is introduced through an anvil by maintaining immense pressure and kept under high temperature. Thereby the C results into a highly stable compound called as diamond. The synthetic form of diamond formed through this procedure consists of 100 ppm to 300 ppm of N.[44] By making use of extreme energy radiations, the diamond carbon is knocked out of the structure thus creating vacancies (V). The nitrogen vacancy (N-V) color defect centers are liable for the emission of fluorescence.[44,45]

C. Chemical Vapor Deposition (CVD) Method

Chemical vapor deposition (CVD) is known to be one of well-known methods for both crystalline and polycrystalline forms where in each of the case the substrate required is diamond. Various forms of CVD method exist and process depends on the precursor gases activation such as microwave energy is used in microwave plasma enhanced CVD method in order to energize the gases. This method of CVD is most popular but very expensive to run and provides huge areas for the deposition of ND films. These films are produced through vapors of carbon on substrates of non-diamond/diamond.[46] Amidst the various films ultra and nanocrystalline kinds are highly resistant to pressure and possess superior mechanical properties. Size of these films can be restrained by precursors which are H rich and C poor, pressure, voltage and temperature.[47] The diamond films of ultrananocrystalline form which usually range from 3nm to 5nm are produced under H poor and argon rich conditions.[48] Along with the size difference these films also display dissimilarity in the sp^2 C content. The sp^2 C content is 50% in the nano form while it is 2–5% in ultranano form.[49] For example, the coating of biomedical implants is done by using ultrananocrystalline films which is of higher quality to that of silicon, quartz, and platinum used as substrates. This superior quality is ascribed to their opaque structure, roughness of the surface, reduced cytotoxicity and structural boundaries. Likewise, the

nanocrystalline films are highly stable, more biocompatible and selective in nature and have immense electrochemical possessions.[50]

D. HPHT Ball Milling

HPHT-based ball milling method is the most prominent and widely accepted method employed for fabrication of stable and FNDs. It is seven process in which very first step is genesis of μdiamonds using HPHT (approximate size is > 150 μm) and followed by annealing and irradiation of diamonds for generating nitrogen vacancy centre (approximate size is > 50 μm). After generation of uniform μdiamonds two series of milling process is formed i.e., jet milling (approximate size is > 1 μm), followed by bead milling (approximate size is > 200 nm). After this step purification and size fractionalization is done with ultimately end stage of ultracentrifugation generating ultra-nano-sized NDs. Size of isolated NDs prepared using HPHT method can be tuned within range of 4 to 25 nm with appropriate application of centrifugation and acceleration.[51]

E. Laser Ablation

In 1960s there were reports of development of ruby laser from laser ablation. Iron oxide nanoparticles were firstly synthesized using laser ablation techniques in 1987 with the help of high-power pulsed laser radiation on solid-liquid interfaces. Laser radiation is composed of many methods but out of all these methods, pulsed laser ablation in liquids (PLAL) is most attractive and well accepted method with special emphasis on growth of NDs at solid-liquid interfaces. Methodology behind PLAL is combination of pulse laser deposition and chemical routes which produces stable colloidal suspensions. Parameters which determine the property of NDs are as follows: a) laser impulsion along with excitation, b) temperature and pressure of system, c) solvent system used. In this method intensity of laser on material is 10^8 W/cm^2 which finally leads to ejection and evaporation of targeted material. Synthesis is done by submerging powder or solid form of material in suitable solvent under defined temperature and pressure with interaction of targeted atoms and liquid evaporation.[52]

F. Carbide-Derived Diamonds

Carbon derived from metal carbides extraction is known as carbides derived carbon. Synthesis of various carbon structures by selectively etching carbides produces nanocrystalline diamonds. Various techniques are employed for removing metals from carbides and genesis of carbon coating or powdered carbon from supercritical water leaching, halogen treatment at high temperature, decomposition via vacuum. Nanoporous carbon was produced using chlorination of carbon. In case of silicon extraction from silicon carbide operating near temperature of 1000°C generates nanocrystalline diamonds with size of 5 nm in chlorinated gaseous environment.[53]

V. ND SURFACE MODIFICATIONS

NDs nano scale size, greater surface area, and the probability of distillation with the help of oxidizing agents allow them to be a practicable applicant for any surface modification and activity. Figure 4 summarizes approaches establish various functionalities on the surface of NDs.[55–62] Few of the primary alterations of the ND surface include surface radical's generation, substrate for producing dicarboxylic acid-60 and carboxylic acid-59 NDs. For better functionality of the surface area, it is required for the surface to be uniform all over and this can be achieved by reactions using hydrogen, fluorine, and chlorine and was successful in earning homogeneity of the surface and boosting reactivity.[56–58] Under reaction with amine, hydroxyl and carbon fluoride, the chlorinated NDs

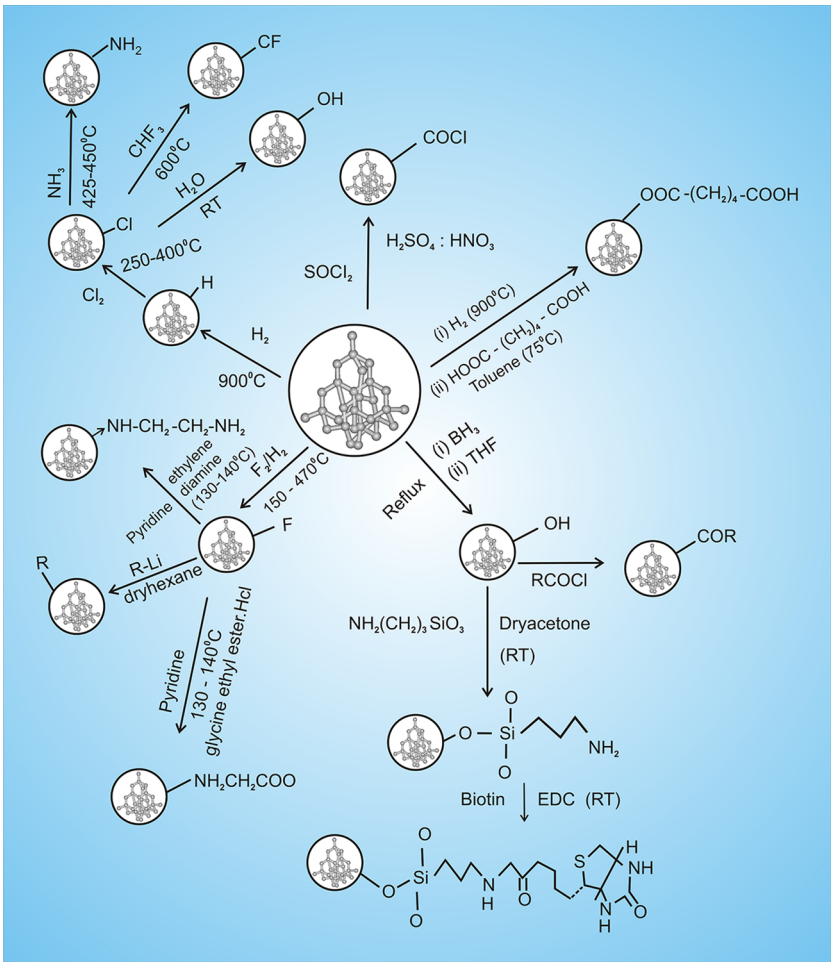

FIG. 4: Schematic representation of modification on ND surfaces for functionalization (reprinted from Karami et al. with permission from Elsevier, copyright 2019)[54]

are altered. At the end, the NDs are kept under reaction with ethylenediamine, alkyllithium, and glycine ethyl ester HCL etc.[58] Through surface modification and functionalization, the reduction of the complex NDs size occurs which is one of the novel treatments.

Surface modification with alkyl groups shortened the size to 150–450 nm from 15 μm. Compared to that of pristine, long alkyl chain functionalization of NDs displayed an improved organic solvent solubility.[59] Similarly, alterations using fluorine lead to the reduction of size by 160 nm from 1930 nm.[8] On reaction with borane, μm sized pristine NDs was reduced to 50 nm.[59] After hybridization with alkyl silane, modified NDs are utilized to produce biotinylated NDs by modifying the surface. While, the Lysine particles at the surface will get lowered to 21 nm from 1281 nm. Hence, the final product with lysine modification and surface stowing of 1.7 mmol/g displayed higher solubility in H_2O when compared with other NDs-carboxylated.[62]

VI. CHARACTERISTICS OF NDS

A. Chemical Features

Among the group of carbon nanoparticles, NDs are found to be having unique characteristics because of the surface hydrophilic nature to use these nanomaterials for various biomolecules. Due to their larger surface area, small size, ability to react with various oxidizing solutions, NDs are accessible particles for functionalization of the surface. Several groups like ethers, carboxylic acid, esters, lactones and amines encircle the surface of ND. The initial alteration performed on the surface of NDs is the creation of radicals, from which carboxylic acid, and decarboxylic acid NDs were produced.[63,64] In gas and liquid media, the ND surface modification was examined by. The effect of alteration on sorption properties and catalyst of NDs was analyzed Kulakova et al.[65]

B. Structural Features

While defining the structural features, two important features of NDs are to be mentioned which effects its properties: (i) number of surface atoms (which defines the size) and (ii) shape of the individual ND molecules. In globular particle of diamond, the number of atoms is determined by using the following formulas:

$$\begin{aligned} N_{total} &= \frac{4}{3V_0}\pi R^2 \\ n_s &= (n_{bulk})^{2/3} \\ \frac{n_s}{N_{total}} &= \frac{3}{4Rn_{bulk}^{1/3}} \end{aligned} \tag{1}$$

While the count of the surface atoms can be computed using the expression (ns), whereas, nbulk = bulk atomic density; ns = surface density.

Specifically, sum of surface atoms for spherical particles can be calculated by the below set of rule. Through the experiments made by detonation methods, the shape of ND HRTEM images and clusters of ND were displayed as spherical. Nevertheless, on the superficial layers of Mo tip, the HRTEM images of individual NDs group displayed the survival of matter on the surface of particles in the shape of polyhedral (Table 1). This particular shape is very much alike to the particles of ND produced by Matsumoto and Matsui.[66] Regularly shaped twinned crystals and CO are typical habit of these clusters. The shape of diamond cluster is associated to its stability which in turn depends on the surface atoms state. The cluster stability is influenced by many factors such as presence of active groups on ND surface: surface hydrogenation and surface reconstruction. Based on Ab initio calculation, the spherical shape was observed for ND particles having diamond surface with (111) plane and undergo bukification.[67] Paired crystals with common shape and CO shape are few of habits these groups display. The stability of the group is affected through certain determinants like hydrogenation of the surface, existence of active groups over the particle surface and reconstruction of the surface. Another study by Kern and Hafner[68] documented that

TABLE 1: Physicochemical characterization of ND properties and techniques employed

Physicochemical feature	Property	Characterization technique
Surface features	sp^2 & sp^3 content	XRD, Raman, XPS, EELS
	Surface functional groups	XPS, FTIR, TDMS, NMR, Electrophoretic mobility, Titration
	Metal content (surface)	ICP-MS, PIXE
Diamond core	Fluorescence	Quantum efficiency, STED, FL lifetime, PL spectroscopy/microscopy, EPR (paramagnetic centers)
	Lattice quality	XRD, HRTEM
	Dopants	Conductivity (BDD), XPS, IGA (C, H, O, N, S) Bulk
	Metal content (bulk)	ICP-MS, PIXE
Size	Aggregate size	DLS (RH) (volumetric)
	Monocrystalline size	XRD, DLS (RH) (volumetric), Disc centrifugation (number)
Shape	—	HRTEM

DLS, dynamic light scattering; EELS, electron energy loss spectroscopy; EPR, electron paramagnetic resonance; FTIR, Fourier transform infrared spectroscopy; HRTEM, high-resolution transmission electron microscopy; ICP-MS, inductively coupled plasmon mass spectroscopy; IGA, instrumental gas analysis; NMR, nuclear magnetic resonance; PIXE, proton induced X-ray emission; STED, stimulated emission depletion; TDMS, thermal desorption mass spectroscopy; XPS, X-ray photoelectron spectroscopy; XRD, X-ray diffraction.

the clusters of truncated octahedron cluster are found to be higher than that of spherical forms and CO. The difference of binding energy amidst spherical forms and CO is very small ~ 0.01–0.02 eV/atom. Distinct C nanomaterials possess limited stability distinctness and the change in the shape of particle is inferred through agitation and hence varied forms for ND groups were noticed. For example, in the phase transition, the conversion to ND particles can be inferred by utilizing irradiation through electron beam. In case if the ND particles surface is not terminated by H, the end structures can be of hybrid type like bucky diamonds. The blockade amidst the ideal and the reconstructed surface in bucky diamonds rely upon mainly on the size and expand as the particle size increases.

C. Electronic Features

In the year 1999, the films of diamond were analyzed by making use of edge structural studies in-order to figure out the development of nanomaterials gap with size.[69] This helped to depict the endurance of quantum effect up to a range of 27 nm. However, in Ge and Si, the quantum effect will dissolve later 5–7 nm. The quantum effect was found vanished in particles greater than nanometer.[70,71] Thus, this revealed that the quantum effect would not impact the particle's structure of around 44 nm. DND emission spectra and X-ray absorption methods were found analogous to bulk diamond with secondary minimum of 302 eV, exciton broadening 289.3 eV. Runge make use of time independent and dependent density-functional theory (DFT) evaluation to analyze the dependence of size on optical gap.[72] It was also concluded that in nano materials with size larger than 1nm the quantum effect vanishes. The diamondoid gaps are observed to be below the bulk diamonds gaps if the size is amidst 1 and 1.5 nm. This is totally dissimilar compared to the action of H terminated Si and Ge nano materials.[73] There are two classes of nanoparticles classes that have been documented; (i) diamondoids made out from admantine cages and (ii) spherical, H-bond ND and huge amounts of diamondoids are derived from petrol and HPLC aids in distillation (Table 1).

D. Biomedical Features

NDs find their application in the biomedical field such as sensing, drug delivery, purification and imaging depending on the physical chemical and biological features (Table 2). NDs are usually produced at lesser price by using the detonation methods in greater quantities and displayed reduced toxicity and huge compatibility. Though NDs were commercialized recently (Alit, Sinta, ITC, Aldrich, and others), a variety of purities and size distribution with varied uniformity exists. For example, monocrystalline forms of NDs (4 to 5 nm) are determined to be stable and offer an interface, which is biocompatible, and the absence of reactive O species (ROS) generation.[74] The particles of ND are incorporated at varied concentrations through animal systems and individual cells. NDs act as biomedical probes and offer therapeutic

TABLE 2: Various physiochemical features and applications of NDs

Property	Features	Applications
Structural	NDs having small size range (~ 4–5 nm) NDs having larger surface area (~ 300–400 m^2)	Interact effectively with same size range bioactives. Having greater potency and efficacy to conjugate with drug, proteins etc.
Biological	Actively conjugates with biomacromolecules (polymers, proteins, bioactives, DNA, etc) Particle having high biocompatibility and low cellular toxicity	Targeted therapy. Utilized for cell organism studies.
Chemical	Chemically inert to corrosion, pH and degradation and stability Consisting large number of unpaired electron for radiations/ ozone resistance Potential sp^2 carbon shells Having high chemical purity	Coating of pharmaceutical formulations, implants, films forming agent and substrate for cell growth etc. Provide X-ray protective surfaces and detection devices. Enhanced physical adsorption of lipophillic biomolecules. Design biocompatible and stable interphase.
	Having larger variety of surface functionalization features Functional oxygen moiety consisting on ND surface	Enhanced attachment and coupling with drug molecules and other polymeric systems and metal composition materials. Provide water-dispensability and hydrophilicity to form suspensions for further binding to other molecular entity.
Technical	Economical, Synthesized efficiently in laboratory by diverse techniques	Due to commercial availability utilized for mass production (i.e., detonation synthesis). Accessibility of a variety of superiority/ purity samples.
Mechanical	Fine coarse High potency and rigidity	Skin polishing, dispersion of bioactive or polymer composites. Utilized as additives, ballistic delivery to tissues and cells.
Electro-chemical	Redox activities of detonated ND Electrochemical coating with metals	As an effective chemical/biosensing agent. Enhance durability and life of medical instruments/formulation/stability.
Thermal	Withstand in variety of high and low temperatures range	Composite formulation, sterilization (autoclave) and liquid nitrogen storage.

benefits meanwhile refraining impairment to healthy tissues and cells. They can be used as additives to improve the action of medicines used for dermatology, oncology

and other diseases. Pure forms of NDs are known to control BP, clean out the gastrointestinal system and cure for various cancers. Presence of unpaired e-over the ND surface enables each particle to an effective radical donor that stroll the free radicals and helps in treating various illnesses. NDs, due to their large area of surface promotes to have stronger affinity towards adsorbing enzymes, proteins and other biological molecules, greater inclination for binding to bacteria and viruses, removing and absorbing them.[74] They also help to clean protein solutions and may also act as enterosorbent within the body. NDs consist of abundant functional groups containing O which are actually included all along modification and purification stages, though the bulk diamond surface studied to be inert chemically. For instance, treatment of samples with acid produces highly pure material by eradicating the sp^2 C atoms and residues of metals during hydrophilicity for the sake of solubility. By using high temperatures and through chemical analysis without degrading its inert core, the contribution of NDs in medicine shows up (Table 1). Through various methods of functionalization, the use of NDs in multiple methods come across where they get effortlessly integrated into certain biological materials like enzymes, proteins, antigens, hormones or any drugs through covalent and electrostatic communication.[75] NDs act as effective delivery systems with the main aim of manageable discharge of disabled materials that may take place through certain enzymes like proteases, esterase, and lipases. The most important part of this mechanism is that the functionality and conformation of the molecule and its flexibility towards the desired treatment is maintained. In addition, NDs can be transferred through multiple methods and one such is through ballistic delivery.[37]

E. Optical Features

NDs optical features are found to be extraordinary because of their translucent nature in the wavelength range of visible light that is found to be higher than that of glass and high refraction. These particular features grant both *in vivo* and *in vitro* imaging either without or with modifications through numerous methods.[76] NDs as fluorescent labels show up non-photo bleaching, stable and bright fluorescence from N vacancy defects in the lattice.[77–79] Through the Raman spectrum, NDs admits devastating discovery with living cells.[80,81] Whole of these schemes have displayed exceptional congeniality with living cells compared to that of other nanoparticle dependent labels like quantum dots which usually release toxic materials during the process.[78] Specifically, the radiation in the red region helps to prove beneficial for *in vivo* imaging while the emission in the green region is likely with 1a kind diamonds that consist of H3 defects.[82,83] In polymers, NDs have the capability to raise the diffusion of additives meanwhile enhancing the hardness, strength and radiation. NDs can be used as an abrasive on both soft and hard surfaces for polishing. Lower permeability and porosity of complexed NDs can be utilized in bringing up separation and bio-filtration equipment comprised of microscopic pore membranes to carry ultrafiltration or non-porous layers for prolonged storage in the presence of low or high temperatures.

VII. ND BIOCOMPATIBILITY AND REGULATORY STATUS

For nanoparticles to be incorporated for biomedical applications, it must be verified for any interaction with biological system. For detailed study different cytotoxicity studies were performed. Toxicity of any system depends on many factors like starting material or method involved. NDs synthesized using HPHT method shows low or no sign of cytotoxicity in comparison to NDs synthesized from detonation method.

Numerous researchers have determined the lethal nature of NDs that can differ based on the surface chemistry of the cell line type and the medium.[84,85] NDs with amine termination displayed greater toxicity compared to that of NDs with hydroxyl end and carboxyl end when study have performed on embryonic cells of kidney with 200 μg/mL concentration.[85] While the NDs with carboxyl ends did not display any kind of genotoxic impact in mouse fibroblasts[86] however promoted damage to DNA in mouse stem cells to a certain extent than what raised in case of carbon-nanotubes.[87] Though there is not enough evidence with respect to the nanoparticle's serum cytotoxicity, various theories have been kept forward. Serum helps to act as a layer of protective cells over the particles for which it is believed that they may possess certain cytotoxicity.[88] In addition, it has been observed that serum has the ability to improve the nanoparticle's diffusion constancy and enhances aggregation. Further, the internalization of the nanomaterials was seen to be greater in the no show of serum comparatively to its existence.[89,90] Through other studies it was observed that the nanomaterials has the ability to adsorb certain micronutrients present in the media, hence worth, cytotoxic effects are produced through degrading the cells with vital nutrients.[91] For instance, when IV infusion of altered NDs with the dose ranges about 125 mg into the group of rabbit did not lead to any side effects or death. Not either of the hemoglobin level or blood cell count was observed to be decreased after fifteen minutes after infusing with 50 mg of altered NDs. The impact was detected after 2 days where the bilirubin content, triglycerides and other lipoprotein contents displayed changes. More of animal studies have to be taken up before going to human trials in order to check on their safety.[38]

On administration of NDs into blood stream of rats in preclinical assessment, NDs circulate in blood stream in several cycles without any instance of excretion. After 2 h of administration accumulation in liver and lungs was observed. In one study reported by Zhang et al., inflammatory response was observed in lungs.[92] Possible reason for this observation might be retention of NDs in lung. In another study, Yuan et al. demonstrated retention of NDs in liver and lung of murine model for 28 days.[93] Specifically, accumulation takes place in liver macrophages because capturing of NDs in reticuloendothelial system. NDs were also found deeply seated in the abdominal surfaces including peritoneum. But no reports were on the excretion of drugs via urinary and faecal route.

Despite the advantages of NDs, it has some limitations which limit its biomedical application to preclinical stages only. Few considerations which limits its applications is low emission from NDs N-V centers in comparison to standard organic dyes. Also large size of NDs limits its functionality because of biocompatibility issues, further alteration in functional protein upon interaction.

VIII. APPLICATIONS OF NDS

A. Anticancer Therapy

Recent studies show that NDs have the ability to activate the enhanced vascular permeability irrespective of the enhanced permeability and retention (EPR) effect (passive tumor targeting).[94] Among various types of NDs with various surface chemistries, ND-NH_2 was found to cause and have the greatest degree of vascular leak comparatively to ND-COOH. The actual process includes a series of biochemical processes triggered by ND thus resulting in the unclosing of junctions in between the endothelial cells. This particular process is reversible and can be revived at the end of the ND treatment. Application of ND to kill the cancer cells through tissue leakiness was performed under *in vitro* by using transwell model. While in their absence, the barrier will guard the cells present in the below well against doxorubicin that has been added to the upper well. Nevertheless, by taking up pre-treatment using NDs allows the barrier translucent to doxorubicin thus leading in higher death rate of cancer cells in comparatively to the death rate monitored in the control sample. Because of its fully approachable nature and large area, NDs were analyzed for triggered release and adsorption studies of numerous antitumor drugs which includes tetra cyclines, 4-hydroxytamoxifen, tetracyclines and paclitaxel.[95–98] One of the most known mechanisms of chemo resistance of cancer cells is the therapeutic efflux that helps to curb the performance of the cytotoxic medicines. Drug complexes with NDs have the ability to cross the protective layers and convey the antitumor complex to the cytosol by endosomal delivery. Antitumor treatments with NDs display many exciting opportunities. For instance, recent developments in infusing leakiness of the vascular cells will aid to convey greater concentrations of drugs to cancer cells during primary stages of tumorigenesis, earlier when EPR was not been kept forward. A considerable progress was seen in conveying water insoluble antitumor drugs through ND platforms. NDs will help promote controlled delivery of antitumor drugs under the changes in pH and stimuli. The adsorption complex of ND plays a key role in slaying the cancer cells that are resistant to drugs, circumventing the drug efflux and cutting down antitumor drug side effects. Additionally, the ND complexes were also utilized in combination therapy in order to treat tumors with multi drug resistance and battle against tumor stem cells thus causing metastasis. Table 3 represents the different ND system for cancer treatment strategy.

B. Gene Delivery

As we know that gene delivery is the admittance of genetic material into the cells with the aim of restoring defective genes in order to gain a certain function or repair a gene to set off other functions.[138] Earlier, virus particles have been identified to actually transfer the genetic matter into the cell genome.[139] Considering, viruses (through viral vectors) have been used for the transfer of genetic material to alter the cell functions permanently that is known as *permanent transfection*. Non-viral methods are efficient to deliver the

TABLE 3: ND systems and their potential applications

Serial no.	System	Activity/methodology	Conclusion	Application	Ref.
1	Self-assembled ND supra-particles	The perfluorooctanoic acid-functionalized NDs instinctively convert into well-dispersed supraparticle (SP) nanoclusters and the prepared system ND-based SPs (ND-SPs) demonstrate the high diffusion throughout the cell membrane	The synthesized ND-SPs are effective carrier for drug delivery targeting and in a wide range of biological applications	Anticancer chemotherapy	29
2	Endocytic carboxylated ND	This study, Liu and his team investigated the site and allocation of carboxylated ND (100 nm) particles in cell	Findings provide that endocytic ND particles are non-cytotoxic in cell division and differentiation, which can be applied for the labeling and tracking of cancer and stem cells	Labeling and tracking of cancer and stem cells	86
3	Growth-hormone-conjugated ND complex (GH-ND)	In the present work, the authors demonstrate to synthesized by GH-ND complex by conjugating GH with green fluorescence protein and carboxylated ND and low toxic, therapeutic, biocompatible and evident GH-nanoparticle composite for distinctively targeting growth hormone receptor (GHR) in cancer cells	The results have demonstrated that GH-ND complex efficiently induced cell death in the A549 non-small-cell lung cancer cell line via the apoptotic pathway. Moreover this laser-mediated, cancer-targeting strategy can be extensively utilized in cancer therapy	Cancer therapy	99
4	Fructose-coated NDs	A glycopolymer/ ND conjugate system was prepared by grafting amonafide-conjugated glycopolymers in the ND surface of through oxime ligation	Effectively distribute complex into breast cancer cell and significantly reduce the cancer cell viability	Breast cancer treatment	100

TABLE 3: (*continued*)

5	Co-delivery of paclitaxel and cetuximab by ND	Here researchers exhibit a carbon-based nanomaterial ND that consists paclitaxel (PTX) action as a microtubule inhibitor, and cetuximab (Cet), a specific monoclonal antibody against epidermal growth factor receptor (EGFR), inducing karyokinetic catastrophe and neoplasm inhibition in human colorectal cancer (CRC)	ND-PTX composite blocked the mitotic progress, chromosomal separation, and induced apoptosis in the CRC cells. This study established that the co-delivery of PTX and Cet through ND amended the consequence of mitotic catastrophe and apoptosis *in vitro* and *in vivo*	Human CRC therapy	101
6	Polyglycerol-coated ND	Development of detonation ND (dND) composite with hyperbranched polyglycerol (PG) coating (dND-PG). It was first established to prevaricate non-specific vacuole apprehension, principally by macrophages (U937). RGD targeting peptide was added to dND-PG to relinquish dND-PG-RGD which exhibit auspicious prevaricate macrophage apprehension by targeted A549 malignancy cells (signify RGD peptide receptors)	dND-PG and dND-PG-RGD goods emend water solubility and cytocompatibitlity. Then doxorubicin (DOX) was loaded through acid-labile hydrazone association to constitution dND-PG-DOX and dND-PG-RGD-DOX. The event exhibit that dND-PG-RGD-DOX display discriminative poisonousness to A549 cells over U937 macrophages	Promising drug carrier in tumor cells	102
7	Chemo-therapeutic drug-bearing ND particles	This study result of ND and ND-DOX complicated against HepG2 cells (a human internal organ cancer cellline) and sophisticated concerned by cells analyse *in vitro* by exploitation optical device scanning confocal research and qualitative analysis experiments and conjointly studied the survival rate and histopathology of tumor-bearing mice when treatment with NDs or ND-DOX *in vivo*	*In vitro* examination disclosed that ND-DOX advanced has drug sustained unharness characteristics compared with free antibiotic. Still as each the NDs and ND-DOX may suppress tumour growth effectively	Enhancing chemo-therapeutic efficacy and safety	103

TABLE 3: (*continued*)

Serail no.	System	Activity/methodology	Conclusion	Application	Ref.
8	Carboxyl ND (CND)-podophyllotoxin (PPT)	CND-PPT conjugate prepared by treatment of ND with carboxylic acid. The effect of CND, PPT and CND-PPT on HeLa cell was analyzed by MTT assay	The results revealed according to the MTT assay that CND has low cytotoxicity and CND-PPT has enhanced antitumor activity against HeLa cell	Anticancer drug delivery carrier	104
9	ND as a vehicle for siRNA delivery	The capacity of NDs to transmit small interfering RNA (siRNA) into Ewing sarcoma cells is observed with a prospect to the convenience of *in vivo* anticancer nucleic-acid medicate liberation. siRNA is surface assimilation onto NDs exterior which further coated with polymer (cationic in character)	The result demonstrated the prepared ND-siRNA complex exhibit greater cell toxicity against sarcoma cell	Drug delivery carrier	105
10	ND and nanoplatinum (NP)-coated material (DPV576-C)	Human monocyte-derived dendritic cells (DCs) were treated with DPV576 and activation of DCs was observed by assessing the expression of co-stimulatory and maturation markers, expression of co-stimulatory molecules and cell proliferation were analysed by flow cytometry and cytokine secretion by ELISA	DPV576 treatment of DCs results revealed that the solution consists ND/NP (DPV576), activated human DCs and DCs-driven CD4 naive T-cell proliferation *in vitro*, and may be utilized to boost the immune responses in cancer treatment	Cancer therapy	106
11	ND-paclitaxel conjugate for drug delivery	ND, bound covalently with paclitaxel. An efficient covalent conjugation of ND-paclitaxel, which can be delivered into lung carcinoma cells	The anticancer behavior on the introduction of mitotic obstruction, apoptosis and anti-tumorigenesis activity was observed	Cancer therapy	107

TABLE 3: (*continued*)

12	NDs decorated with doxorubicin and folic acid	The ND clusters are prepared by utilizing precipitation technique and further conjugated with folic acid (FA) and doxorubicin (DOX) through carbodiimide conjugation to yield FA/Dox-ND clusters	*In vivo* results demonstrated that the FA/DOX-ND clusters are particularly bind in tumor sites after IV injection and effectively reducing the volume of tumor	Targeted tumor therapy	108
13	Modified detonation NDs and with doxorubicin	ND-DOX system was formulated and injected intraperitoneally to evaluate antitumor activity by of on *in vivo* model of Ehrlich ascites carcinoma	The result revealed that the proposed system potentially reduced the tumor and represent greater cytotoxic effect against Ehrlich ascites carcinoma	Antitumor activity	109
14	ND-based drug carriers conjugated with alendronate	This study represents the formulation of alendronate-conjugated NDs (Alen-NDs) and evaluation of their efficacy for bone targeted delivery. The prepared Alen-NDs were effectively taken up by MC3T3-E1 osteoblast-like cells, compared to NIH3T3 and HepG2 cells, suggesting their cellular specificity	*In vivo* study revealed that Alen-NDs efficiently adhered in bone tissues after IV injection through tail vein and the results verify the greater properties of Alen-NDs with specific uptake by MC3T3-E1 cells, high HAp affinity, constructive effect for ALP action and also *in vivo* bone targeting ability	Osteoporosis treatment	110
15	Diamond-lipid hybrids	The self-assembled ND-lipid hybrid particles (NDLPs) are formulated by effective conjugation between the ND-surface and small molecules, for targeting of selective cancer cell therapy	The result revealed NDLPs are extreme biocompatible system which gives cell-specific imaging, stop epirubicin toxicities, enhance tumor retention of ND-composite and mediate regression of triple negative breast cancers	Enhance chemo-therapeutic tolerance and mediate tumor regression	111

TABLE 3: (*continued*)

Serial no.	System	Activity/methodology	Conclusion	Application	Ref.
16	ND-based biosensor	The research developing technology ND-MMP9 (contains NDs functionalized with matrix metalloproteinase 9 (MMP 9) and fluorescent-labeled substrate peptides) to enhance the cancer metastases detection biomarkers for improve both diagnosis and treatment	This work demonstrates the use of ND particle as a stimuli-responsive biosensors platform complexes having extensive range of biomedical applications	Metastatic tumor site detection	112
17	ND-manganese dual mode MRI contrast agents	In this work formulation of ND-manganese mediator that improved T1 and T2-weighted MRI	The result concluded that, ND-manganese composite may serve as efficient dual mode MRI contrast agent, mainly in cancer	Liver tumor detection	113
18	Fluorescent-magnetic ND	The aim of present work to formulate fluorescent and magnetic ND (FMND) and treatment with HFL-1 normal lung fibroblasts and A549 lung cancer cells	These results revealed that the FMND should be effective carrier for specific cancer cell labeling and tracking	Cancer cell labeling and tracking	114
19	HER2-targeted NDs	The HER2-PEG-NDs conjugates was formulated by utilizing carboxylated ND conjugates with polyethylene glycol (PEG) and human epidermal growth factor receptor 2 (HER2) targeting ligand for specific delivery and breast cancer tumor imaging	This result demonstrates that HER2-PEG-NDs have enormous potential for the detection of cancer and provide an attractive delivery approach for anti-cancer bioactives	*In vivo* photoacoustic imaging of breast cancer tumor	115
20	Detonation NDs	In this study, developments of a method to streamline recognition of Mycobacterium tuberculosis complex (MTBC) by the examination of MALDI-TOF MS in broth culture medium by means of detonation NDs (DNDs)	The result demonstrates that, DND MALDI-TOF MS for the recognition of MTBC is fast, precise, secure, consistent, and economical	Rapid recognition of clinical isolates of Myco-bacterium tuberculosis complex in broth culture media	116

TABLE 3: (*continued*)

21	ND-extracted CFP-10 antigen	In this current work, MS was demonstrated the sensitivity and specificity of the Mycobacterium tuberculosis complex	The obtained result revealed that the CFP-10 antigen should be utilized as premature analysis biomarker in medical platform	As an biomarker in clinical isolates of Myco-bacterium tuberculosis complex	117
22	Collagen-model ND-peptide conjugates	The current work suggested procedure for effective solid-phase conjugates and characterization of ND-peptides conjugates	The collagen resultant peptides, ND was established to maintain or still improve the cell linkage and feasibility behavior of the conjugated series and could be able to potentially increase the *in vivo* actions of the biomolecule it is attached to	Tissue regeneration and wound healing	118
23	NDs and silica nanoparticles (SiO_2-NP)	The aim of current study was to formulate and characterize biphasic dose response of ND and SiO_2-NP in modulating normal human facial skin fibroblasts (FSF1) in culture	The results revealed that ND and SiO_2-NP at low doses are effective hormetins, which express mild stress-induced favorable hormetic property through enhanced repair, longevity, survival, maintenance and function of human cells	Wound healing	119
24	ND-based injectable hydrogel	The amalgamation and characterization of prepared thermo-sensitive hydrogel with NDs, gelatin and chitosan that provides a constant and extended release of VEGF	These results propose that NDs-hydrogel formulation was biocompatible, thermosensitive and multifunctional characteristics	Sustainable release of growth factor	120
25	ND-modified polysaccharide nanofibers	Electro-spinning of chitosan- consisting bacterial cellulous and NDs of medical grade (MND)	The prepared ND modified polysaccharide nanofibers are potentially appropriate for wound therapeutic applications	Wound healing therapy	121

TABLE 3: (*continued*)

Serial no.	System	Activity/methodology	Conclusion	Application	Ref.
26	Fluorescent and nanodiamod labelled micropipettes	In this work, various approaches were performed for developing broad-band fluorescently labelled glass micropipettes together with: UV cured glass glues, baked glass enamel consisting fluorescent dyes and also NDs attached during pipette configuration in the microforge	The pipette (~ 30 µm diameter) was simply detected in the microscopy view and tolerated multiple insertions through the skin. This approach was simple and inexpensive to fluorescently labelling micropipettes to develop of protocols under the fluorescent microscope	Application to the observation of a mosquito born parasite infection	122
27	NDs-composited poly(ε-caprolactone) fibrous matrices	The system was prepared by intermolecular interaction between NDs and polymer chain of poly (ε-caprolactone) (PCL) fibrous matrices through electrospinning and studies their effect in terms of mechanical potency and cell behaviors	The result revealed that increased tensile force and the positive interfacial adhesion in the ND-PCL fibrous matrices as well as improved proliferation and differentiation of osteoblast precursor cell (MC3T3-E1 cells)	Bone and dental tissue engineering	123
28	ND-reinforced hydrogel	In this work synthesis of a hydrogel utilizing photo-cross-linkable gelatin methacrylamide (GelMA) and NDs as a three-dimensional scaffold for drug delivery application and stem cell-guided bone regeneration	These results suggest that synthesized GelMA hydrogels system coupled with conjugated NDs to build up a novel carrier for bone tissue engineering therapy	Bone tissue engineering	121
29	Scaffold functionalized with ND particles	The development of poly(l-lactide-co-ε-caprolactone)-(poly(LLA-co-CL) scaffolds with ND particles to evaluate bone regeneration efficacy on a rat	The results revealed that prepared system promote osteogenic metabolic activity, mineralization ability, and should be effective complex for bone tissue engineering	Bone tissue engineering	124

TABLE 3: (*continued*)

30	Poly(lactide-co-glycolide)-ND scaffolds	In this present work diamond nanoparticles were included into a polymeric solution to design a nanocomposite scaffold consisting poly(lactide-co-glycolide) (PLGA) loaded with diamond nanoparticles to examine the efficacy of scaffolds and its utility on bone repairing	This study represents that PLGA nanofibers can be synthesized with ND adversely affecting cell performance ad utilizing for future application of these scaffolds in bone tissue engineering	Bone tissue engineering	125
31	ND reinforced chitosan	The aim of current work to design of composite of ND-chitosan (CS) complex through a solution casting method	The result concluded that strong contact between ND functional groups with chitosan matrix perform a significant role in enhancing mechanical characteristics	Bone tissue engineering	126
32	PLGA with ND-phospholipid composite	An effective and potential system as formulated via physical mixing of poly(lactic-co-glycolic acid) loaded with ND phospholipid compound (NDPC) for bone tissue engineering material	Results represent the elevated mechanical characteristics, excellent biocompatibility and also suggest it useful for a variety of biomedical applications, especially bone tissue engineering	Bone tissue engineering	127
33	Nanofibrous poly(lactide-co-glycolide) membranes loaded with diamond nanoparticles	In this current work, system was fabricated utilizing copolymer of L-lactide and glycolide (PLGA) and diamond nanoparticles by an electrospinning technique	The result revealed that nanofibrous PLGA membranes loaded with diamond nanoparticles having greater potential for bone tissue engineering	Bone tissue engineering	127
34	Multifunctional ND-PLLA composites	Multifunctional bone scaffold system has been fabricated by utilizing poly (L-lactic acid) (PLLA) and octadecylamine-functionalized ND (ND-ODA) utilizing solution casting followed by compression molding	The result revealed that the system having effective mechanical properties and the enhanced mineralization capability and also be useful for biomedical applications and orthopedic regenerative engineering	Bone tissue engineering	128

TABLE 3: (*continued*)

Serial No.	System	Activity/methodology	Conclusion	Application	Ref.
35	Fluorescent PLLA-NDs composites	The recent work was to design a multifunctional fluorescent composite bone scaffold material through a biodegradable polymer poly(l-lactic acid) (PLLA) and octadecylamine-functionalized ND (ND-ODA)	The result suggested that the fabricated ND-ODA/ PLLA composites employ as regenerative medicine and tissue engineering	Bone tissue engineering	92
36	Injectable estrogen-ND Hydrogel	In this work, developed a system with ND and photo-cross-linkable hydrogel to provide effective treatment strategy for sustained and targeted delivery of estrogen to promote bone formation	The result concluded that the E2/ND/G group demonstrated superior and applicable E2 delivery platform	Decreasing post-treatment relapse in cleft lip palatal expansion	129
37	NDs mediate oral delivery of proteins	In this study, developed a NDs-protein delivery system utilizing cultured cells and demonstrates effective cytosolic release of fully functional proteins	More significantly, the result demonstrated that NDs-RNase motivating regenerative divisions in intestinal stem cells, induced apoptosis in enterocytes and increasing the number of stem cells and precursor cells in Drosophila intestine	Stem cell activation and intestinal remodeling in drosophila	130
38	Fluorescent NDs	In this work it has been demonstrated that fluorescent NDs (FNDs) are suitable for genotoxicity study of FNDs with comet and micronucleus assays for human fibroblasts and breast cancer cells specify that the nanoparticles neither cause DNA damage nor impair cell growth	In this work, the result revealed that the FND labeling outperforms provides an efficient and successful new device for tracking and verdict slow-proliferating/quiescent CSCs in cancer research	Tracking and finding slow-proliferating/ quiescent cancer stem cells	131

TABLE 3: (*continued*)

39	Detonation ND particles	In the current study, researcher evaluated the cytotoxicity potential of ND particles on two cell models: A human osteosarcoma cell line MG-63, and primary rat mesenchymal stem cells (rMSCs)	These results exhibit the function of the purification method on the characteristics of DND particles on cytotoxicity	Anticancer activity	132
40	Epirubicin-adsorbed NDs	The system was formulated by potent physical adsorption of Epirubicin into NDs	The results concluded that ND mediated system should be an efficient for reducing the chemoresistance in cancer stem cells and also treat hepatic cancers	Kill chemo-resistant hepatic cancer stem cells	133
41	Polyglycerol-functionalized ND	The ND, polyglycerol, and basic polypeptide was formulated utilizing by polyglycerol functionalization of ND	The study confirmed by gel retardation assay that ND-PG-Arg8 and ND-PG-Lys8 having higher zeta potential hybridized with plasmid DNA (pDNA) by electrostatic attraction, making them efficient as nonviral vectors for gene delivery	Gene delivery	134
42	ND-poly-ethylenimine system	In this current study NDs functionalized with the polymer polyethylenimine (PEI) having ability to transfer small interfering RNAs (siRNA) *in vitro* with high efficacy and lower cytotoxicity	These results demonstrate that the ND system was effective framework and should be a powerful device in drug delivery development	Gene delivery	135
43	Poly-amidoamine-decorated NDs	In this work, authors demonstrated a ND, polyamidoamine-decorated NDs (PAMAM-NDs) system were formulated for E7 or E6 oncoprotein-suppressing siRNA gene delivery	The study revealed that the siRNA polyamidoamine-decorated NDssystem supply a efficient material source for gene delivery carriers	Gene delivery	136

TABLE 3: (*continued*)

Serial No.	System	Activity/methodology	Conclusion	Application	Ref.
44	Lysine-functionalized NDs	Lysine-functionalized ND (lys-ND) were prepared through covalent conjugation of amino acid moiety of lysine with carboxylated NDs surface	This study set up that spreading of lys-NDs in aqueous system preserve long-term stability and also provides confirmation that lysine functionalization NDs effectively interact with the biological system and may should used for RNAi therapeutics	Gene delivery	137
45	Polymer-functionalized ND	The work introduces NDs as efficient vectors for gene delivery by surface-modification and covalently conjugates through amine groups with polyethyleneimine (PEI-800)	This formulated device represents a potential system for gene delivery and should be an appropriate carrier system for gene therapy approach	Gene delivery	135

genetic matter to the cytoplasm which is known as *transient transfection*. The genetic matter will survive in the cytoplasm for an extent and later disappear when the cells undergo division. Transfer of genetic matter through non-viral vehicles is found to be less efficient than the viral vectors.[140] By the process of passive diffusion of non-viral vectors delivered the genetic matter to the nucleus via the nuclear pore.[141] This kind of diffusion through the nuclear pore totally relies on the vector size and amount of genetic material. Quite a number of carriers such as gold and magnetic iron oxide particles have been studied for genetic matter delivery.[142–144] The small size of ND makes it feasible for the passive diffusion into the nucleus. An exceptional example of the ND particle was determined with ND treated with Fenton. The oxidation through Fenton forms ND to be free from amorphous carbon and of smaller size where it can get in through the HeLa cell membrane to the nucleus.[145] The capability of the NDs to skip off from the endosomes is also vital for the genetic material delivery into the nucleus.[99]

C. Antimicrobial Agents

Contagious diseases are few among the main causes of death across the world, especially the bacterial infections being the one subsidizing to immense death rate. Hence, nanoparticles complexed with bactericidal agents contribute as an alternative approach to the existing antibiotic treatments.[146] The production of these nanoparticles needs a thorough understanding on the toxicity and biocompatibility, the design and efficiency of the nanoparticles.[147] Knowing about the pathogenesis of bacteria helps to understand the inhibition process beyond changing the gut bacteria or activating any kind of resistance against bacteria.[148] Among the various types of antibacterial agents, ND particles complexed with proteins, carbohydrates and antibiotics have been analyzed and studied.[81,149] Not just NDs has a role as an antibacterial treatment carrier, exceptionally ND by itself bring about bacterial cell death.[150,151]

D. Tissue and Bone Implants

Bone tissue engineering (BTE) came into picture around 30 years ago and depends on the initiation of stem cells with unnatural scaffolds which are then extricated to bone tissue. This approach admits to rebuild the damaged bones and hence may be used in bone surgery. Once the bone is reformed, the need of scaffold is not required and can be evacuated through surgery or degraded. Degradation of the scaffold should go along with the rate of tissue regeneration. As bones withheld heavy loads, the scaffolds used should have greater mechanical strength. This makes the primary reason why the fixation devices are prepared with metals. Additionally, the scaffold's chemical properties are vital to cut down the immune response and adverse effects. Young's modulus of ND, hardness, great surface chemistry and stability of the core region are highly beneficial for enhancing chemical and mechanical features of scaffolds made of bio-absorbable polymer. It was documented that octadeclamine-ND complex entrenched in PLLA or poly L-lactic acid have shown a rise of 800% hardness and 200% young's modulus

correlated to PLLA.[92] While the usage of phospholipid-ND complex gains a constant ND particle dispersion in PLGA or polylactic-co-glycolic acid.[152] Compared to the purified form, 10% of PLGA/ND displayed a rise of 100% in young's modulus and 550% hardness. Additionally, the complex of ND-PLGA curtailed down the degradation, thus allowing hFOB1.19 osteoblasts growth. Numerous applications of ND based DDS for tissue implants and regeneration are documented in Table 3.

E. Stem Cell Regeneration and Delivery

Stem cells have become the key focus in the human cellular therapy development and translation research in order to cure diseases. A critical content of data is found to be available on NDs and its uses for apprehending stem cells without disturbing their normal nature. For example, it was documented that the iron oxide particles with fluorescent labelling (0.9 μm) and carboxylated NDs (0.25 μm) did not show any adverse effect on the normal adipogenic and osteogenic differentiation potential, morphology, secretion of cytokines, CD marker expression and other biochemical features of stem cells of adipose-derived mesenchyme.[152] In several studies, NDs have displayed excellent biocompatibility in the cell lines without any cytotoxicity.[41] Nevertheless, it has been documented that the NDs will provoke the interpretation of DNA repair proteins like MOGG-1 and p53 in stem cells of embryos indicating damage of DNA. Moreover, it was found that the NDs with oxidation possess more potential for DNA damage compared to the NDs which are raw in nature, which might be because of the surface chemistry. Precise monitoring of the stem cells under *in vivo* conditions is a vital step in understanding the regeneration and differentiation of stem cells. Different types of photo-probes and optical processes have been deployed for this determination however majority of these methods are restricted because of toxicity, photo bleaching and background tissue conflict. Figure 5 represents the ND potential for stem cell delivery and regeneration.

F. Bioanalysis (Biolabeling and Biosensing)

In addition to the application in bio-labeling and drug delivery, functionalized NDs can be used for application in analysis and sensing. Various attempts were made by making use of bio arrays, nano-films and were documented by Huang et al.[168] NDs complexed with antibodies and bacteria for biosensor applications were put forward by Smirnov et al.[169] Diamond nanowires were used for this kind of investigations. By using electrochemical analysis, the electro chemical properties of the nanowires were studied along with the characterization of surface properties. The surface and adsorption properties make them to attract proteins in spectrometry analysis. Not to mention, NDs do possess greater affinity towards proteins and their mixtures can be examined even at very low concentrations and the proteins that have been adsorbed need not be detached from NDs. Studies carried out by Hens et al.[170] and determined NDs as probes to carry out electrophoretic collection for analytical uses.

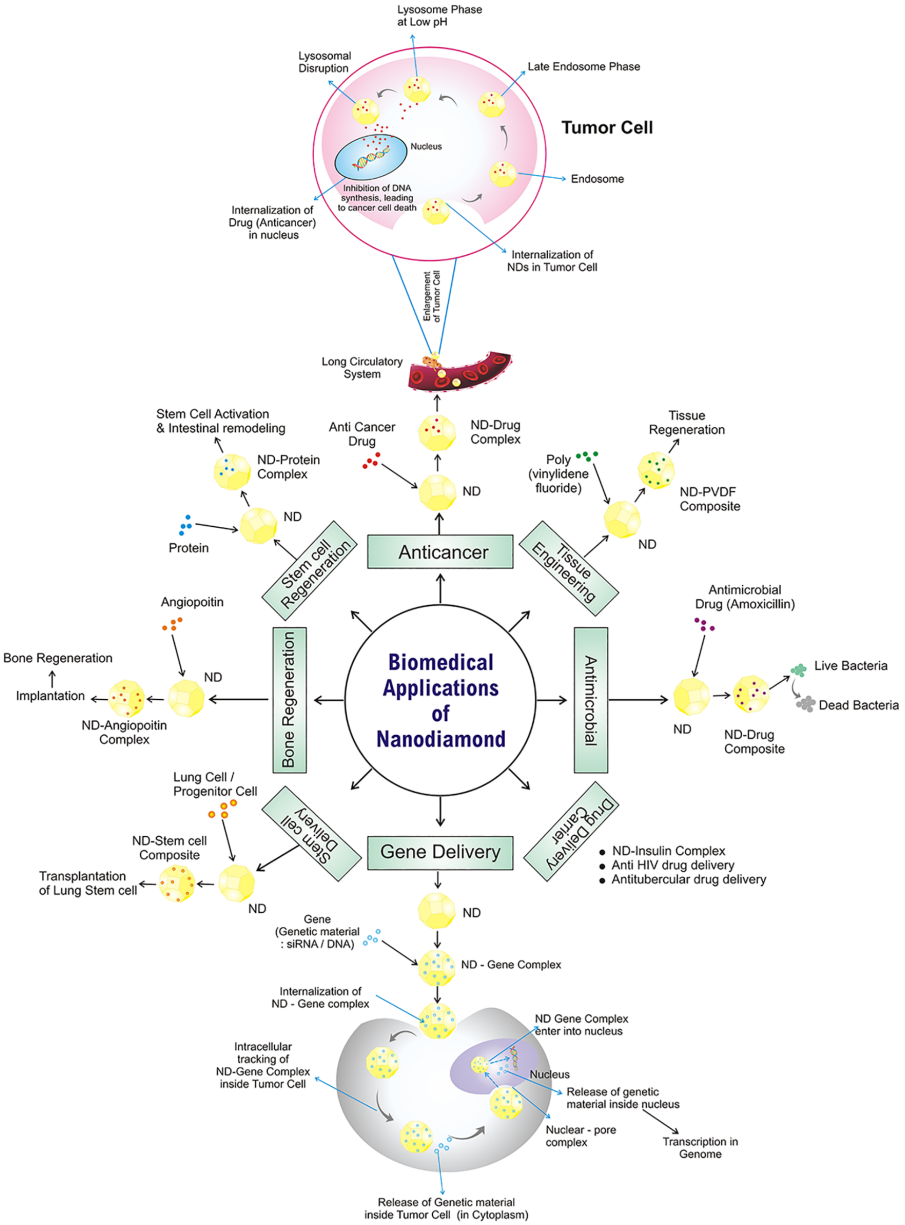

FIG. 5: Biomedical applications of NDs: tissue engineering;[127,153,154] antimicrobial activity;[155,156] drug-delivery carrier: ND-insulin complex;[157] anti-HIV drug delivery;[158] anti-tubercular drug delivery;[159,160] gene delivery;[135,161,162] stem cell delivery;[163] bone regeneration;[164] stem cell regeneration;[130] and as chemotherapeutic drugs;[165,166] nanodiamond-modified polysaccharide nanofibers.[167]

Zavala and coworkers synthesized non cytotoxic functionalized fluorescent NDs using bifunctional peptides for reorganization of amyloid β (Aβ) aggregates as biomarker

for Alzheimer disease. Prepared functionalized NDs are highly sensitive even in picomolar concentration when examined both in *in vitro* and *in vivo* studies.[171] Bergmann et al. synthesized fluorescent NDs which can be coupled with endotoxins because of N-V defect centres within lattice.[172] In this study, researchers observe endotoxin filtration through membranes using confocal microscopy. Fu et al. characterized single ND stability in comparison to Alexa Fluor 546 with first one predicting more stable in comparison to latter one in terms of photobleaching and fluorescence bleaching establishing a new entity as promising biomarker.[173] Su and coworkers demonstrated biocompatible albumin-conjugated fluorescent NDs (FNDs) as time dependent fluorescent imaging in miniature pigs with induction of human placenta choriodecidual membrane-derived mesenchymal stem cells (pcMSCs) when administered intravenously.[174] Posokhina developed reusable supramolecular indicator system by covalently binding cellulose-urease complex on the modified ND surface for detection of urea in blood samples.[175] A list of ND applications is provided in Table 3.

IX. PATENT MAPPING OF NDS

NDs have open an innovative field of drug delivery. Many researchers are exploring the best outcomes of NDs with its wider biomedical application as therapeutic and diagnostic tool. Preclinical studies must be well established before moving on to clinical trials. Table 4 discusses the patent filed or granted in the field of NDs.[176,177]

X. THE FUTURE OF NDS AND CONCLUSION

Investigators and researchers who support and provide their efforts to identify and determine the variety of biomedical applications of NDs they also deal very closely with chemists, scientists and materials. The importance of purification, characterization and the surface properties has to be studied to gain adequate profits of NDs in both medicine and biology. NDs composed of organic carbon are convenient forms for the chemist to work on. Additionally, the surface of NDs can be layered using polymer shells and silica which helps to improve stability and solubility. Along with, the nanoparticle's size plays a vital role in their application. For instance, passive transfer of the NDs into the nucleolemma is possible only when the size is 5 nm or less. In tumor treatment procedures, NDs functionalized with surface chemistry are used to cause vascular leakiness which is an effect very much alike EPR that kills the cancer cells during initial stages of tumorigenesis. As NDs have adjustable surface properties they can be used to transfer various types of antitumor drugs. These drug-ND complex offer uninterrupted release of drug and residence time inside the cells hence so conquering the cancer cells resistance and cutting down the chemotherapy side effects. Medicine and Biology are highly benefitted from non-photo bleaching effects and bright NDs. A certain known defect of NDs like silicon vacancy (SiV), nitrogen vacancy (NV), europium vacancy (EuV) was investigated for imaging in varied wavelengths especially to the infrared range. It was seen that there is a considerable rise in the ND applications in various fields of drug

TABLE 4: Patents on NDs with application in biomedical field

S. No.	Title of work	Work done	Application number
1	NDs enhanced drugs	Efficacy of drugs like analgesics, cholesterol reducing drugs and other substances are increased with covalent binding to functional groups on ND surface	US 20100129457A1
2	ND UV protectant formulations	Preparation of cosmetic or sunscreen comprising diamond nanoparticle in a physiological medium	8,753,614
3	Skin treatment for promoting hair growth	Mineral carrier for blood product infusion	9,227,089
4	ND particle complexes	Preparation of soluble ND particles and therapeutic agents by conjugation with insoluble anthracycline, tetracycline compounds, nucleic acids, proteins	EP 2435360 A2
5	Healthcare and cosmetic compositions containing ND	Formulation of deodorants, toothpastes, shampoos, antibiotics, dermal strips, DNA test strips, skin cleansers	US7294340
6	Composite materials containing nanoparticles and their use in chromatography	Synthesizes of porous inorganic/ organic hybrid particles embedded with nanoparticles	9,248,383
7	Method of making a diamond particle suspension and method of making a polycrystalline diamond article there from	Preparation method for polycrystalline diamond in homogeneous suspension of ND and microdiamond particles	9,283,657
8	High shear application in medical therapy	Method for preparation with therapeutic gas or a therapeutic liquid or a combination thereof and a liquid carrier in a high shear	8,888,736B2
9	Cleaning oral care compositions	Oral care preparation comprising of fused silica with improved cleaning	8,293,216B2
10	ND fractional and the products thereof	Method of detonation for ND fabrication	7,569,205B1

delivery and bio-imaging in the recent years. Nevertheless, few obstacles do exist which are to be beaten up. NDs aggregation is one of the serious issues, especially when the size is less than 50 nm. Henceforth, an efficient method is required in order to avoid aggregation. Interaction of the animal organs with NDs and the outcome of the complex in the body is not been well studied. Research and investigation on NDs persists to look for further progress like including magnetism and other optical properties. These properties like FRET, optical trapping and magnetic resonance NDs will help in the validation of labeling, drug delivery and bio-imaging for applications in the biomedical field in the coming future.

ACKNOWLEDGMENT

We are thankful to DoP, Ministry of Chemical and Fertilizer, New Delhi. The NIPER-R communication number of this article is NIPER-R/Communication/137.

REFERENCES

1. Greiner NR, Phillips DS, Johnson JD, Volk F. Diamonds in detonation soot. Nature 1988;333:440–2.
2. Vereschagin AL, Sakovich, GV, Komarov VF, Petrov EA. Properties of ultrafine diamond clusters from detonation synthesis. Diam Relat Mater. 1994;3:160–2.
3. Kuznetsov VL, Chuvilin, AL, Butenko YV, Malkov IY, Titov VM. Onion like carbon from ultadispersed diamond. Chem Phys Lett. 1994;209:72.
4. Liu Y, Gu Z, Margrave JL, Khabashesku VN. Functionalization of nanoscale diamond powder: Fluro-, alkyl-, amino-, and amino acid-nanodiamond derivatives. Chem Mater. 2004;16:3924–30.
5. Shenderova OA, Zhirnov VV, Brenner DW. Carbon nanostructures. Crit Rev Solid State Mat Sci. 2002;27:227–356.
6. Dolmatov VY. Detonation synthesis ultradisperse diamonds: Properties and applications Russ Chem Rev. 2001;70:607–26.
7. Ji SF, Jiang TL, Xu K, Li SB. FTIR study of the absorption of water on ultradispersed diamond powder surface. Appl Surf Sci. 1998;133:231–8.
8. Kuznetsov VL, Aleksandrov MN, Zagoruiko IV, Chuvilin AL, Moroz EM, Kolomichuk VN, Likholobov VA, Brylyakov PM, Sakovitch GV. Study of ultra dispersed diamond powders obtained using explosion energy. Carbon. 1991;29:665–6.
9. Kruger A, Ozawa M, Kataoka F, Fujino T, Suzuki Y, Aleksenskii AE, Vul AY, Osawa E. Unusually tight aggregation in detonation nanodiamond: Identification and disintegration. Carbon. 2005;43:1722–30.
10. Tapraeva FM, Pushkin AN, Kulakova II, Rudenko AP, Elagin AA, Tikhomirov CV. Funtional coating of the diamond surface under various conditions of modifications by gas. Zhurnal Fizicheskoi Khimii. 1990;64:2445–51.
11. Baidakova M, Vul AA. New prospects and frontiers of nanodiamond clusters. J Phys D Appl Phys. 2007;40:6300–11.
12. Freitas RJ. Nanomedicine volume IIA: Biocompatibility. Georgetown, TX: Routledge; 2003.
13. Bianco A. Carbon nanotubes for the delivery of therapeutic molecules. Expert Opin Drug Deliv. 2004;1(1):57–65.
14. Bianco A, Hoebeke J, Kostarelos K, Prato M, Partidos CD. Carbon nanotubes: On the road to delivery. Curr Drug Deliv. 2005;2:253.
15. Prato M, Kostarelos K, Bianco A. Functionalized carbon nanotubes in drug design and discovery. Acc Chem Res. 2008;41:60.

16. Gulka M, Salehi H, Varga B, Middendorp E, Pall O, Raabova H, Cloitre T, Cuisinier FJ, Cigler P, Nesladek M, Gergely C. Simultaneous label-free live imaging of cell nucleus and luminescent nanodiamonds. Sci Rep. 2020;10(1):1–9.
17. Gonsalves K, Halberstadt C, Laurencin CT, Nair L, editors. Biomedical nanostructures. Hoboken, NJ: Wiley-Interscience; 2007.
18. Shenderova O. Detonation nanodiamonds: Science and Applications. San Diego: CRC Press; 2014.
19. Labhasetwar V, Leslie-Pelecky DL, editors. Biomedical applications of nanotechnology. Hoboken, NJ: Wiley-Interscience; 2007.
20. Salata O. Applications of nanoparticles in biology and medicine. J Nanobiotechnol. 2004;2:3.
21. Urban GA, editor. BioMEMS. Dordrecht, The Netherlands: Springer; 2006.
22. Bera M, Gupta P, Maji PK. Structural/load-bearing characteristics of polymer–carbon composites. In: Rahaman M, Khastgir D, Aldalbahi A, editors. Carbon-containing polymer composites. springer series on polymer and composite materials. Singapore: Springer; 2019. p. 457–502.
23. Merkoci A. Electrochemical biosensing with nanoparticles. FEBS J. 2007;274:310.
24. Shoseyov O, Levy I, editors, NanoBioTechnology: Bioinspired devices and materials of the future. Totowa, NJ: Humana Press; 2008.
25. Sattler KD. Carbon nanomaterials sourcebook: Graphene, fullerenes, nanotubes, and nanodiamonds. Volume I. San Diego: CRC Press; 2016.
26. Barnard AS, Russo SP, Snook IK. Structural relaxation and relative stability of nanodiamond morphologies. Diam Relat Mater. 2003;12:1867–72.
27. Barnard AS, Russo SP, Snook IK. Coexistence of bucky diamond with nanodiamond and fullerence carbon phases. Phys Rev B. 2003;68:073406.
28. Barnard AS. Stability of nanodiamond. In: Shenderova OA, Gruen DM, editors. Ultrananocrystalline diamond: Synthesis, properties and applications. New York: William Andrew Publishing; 2006. p. 117–54.
29. Yu Y, Nishikawa M, Liu M, Tei T, Kaul S, Wadhawa R, Zhang M, Takahashi J, Miyako E. Self-assembled nanodiamond supraparticles for anticancer chemotherapy. Nanoscale. 2018; 10(19):8969–78.
30. Fu CC, Lee HY, Chen K, Lim TS, Wu HY, Lin PK, Wei PK, Tsao PH, Chang HC, Fann W. Characterization and application of single fluorescent nanodiamonds as cellular biomarkers. Proc Natl Acad Sci U S A. 2007;104(3):727–32.
31. Sonnefraud Y, Cuche A, Faklaris O, Boudou JP, Sauvage T, Roch JF, Treussart F, Huant S. Diamond nanocrystal hosting single nitrogen-vacancy color centers sorted by photon-correlation near-field microscopy. Opt Lett. 2008;33:611–3.
32. Danilenko VV. Assessment of the influence of particle size and degree of cohesion of detonation nanodiamonds on their thermal stability. J Superhard Mat. 2009;4:218–25.
33. Huang H, Pierstorff E, Osawa E, Ho D. Active nanodiamond hydrogels for chemotherapeutic delivery. Nano Lett. 2007;7:3305–14.
34. Huang LC, Chang HC. Adsorption and immobilization of cytochrome C on nanodiamonds. Langmuir. 2004;20:5879–84.
35. Kong X, Huang LC, Liau SC, Han CC, Chang HC. Polylysine-coated diamond nanocrystals for MALDI-TOF mass analysis of DNA oligonucleotides. Anal Chem. 2005;77:134273–7.
36. Kong XL, Huang LC, Hsu CM, Chen WH, Han CC, Chang HC. High-affinity capture of proteins by diamond nanoparticles for mass spectrometric analysis. Anal Chem. 2005;77(1):259–65.
37. Grichko V, Grishko V, Shenderova O. Nanodiamond bullets and their biological targets. Nanobiotechnol. 2007;2:37–42.
38. Puzyr AP, Baron AV, Purtov KV, Bortnikov EV, Skobelev NN, Moginaya OA, Bondar VS. Nanodiamonds with novel properties: A biological study. Diam Relat Mater. 2007;16:2124–8.
39. Schwertfeger H, Fokin AA, Schreiner PR. Diamonds area chemist's best friend: Diamondoid chemistry beyond adamantine. Angew Chem Int Ed Engl. 2008;247:61022.

40. Dahl JE, Liu SG, Carlson RMK. Isolation and structure of higher diamondoids, nanometer-sized diamond molecules. Science. 2003;299(5603):96–9.
41. Puzyr AP, Purtov KV, Shenderova OA, Luo M, Brenner DW, Bondar S. The adsorption of aflatoxin B1 by detonation-synthesis nanodiamonds. Dokl Biochem. Biophys. 2007;417:299–301.
42. Baidakova M, Vul AA. New prospects and frontiers of nanodiamond clusters. J Phys D: Appl Phys. 2007;40:6300–11.
43. Carlson RMK, Dahl JEP, Liu SG, Gruen DM, Vul A, Shenderova OA, editors. Diamond molecules found in petroleum. In: Synthesis, properties, and applications of ultrananocrystallline diamond. Dordrecht, The Netherlands: Springer; 2005. p. 63–8.
44. Vereschagin AL. Detonation nanodiamonds. Altai State Technical University, Barnaul, Russian Federation, 2001.
45. Boudou JP, Curmi PA, Jelezko F. High yield fabrication of fluorescent nanodiamonds. Nanotechnology. 2009;20:235602.
46. Davies G, Lawson SC, Collins AT, Mainwood A, Sharp SJ. Vacancy-related centers in diamond. Phys Rev B Condens Matter. 1992;46:13157–70.
47. Gracio JJ, Fan QH, Madaleno JC. Diamond growth by chemical vapour deposition. J Phys D Appl Phys. 2010;43:374017.
48. Philip J, Hess P, Feygelson T. Elastic, mechanical, and thermal properties of nanocrystalline diamond films. J Appl Phys. 2003;93:2164–71.
49. Qin LC, Zhou D, Krauss AR, Gruen DM. TEM characterization of nanodiamond thin films. Nanostruct Mater. 1998;10:649–60.
50. Butler JE, Sumant AV. The CVD of nanodiamond materials. Chem Vap Depos. 2008;14:145–60.
51. Yavkin BV, Mamin GV, Gafurov MR, Orlinskii SB. Size-dependent concentration of N0 paramagnetic centres in HPHT nanodiamonds. Magnetic Resonance in Solids. 2015;17(1):1–9.
52. Amans D, Chenus AC, Ledoux G, Dujardin C, Reynaud C, Sublemontier O, Masenelli-Varlot K, Guillois O. Nanodiamond synthesis by pulsed laser ablation in liquids. Diam Relat Mater. 2009;18(2-3):177–80.
53. Gogotsi Y, Welz S, Ersoy DA, McNallan MJ. Conversion of silicon carbide to crystalline diamond-structured carbon at ambient pressure. Nature. 2001;411(6835):283–7.
54. Karami P, Khasraghi PS, Hashemi M, Rabiei S, Shojaei A. Polymer/nanodiamond composites - A comprehensive review from synthesis and fabrication to properties and applications. Adv Colloid Interface Sci. 2019;269:122–51.
55. Bajaj P, Akin D, Gupta A. Ultrananocrystalline diamond film as an optimal cell interface for biomedical applications. Biomed Microdevices. 2007;9(6):787–94.
56. Krüger A, Liang Y, Jarre G, Stegk J. Surface functionalisation of detonation diamond suitable for biological applications. J Mater Chem. 2006;16(24):2322–8.
57. Tsubota T, Tanii S, Ida S, Nagata M, Matsumoto Y. Chemical modification of diamond surface with various carboxylic acids by radical reaction in liquid phase. Diam Relat Mater. 2004;134(8):1093–7.
58. Ida S, Tsubota T, Tanii S, Nagata M, Matsumoto Y. Chemical modification of the diamond surface using benzoyl peroxide and dicarboxylic acids. Langmuir. 2003;19(23):9693–8.
59. Ando T, Nishitani-Gamo M, Rawles RE, Yamamoto K, Kamo M, Sato Y. Chemical modification of diamond surfaces using a chlorinated surface as an intermediate state. Diam Relat Mater. 1996;5(10):1136–42.
60. Krueger A, Boedeker T. Deagglomeration and functionalisation of detonation nanodiamond with long alkyl chains. Diam Relat Mater. 2008;17(7-10):1367–70.
61. Krueger A, Ozawa M, Jarre G, Liang Y, Stegk J, Lu L. Deagglomeration and functionalisation of detonation diamond. Physica Status Solidi A. 2007;204(9):2881–7.
62. Krueger A, Stegk J, Liang Y, Lu L, Jarre G. Biotinylated nanodiamond: Simple and efficient functionalization of detonation diamond. Langmuir. 2008;24(8):4200–4.

63. Adair JJ, Singh RK, inventor; University of Florida, assignee. Enhanced chemical vapor deposition of diamond and related materials. United States patent US 5861349. 1996 Jan 23.
64. Kuznetsov VL, Chuvilin AL, Moroz EM, Kolomiichuk VN, Shaikhutdinov SK, Butenko YV. Effect of explosions on the structure of detonation soots: Ultradisperse diamond and onion carbon. Carbon 1994;32:873–82.
65. Kulakova I. Surface chemistry of nanodiamonds. Phys Solid State. 2004;46(4):636–43.
66. Matsumoto S, Matsui Y. Electron microscopic observation of diamond particles grown from the vapour phase. J Mater Sci. 1983;18:1785–91.
67. Barnard AS, Russo SP, Snook IK. Ab initio modelling of the stability of nanocrystalline diamond morphologies. Phil Mag Lett. 2010;83:39–45.
68. Kern G, Hafner J. Ab-initio calculations of the atomic and electronic-structure of clean and hydrogenated diamond (110) surfaces. Phys Rev B. 1997;56:4203–10.
69. Chang YK, Hsieh HH, Pong W, Tsai MH, Chien FZ, Tseng PK, Chen LC, Wang T, Chen Y, Bhusari KHDM, Yan JR, Lin ST. Quantum confinement effect in diamond nanocrystals studied by X-ray-absorption spectroscopy. Phys Rev Lett. 1999;82:5377–80.
70. Tang YH, Zhou XT, Hu YF, Lee CS, Lee ST, Sham TK. A soft X-ray absorption study of nanodiamond films prepared by hot-filament chemical vapor deposition. Chem Phys Lett. 2003;372:320–4.
71. Raty JY, Galli G, Bostedt C, van Buuren TW, Terminello LJ. Quantum confinement and fullerene like surface reconstructions in nanodiamonds. Phys Rev Lett. 2003;90:037401.
72. Runge E, Gross EKU. Density-functional theory for time-dependent systems. Phys Rev Lett. 1984;52:997–1000.
73. Williamson AJ, Grossman JC, Hood RQ, Puzder A, Galli G. Quantum monte carlo calculations of nanostructure optical gaps: Application to silicon quantum dots. Phys Rev Lett. 2002;89:196803.
74. Schrand AM, Huang H, Carlson C, Schlager JJ, Omacr E, Hussain SM, Dai L. Are diamond nanoparticles cytotoxic? J Phys Chem. 2007;111:2–7.
75. Dolmatov, VY. Application of detonation nanodiamond. In: Shenderova O, Gruen D, editors, Ultrananocrystalline diamond: Synthesis, properties, and applications. Norwich, NY: William Andrew Publishing; 2006. p. 513.
76. Skebo JE, Grabinski CM, Schrand AM, Schlager JJ, Hussain SM. Assessment of metal nanoparticle agglomeration, uptake, and interaction using high-illuminating system. Int J Toxicol. 2007;26:135–41.
77. Rabeau JR, Stacey A, Rabeau A, Prawer S, Jelezko F, Mirza I, Wrachtrup J. Single nitrogen vacancy centers in chemical vapor deposited diamond nanocrystals. Nano Lett. 2007;7(11):3433–7.
78. Treussart F, Jacques V, Wu E, Gacoln T, Grangier P, Roch JF. Photoluminescence of single colour defects in 50 nm diamond nanocrystals. Physica B Condens Matter. 2006;37:6926–9.
79. Faklaris O, Sonnefraud Y, Cuche A, Sauvage T, Joshi V, Boudou JP, Curmi PA, Roch JF, Huant S, Treussart F. Diamond nanoparticles as photoluminescent nanoprobes. Annales De Physique. 2007;32:155–8.
80. Cheng CY, Perevedentseva E, Tu JS, Chung PH, Cheng CL, Liu KK, Chao JI, Chen PH, Chang CC. Direct and in vitro observation of growth hormone receptor molecules in A549 human lung epithelial cells by nanodiamond labeling. Appl Phys Lett. 2007;90:163903.
81. Perevedentseva E, Cheng CY, Chung PH, Tu JS, Hsieh YH, Cheng CL. The interaction of the protein lysozyme with bacteria E coli observed using nanodiamond labelling. Nanotechnology. 2007;18:315102.
82. Lim YT, Kim S, Nakayama A, Stott NE, Bawendi MG, Frangioni JV. Selection of quantum dot wavelengths for biomedical assays and imaging. Mol Imaging. 2003;2:50–64.
83. Gaebel T, Popa I, Gruber A, Domhan M, Jelezko F, Wrachtrup J. Stable single-photon source in the near infrared. New J Phys. 2004;6:98.
84. Xing Y, Xiong W, Zhu L, Osawa E, Hussin S, Dai L. DNA damage in embryonic stem cells caused by nanodiamonds. ACS Nano. 2011;5:2376–84.

85. Marcon L, Riquet F, Vicogne D, Szunerits S, Bodart JF, Boukherroub R. Cellular and in vivo toxicity of functionalized nanodiamond in Xenopus embryos. J Mater Chem. 2010;20:8064–9.
86. Liu KK, Wang CC, Cheng CL, Chao JI. Endocytic carboxylated nanodiamond for the labeling and tracking of cell division and differentiation in cancer and stem cells. Biomaterials. 2009;30:4249–59.
87. Zhu L, Chang DW, Dai L, Hong Y. DNA damage induced by multiwalled carbon nanotubes in mouse embryonic stem cells Nano Lett. 2007;7:3592–7.
88. Kittler S, Greulich C, Gebauer JS, Diendorf J, Treuel L, Ruiz L, Gonzalez-Calbet JM, Vallet-Regi M, Zellner R, Köller M, Epple M. The influence of proteins on the dispersability and cell-biological activity of silver nanoparticles. J Mater Chem. 2010;20:512–8.
89. Casey A, Davoren M, Herzog E, Lyng FM, Byrne HJ, Chambers G. Probing the interaction of single walled carbon nanotubes within cell culture medium as a precursor to toxicity testing. Carbon. 2007;45(1):34–40.
90. Drescher D, Orts-Gil G, Laube G, Natte K, Veh RW, Osterle W, Kneipp J. Toxicity of amorphous silica nanoparticles on eukaryotic cell model is determined by particle agglomeration and serum protein adsorption effects. Anal Bio Anal Chem. 2011;400:1367–73.
91. Guo L, Von Dem Bussche A, Buechner M, Yan A, Kane AB, Hurt RH. Adsorption of essential micronutrients by carbon nanotubes and the implications for nanotoxicity testing. Small. 2008;4(6):721–7.
92. Zhang Q, Mochalin VN, Neitzel I, Knoke IY, Han J, Klug CA, Zhou JG, Lelkes PI, Gogotsi Y. Fluorescent PLLA-nanodiamond composites for bone tissue engineering. Biomaterials. 2011; 32:87–94.
93. Yuan Y, Wang X, Jia G, Liu JH, Wang T, Gu Y, Yang ST, Zhen S, Wang H, Liu Y. Pulmonary toxicity and translocation of nanodiamonds in mice. Diam Relat Mater. 2010;19(4):291–9.
94. Setyawati MI, Mochalin VN, Leong DT. Tuning endothelial permeability with functionalized nanodiamonds. ACS Nano. 2015;10:1170–81.
95. Turcheniuk K, Mochalin V. Adsorption behavior and reduction of copper (ii)acetate on the surface of detonation nanodiamond with well defined surface chemistry. Carbon. 2016;10:998–105.
96. Chen M, Pierstorff E D, Lam R, Li S Y, Huang H, Osawa E, Ho D. Nanodiamond-mediated delivery of water-insoluble therapeutics. ACS Nano. 2009;3:2016–22.
97. Chow EK, Zhang XQ, Chen M, Lam R, Robinson E, Huang H, Schaffer D, Osawa E, Goga A, Ho D. Nanodiamond therapeutic delivery agents mediate enhanced chemoresistant tumor treatment. Sci Transl Med. 2011;3:73ra21.
98. Lim DG, Jung JH, Ko HW, Kang E, Jeong SH. Paclitaxel-nanodiamond nanocomplexes enhance aqueous dispersibility and drug retention in cells. ACS Appl Mater Interfaces. 2016;82: 3558–67.
99. Chu H, Chen H, Tseng S, Hsu M, Ho L, Chou F, Li M, Chang Y, Chen P, Tsai L. Development of a growth-hormone-conjugated nanodiamond complex for cancer therapy. Chem Med Chem. 2014;9:1023–9.
100. Zhao J, Lai H, Lu H, Barner-Kowollik C, Stenzel MH, Xiao P. Fructose-coated nanodiamonds: Promising platforms for treatment of human breast cancer. Biomacromolecules. 2016;17(9):2946–55.
101. Lin Y, Raj E, Liao W, Lin J, Liu K, Chen T, Cheng H, Wang C, Li L, Chen C. Co-delivery of paclitaxel and cetuximab by nanodiamond enhances mitotic catastrophe and tumor inhibition. Sci Rep. 2017;7:9814.
102. Zhao L, Nakae Y, Qin H, Ito T, Kimura T, Kojima H, Chan L, Komatsu N. Polyglycerol-functionalized nanodiamond as a platform for gene delivery: Derivatization, characterization, and hybridization with DNA. Beilstein J Org Chem. 2014;10:707–13.
103. Li Y, Tong Y, Cao R, Tian Z, Yang B, Yang P. In vivo enhancement of anticancer therapy using bare or chemotherapeutic drug-bearing nanodiamond particles. Int J Nanomed. 2014;9:1065–82.
104. Sun TL, Wang B, Peng Y, Ni JM. Carboxylnanodiamond as intracellular transporters of anticancer drug podophyllotoxin. Yao Xue Xue Bao. 2013;48(1):149–54.
105. Alhaddad A, Adam M, Botsoa J, Dantelle G, PerruchEs S, Gacoin T, Mansuy C, Lavielle S, Malvy

C, Treussart F. Nanodiamond as a vector for siRNA delivery to Ewing sarcoma cells. Small. 2011;7(21):3087–95.
106. Ghoneum M, Ghoneum A, Gimzewski J. Nanodiamond and nanoplatinum liquid, DPV576, activates human monocyte-derived dendritic cells in vitro. Anticancer Res. 2010;30(10):4075–9.
107. Liu KK, Zheng WW, Wang CC, Chiu YC, Cheng CL, Lo YS, Chen C, Chao JI. Covalent linkage of nanodiamond-paclitaxel for drug delivery and cancer therapy. Nanotechnology. 2010;21(31):315106.
108. Ryu TK, Baek SW, Lee GJ, Rhee CK, Choi SW. Targeted tumor therapy based on nanodiamonds decorated with doxorubicin and folic acid. Macromol Biosci. 2017;17(2).
109. Medvedeva NN, Zhukov EL, Inzhevatkin EV, Bezzabotnov VE. Antitumor properties of modified detonation nanodiamonds and sorbed doxorubicin on the model of Ehrlich ascites carcinoma. Bull Exp Biol Med. 2016;160(3):372–5.
110. Ryu TK, Kang RH, Jeong KY, Jun DR, Koh JM, Kim D, Bae SK, Choi SW. Bone-targeted delivery of nanodiamond-based drug carriers conjugated with alendronate for potential osteoporosis treatment. J Control Release. 2016;232:152–60.
111. Moore L, Chow E, Osawa E, Bishop J, Ho D. Diamond-lipid hybrids enhance chemotherapeutic tolerance and mediate tumor regression. Adv Mat. 2013;25:3532–41.
112. Wang X, Gu M, Toh T, Abdullah N, Chow E. Stimuli-responsive nanodiamond-based biosensor for enhanced metastatic tumor site detection. SLAS Technol. 2018;23:44–56.
113. Hou W, Toh T, Abdullah L, Yvonne T, Lee K, Guenther I, Chow E. Nanodiamond–manganese dual mode MRI contrast agents for enhanced liver tumor detection. Nanomedicine. 2017;13:783–93.
114. Lien Z, Hsu T, Liu K, Liao W, Hwang K, Chao J. Cancer cell labeling and tracking using fluorescent and magnetic nanodiamond. Biomaterials. 2012;33:6172–85.
115. Zhang T, Cui H, Fang CY, Jo J, Yang X, Chang HC, Forrest ML. In vivo photoacoustic imaging of breast cancer tumor with HER2-targeted nanodiamonds. Proc SPIE Int Soc Opt Eng. 2013;8815:881504.
116. Soo P, Kung C, Horng Y, Chang K, Lee J, Peng W. Detonation nanodiamonds for rapid detection of clinical isolates of mycobacterium tuberculosis complex in broth culture media. Anal Chem. 2012;84:7972–8.
117. Soo P, Horng Y, Chen A, Yang S, Chang K, Lee J, Peng W. Validation of nanodiamond-extracted CFP-10 antigen as a biomarker in clinical isolates of mycobacterium tuberculosis complex in broth culture media. Tuberculosis. 2015;95:620–4.
118. Knapinska A, Tokmina-Roszyk D, Amar S, Tokmina-Roszyk M, Mochalin V, Gogotsi Y, Cosme P, Terentis A, Fields G. Solid-phase synthesis, characterization, and cellular activities of collagen-model nanodiamond-peptide conjugates. Biopolymers. 2015;104:186–95.
119. Mytych J, Wnuk M, Rattan SI. Low doses of nanodiamonds and silica nanoparticles have beneficial hormetic effects in normal human skin fibroblasts in culture. Chemosphere. 2016;148:307–15.
120. Pacelli S, Acosta F, Chakravarti A, Samanta S, Whitlow J, Modaresi S, Ahmed R, Rajasingh J, Paul A. Nanodiamond-based injectable hydrogel for sustained growth factor release:preparation, characterization and in vitro analysis. Acta Biomater. 2017;58:479–91.
121. Pacelli S, Maloney R, Chakravarti AR, Whitlow J, Basu S, Modaresi S, Gehrke S, Paul A. Controlling adult stem cell behavior using nanodiamond-reinforced hydrogel:implication in bone regeneration therapy. Sci Rep. 2017;7(1):6577.
122. Balaban AE, Neuman K, Sinnis P, Balaban RS. Robust fluorescent labelling of micropipettes for use in fluorescence microscopy: Application to the observation of a mosquito borne parasite infection. J Microsc. 2018;269(1):78–84.
123. Ahn GY, Ryu TK, Choi YR, Park JR, Lee MJ, Choi SW. Fabrication and optimization of nanodiamonds-composited poly(ε-caprolactone) fibrous matrices for potential regeneration of hard tissues. Biomater Res. 2018;22:16.
124. Yassin M, Mustafa K, Xing Z, Sun Y, Fasmer K, Waag T, Krueger A, Steinmüller-Nethl D, Finne-Wistrand A, Leknes K. A copolymer scaffold functionalized with nanodiamond particles enhances osteogenic metabolic activity and bone regeneration. Macromol Biosci. 2017;17:1600427.

125. Brady MA, Renzing A, Douglas TE, Liu Q, Wille S, Parizek M, Bacakova L, Kromka, A, Jarosova M, Godier G, Warnkel PH. Development of composite poly(lactide-co-glycolide)-nanodiamond scaffolds for bone cell growth. J Nanosci Nanotechnol. 2015;15(2):1060–9.
126. Sun Y, Yang Q, Wang H. Synthesis and characterization of nanodiamond reinforced chitosan for bone tissue engineering. J Funct Biomater. 2016;7(3):E27.
127. Parizek M, Douglas TE, Novotna K, Kromka A, Brady MA, Renzing A, Voss E, Jarosova M, Palatinus L, Tesarek P, Ryparova P, Lisa V, dos Santos AM, Warnke PH, Bacakova L. Nanofibrouspoly(lactide-co-glycolide) membranes loaded with diamond nanoparticles as promising substrates for bone tissue engineering. Int J Nanomedicine. 2012;7:1931–51.
128. Zhang Q, Mochalin VN, Neitzel I, Hazeli K, Niu J, Kontsos A, Zhou JG, Lelkes PI, Gogotsi Y. Mechanical properties and biomineralization of multifunctional nanodiamond-PLLA composites for bone tissue engineering. Biomaterials. 2012;33(20):5067–75.
129. Hong C, Song D, Lee DK, Lin L, Pan HC, Lee D, Deng P, Liu Z, Hadaya D, Lee HL, Mohammad A, Zhang X, Lee M, Wang CY, Ho D. Reducing post treatment relapse in cleft lip palatal expansion using an injectable estrogen-nanodiamond hydrogel. Proc Natl Acad Sci U S A. 2017;114(35):E7218–25.
130. Hu X, Li X, Yin M, Li P, Huang P, Wang L, Jiang Y, Wang H, Chen N, Fan C, Song H. Nanodiamonds mediate oral delivery of proteins for stem cell activation and intestinal remodeling in Drosophila. ACS Appl Mater Interfaces. 2017;9(22):18575–83.
131. Lin HH, Lee HW, Lin RJ, Huang CW, Liao YC, Chen YT, Fang JM, Lee TC, Yu AL, Chang HC. Tracking and finding slow-proliferating/quiescent cancer stem cells with fluorescent nanodiamonds. Small. 2015;11(34):4394–402.
132. Keremidarska M, Ganeva A, Mitev D, Hikov T, Presker R, Pramatarova L, Krasteva N. Comparative study of cytotoxicity of detonation nanodiamond particles with an osteosarcoma cell line and primary mesenchymal stem cells. Biotechnol Biotechnol Equip. 2014;28(4):733–9.
133. Wang X, Low XC, Hou W, Abdullah LN, Toh TB, Abdul Rashid MM, Ho D, Chow EK. Epirubicin-adsorbed nanodiamonds kill chemoresistant hepatic cancer stem cells. ACS Nano. 2014;8(12):12151–66.
134. Zhao L, Xu Y, Akasaka T, Abe S, Komatsu N, Watari F, Chen X. Polyglycerol-coated nanodiamond as a macrophage-evading platform for selective drug delivery in cancer cells. Biomaterials. 2014;35:5393–406.
135. Kim H, Man HB, Saha B, Kopacz AM, Lee OS, Schatz GC, Ho D, Liu WK. Multiscale simulation as a framework for the enhanced design of nanodiamond-polyethylenimine-based gene delivery. J Phys Chem Lett. 2012;3(24):3791–7.
136. Lim DG, Rajasekaran N, Lee D, Kim NA, Jung HS, Hong S, Shin YK, Kang E, Jeong SH. Polyamidoamine-decorated nanodiamonds as a hybrid gene delivery vector and siRNA structural characterization at the charged interfaces. ACS Appl Mater Interfaces. 2017;9(37):31543–56.
137. Alwani S, Kaur R, Michel D, Chitanda JM, Verrall RE, Karunakaran C, Badea I. Lysine-functionalized nanodiamonds as gene carriers: Development of stable colloidal dispersion for in vitro cellular uptake studies and siRNA delivery application. Int J Nanomedicine. 2016;11:687–702.
138. Coonrod A, Li F, Horwitz M. On the mechanism of DNA transfection: Efficient gene transfer without viruses. Gene Ther. 1997;4:1313–21.
139. Gorman CM, Merlino GT, Willingham MC, Pastan I, Howard BH. The Rous sarcoma virus long terminal repeat is a strong promoter when introduced into a variety of eukaryotic cells by DNA-mediated transfection. Proc Natl Acad Sci U S A. 1982;79:6777–81.
140. Zabner J, Fasbender AJ, Moninger T, Poellinger KA, Welsh MJ. Cellular and molecular barriers to gene transfer by a cationic lipid. J Biol Chem. 1995;270:18997–9007.
141. Huo S, Jin S, Ma X, Xue X, Yang K, Kumar A, Wang PC, Zhang J, Hu Z, Liang XJ. Ultra small gold nanoparticles as carriers for nucleus-based gene therapy due to size-dependent nuclear entry. ACS Nano. 2014;8:5852–62.
142. Qiu L, Chen T, Öçsoy I, Yasun E, Wu C, Zhu G, You M, Han D, Jiang J, Yu R, Tan W. A cell-targeted,

size-photo controllable, nuclear-uptake nano drug delivery system for drug-resistant cancer therapy. Nano Lett. 2014;15:457–63.
143. Dam DHM, Lee JH, Sisco PN, Co DT, Zhang M, Wasielewski MR, Odom TW. Direct observation of nanoparticle–cancer cell nucleus interactions. ACS Nano. 2012;6:3318–26.
144. Wang C, Ding C, Kong M, Dong A, Qian J, Jiang D, Shen Z. Tumor-targeting magnetic lipoplex delivery of short hairpin RNA suppresses IGF-1R over expression of lung adenocarcinoma A549 cells in vitro and in vivo. Biochem Biophys Res Commun. 2011;410(3):537–42.
145. Martin R, Alvaro M, Herance JR, García H. Fenton-treated functionalized diamond nanoparticles as gene delivery system. ACS Nano. 2010;4(1):65–74.
146. Hajipour MJ, Fromm KM, Ashkarran AA, de Aberasturi DJ, de Larramendi IR, Rojo T, Serpooshan V, Parak WJ, Mahmoudi M. Antibacterial properties of nanoparticles. Trends Biotechnol. 2012;30:499–511.
147. Lim YH, Tiemann KM, Heo GS, Wagers PO, Rezenom YH, Zhang S, Zhang F, Youngs WJ, Hunstad DA, Wooley KL. Preparation and in vitro antimicrobial activity of silver-bearing degradable polymeric nanoparticles of poly phosphoester block-poly (L-lactide). ACS Nano. 2015;9:1995–2008.
148. Wilson BA, Salyers AA, Whitt DD, Winkler ME. Bacterial pathogenesis: A molecular approach. 3rd ed. Washington, DC: American Society for Microbiology Press; 2011. p. 526.
149. Lee YC, Lee RT. Carbohydrate-protein interactions: Basis of glycobiology. Acc Chem Res. 1995;28:321–7.
150. Wehling J, Dringen R, Zare RN, Maas M, Rezwan K. Bactericidal activity of partially oxidized nanodiamonds. ACS Nano. 2014;8:6475–83.
151. Beranova J, Seydlova G, Kozak H, Potocky S, Konopasek I, Kromka A. Antibacterial behavior of diamond nanoparticles against Escherichia coli. Physica Status Solidi B. 2012;249:2581–4.
152. Zhang F, Song Q, Huang X, Li F, Wang K, Tang Y, Hou C, Shen HA. Novel high mechanical property PLGA composite matrix loaded with nanodiamond–phospholipid compound for bone tissue engineering. ACS Appl Mater Interfaces. 2016;8:1087–97.
153. Guarino V, Cruz-Maya I, Reineck P, Abe H, Ohshima T, Fox K, Greentree AD, Gibson BC, Ambrosio L. Fluorescent nanodiamonds embedded in poly-ε-caprolactone fibers as biomedical scaffolds. ACS Applied Nano Materials. 2020;3(11):10814–22.
154. Jariwala DH, Patel D, Wairkar S. Surface functionalization of nanodiamonds for biomedical applications. Mater Sci Engineer C Mater Biol Appl. 2020;113:110996.
155. Lee DK, Kim SV, Limansubroto AN, Yen A, Soundia A, Wang CY, Shi W, Hong C, Tetradis S, Kim Y, Park NH, Kang MK. Nanodiamond-gutta percha composite biomaterials for root canal therapy. ACS Nano. 2015;9(11):11490–501.
156. Beranová J, Seydlová G, Kozak H, Potocky S, Konopásek I, Kromka A. Antibacterial behavior of diamond nanoparticles against Escherichia coli. Physica Status Solidi B. 2012;249:2581–84.
157. Shimkunas RA, Robinson E, Lam R, Lu S, Xu X, Zhang XQ, Huang H, Osawa E, Ho D. Nanodiamond-insulin complexes as pH-dependent protein delivery vehicles. Biomaterials. 2009;30:5720–8.
158. Roy U, Drozd V, Durygin A, Rodriguez J, Barber P, Atluri V, Liu X, Voss T, Saxena S, Nair M. Characterization of nanodiamond-based anti-HIV drug delivery to the brain. Sci Rep. 2018;8:1603.
159. Krueger A, Waag T. 23rd International Conference on Diamond and Carbon Materials, Granada Conference and Exhibition Centre, Granada, Spain, September 3-6, 2012; p.O.1.
160. Ye W, Han H, Li H, Jin Q, Wu Y, Chakrabortty S, Weil T, Ji J. Polymer coated nanodiamonds as gemcitabine prodrug with enzymatic sensitivity for pancreatic cancer treatment. Prog Nat Sci. 2020;30(5):711–7.
161. Zhang XQ, Chen M, Lam R, Xu X, Osawa E, Ho D. Polymer-functionalized nanodiamond platforms as vehicles for gene delivery. ACS Nano. 2009;3:2609–16.
162. Chen M, Zhang XQ, Man HB, Lam R, Chow EK, Ho D. Nanodiamond vectors functionalized with polyethylenimine for siRNA delivery. J Phys Chem Lett. 2010;1(21):3167–71.

163. Wu TJ, Tzeng YK, Chang WW, Cheng CA, Kuo Y, Chien CH, Chang HC, Yu J. Tracking the engraftment and regenerative capabilities of transplanted lung stem cells using fluorescent nanodiamonds. Nat Nanotechnol. 2013;8(9):682–9.
164. Wu X, Bruschi M, Waag T, Schweeberg S, Tian Y, Meinhardt T, Stigler R, Larsson K, Funk M, Steinmüller-Nethl D. Functionalization of bone implants with nanodiamond particles and angiopoietin-1 to improve vascularization and bone regeneration. J Mater Chem. 2017;5:6629.
165. Lam R, Chen M, Pierstoff E, Huang H, Osawa E, Ho D. Nanodiamond-embedded microfilm devices for localized chemotherapeutic elution. ACS Nano. 2008;2(10):2095–102.
166. Lai H, Stenzel MH, Xiao P. Surface engineering and applications of nanodiamonds in cancer treatment and imaging. Int Mater Rev. 2020;65(4):189–25.
167. Mahdavi M, Mahmoudi N, Rezaie Anaran F, Simchi A. Electrospinning of nanodiamond-modified polysaccharide nanofibers with physico-mechanical properties close to natural skins. Mar Drugs. 2016;14(7):E128.
168. Huang TS, Tzeng Y, Liu YK, Chen YC, Walker KR, Guntupalli R, Liu C. Immobilization of antibodies and bacterial binding on nanodiamond and carbon nanotubes for biosensor applications. Diam Relat Mater. 2004:13:1098–102.
169. Smirnov W, Kriele A, Yang N, Nebel CE. Aligned diamond nano-wires: Fabrication and characterisation for advanced applications in bio- and electrochemistry. Diam Relat Mater. 2010;19:186–9.
170. Hens SC, Cunningham G, Tyler T, Moseenkov S, Kuznetsov V, Shenderova O. Nanodiamond bioconjugate probes and their collection by electrophoresis. Diam Relat Mater. 2008;17:1858–66.
171. Morales-Zavala F, Casanova-Morales N, Gonzalez RB, Chandía-Cristi A, Estrada LD, Alvizú I, Waselowski V, Guzman F, Guerrero S, Oyarzún-Olave M, Rebolledo C. Functionalization of stable fluorescent nanodiamonds towards reliable detection of biomarkers for Alzheimer's disease. J Nanobiotechnology. 2018;16(1):60.
172. Bergmann T, Burg JM, Lilholt M, Maeder U, Beer S, Salzig D, Ebrahimi M, Czermak P, Fiebich M. Fluorescent nanodiamonds as highly stable biomarker for endotoxin verification. In: Achilefu S, Raghavachari R, editors. Proceedings volume 8233, reporters, markers, dyes, nanoparticles, and molecular probes for biomedical applications IV. San Francisco, CA: SPIE BiOS; 2012.
173. Fu CC, Lee HY, Chen K, Lim TS, Wu HY, Lin PK, Wei PK, Tsao PH, Chang HC, Fann W. Characterization and application of single fluorescent nanodiamonds as cellular biomarkers. Proc Natl Acad Sci U S A. 2007;104(3):727–32.
174. Su LJ, Wu MS, Hui YY, Chang BM, Pan L, Hsu PC, Chen YT, Ho HN, Huang YH, Ling TY, Hsu HH. Fluorescent nanodiamonds enable quantitative tracking of human mesenchymal stem cells in miniature pigs. Sci Repl. 2017;7:45607.
175. Posokhina E, Ronzhin N, Mogilnaya O, Baron A, Bondar V. A supramolecular indicator system for detecting urea based on the cellulose-nanodiamond composite material and urease. Int J Med Nano Res. 2019;6:029.
176. Liu J, Cao Z, Lu Y. Functional nucleic acid sensors. Chem Rev. 2009;109(5):1948–98.
177. Perevedentseva E, Lin YC, Cheng CL. A review of recent advances in nanodiamond-mediated drug delivery in cancer. Expert Opin Drug Deliv. 2010;1–14.