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Carbon nanoparticles for medicine: current and future

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Abstract. Carbon-based nanoparticles create a huge group with substantial applications in the diagnosis and therapy of diseases. Herein, the mechanism of their outstanding properties was discussed to form a new insight for handling their issues and developing new applications in medical field. In addition, the strategies to remove the possible toxicity effects were gathered and a complete literature review about their production by economical methods was done. At the end of this article, the future applications of these nanoparticles and their new derivatives were noted.

Keywords. Carbon-based nanoparticles; medicine; graphene; fullerene; carbon nanotubes (CNTs); carbon dots (CDs).

1. Introduction

There is a famous classification of nanoparticles based on dimensionality; nanoparticles with a single nano-dimension as graphene, with length and breadth dimensions as large as nanoscale such as carbon nanotube (CNTs) and with the nano size of length, breadth and height as carbon dots (CDs) or fullerene. It is clear that these representative examples of each group are classified into carbon materials. Therefore, the carbon element as the inclusion in different compounds could create various structures that dictate new properties. In this manner, it is more informative that nanoparticles are listed at the point of chemical properties as organic, inorganic and carbon-based particles. The organic materials are composed from carbon–hydrogen bonds signifying the importance of carbon atoms in the universe. Also, it is worth to be noted that the carbon-based materials have been classified as a desperate group beside such big groups. The highlights of this review are focused on the nanoparticles that are extensively employed as a substitute of bulk matters. The carbon-based nanomaterials include fullerenes, graphene, CNTs, carbon nanofibres, carbon black and nanoscaled-activated carbon. The fullerene nanoparticles obligate the spherical shape due to sp^2 hybridization of carbon atoms. Alongside, graphene nanosheets obey the lower orbital hybridization number of sp. It must be emphasized that until here, only the hybridization number of carbon has been changed, while different structures are produced with exclusive properties. Herein, for the first time, we consider this small but all-purpose great group in this review. The C–C bonds of carbon-based matters have pure covalent property in opposite to other materials with the bonds of partial ionic character. Inherently, the carbon nanomaterials increase the mechanical and thermal properties of polymeric and non-polymeric materials and have opened a new insight in electronics industry due to efficient electron transporting abilities. There is a big history that the conducting and semiconducting electronic behaviour of carbon nanoparticles are utilized for the regulation of electron transportation. Also, the carbon nanoparticles are low-density materials facilitating their recruitment to develop polymer composites with better properties. Owing to the nanoscale range of these materials and hence, the higher surface interactions with polymer chains, the required concentration of carbon nanoparticles would be small values. These low values could not mostly be toxic impacts when they are employed for medical applications.

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2. Classification and properties of carbon-based nanoparticles

The nanoparticles developed by using carbon atoms could be listed as the spherical structure as fullerene or carbon black or CD or nano-diamond or nano-onion, the sheet-like particles as graphene nanoplatelet and the filamentous architecture as CNTs or carbon fibres or carbon nanohorn or graphene nanoribbon. It is clear that only the carbon hybridization as sp^2-sp, sp^2-sp^2, sp^3-sp and sp^3-sp^3 makes different structures, including graphene, fullerene, CD and nanocrystalline diamond, respectively. The corresponding classification considered here was in accordance with shape and carbon cages orientation, however there are other classification in accordance with dimensionality and properties [1]. The nanoparticles that have been synthesized from the amorphous carbon black with the typical diameters of 10–50 nm are used for electrical improvements. Graphitic sheets could be rolled as tubes with the diameter of 1–50 nm as NTs and in accordance with the amount of graphite particles, CNTs could be single or multi wall. Only covalent bonds are resulted when single-walled carbon nanotubes (SWCNTs) formed, although the secondary van der Waals bonds are added when multi-walled carbon nanotubes (MWCNTs) are produced from the concentric graphene. The diameter of multi-walled nanotubes is strictly depended on the layer number and are in order of 10–50 nm. The typical length of nanotubes are from micrometres to centimetres and the length of cylindrical structure of carbon are ordered as; CNT < carbon nanofibres < carbon fibres. CNT particles have been recognized as quantum wires due to their high conductivity as 1.85×10^3 S cm^{-1} for MWCNTs [2]. Also, these particles could increase mechanical behaviour, fire resistance and thermal stability. In this manner, graphene nanoplatelets obey the similar character of CNTs. The mechanism of the higher electrical conductivity has been suggested due to electron tunnelling or hopping between intra-rings or particles. Herein, the relationship of log $(\sigma)/\phi^{-1/3}$ confirms that at the higher concentration of nanoparticles, higher electrical conductivity values are obtained due to the closer distance between the particles. Also, the higher mechanical properties happen by inhibiting the crack propagation and higher interactions between the nanoparticles with their surroundings [3]. In spite of these particles, carbon fibres have no enough high electrical and thermal conductivities as 3.2×10^{-3} S m^{-1} with a 60% network of unidirectional fibres [4] and 200 W m^{-1} K^{-1} [5], respectively. Regarding the chemical structure of carbon nanofibres, the hybridization number of carbons is sp^2 as value as conductive nanoparticles such as CNTs or graphene nanoparticles. Furthermore, the carbon atoms of nanofibres are not arranged regularly as well as nanotubes and even, the carbons that are placed at edge terminations are similar to graphite rather than nanotubes. Subsequently, the arrangement of carbon atoms could govern the electrical conductivity of the nanoparticles, not their hybridization number. In this manner, in graphite architecture, many graphene layers (2D) make a honeycomb-like lattice (3D), while graphite is a moderate electrical conductive compared to graphene or CNT (1D) particles. The particles show reverse results during compaction state due to exposing of the anisometric effect. The interlayer distance of graphite, graphene and graphene oxide are 3.32 Å [6,7], 1.42 Å [8] and 0.7 nm [9], respectively. That could happen due to larger interlayer spaces leading into higher bandgap and finally lower electrical conductivity. Some hexagonal lattice convert into pentagons to make the closed shape of fullerene with the carbon hybridization number of sp^2. Thus, the delocalized electrons of fullerene particles in contrast to graphene are limited by C60 bunches and not able to jump between individual fullerenes. Fullerene nanoparticles are insulator materials with the electrical conductivity about 10^{-8}–10^{-14} S cm^{-1} [10] and only after doping with conductive polymers such as polyaniline, the conductivity reaches to 10^{-4} S cm^{-1} [11] due to electron hopping between the carbon atoms. The result ascribes clearly that even the doped fullerene with polymers, the conductivity is still down. In this manner, nanodiamond particles with the tetrahedral sp^3 and hexagonal fringes of carbon atoms are known as an insulator material due to the loss of electron mobility and should be modified by appropriate dopants to act as a semiconductor material. Again, CDs as a quasi-spherical structure are 0 D particles likely to fullerene. They are semiconductor with the electrical conductivity of 2×10^{-5} S cm^{-1} [12] and classified into quantum dots (QDs) with graphene base and amorphous carbon. The carbon hybridization number of CDs is sp^3, although there are some sp^2 carbon cores partially. CDs have a diameter range from 1 to 10 nm containing a core with oxidized surface groups, such as amine functionalities, carboxylic acids and alcohols. Thus, in spite of their hexagonal carbon rings, the lower ratio of sp^2 domains and oxygen functional groups, the electron mobility is limited. As a whole, these nanoparticles compared to bulk scale show higher mechanical properties including hardness and elastin modulus due to their high surface area. The surface quality of nanoparticles affects the interfacial adhesion and makes them to play as lubricates when the force is applied. However, the mechanism is different when carbon-based nanoparticles are evaluated. CNTs manifest high mechanical ability as a result of strong resistance against pressure deformations. Herein, the shell thickness as the representative of walls number in MWCNT establishes the mechanical performance remarkably. During force deformations, the shell could bend and the hexagonal plan is forced to be stretched [13]. Graphene nanosheets have mechanical properties as a function of layer-by-layer structure of sp^2 bonds and the low interlayer distance compared to graphite or graphene oxide [14]. Also, graphene particles have a size-dependent manner against the applied loading and provide significant mechanical performance with the radii of 2–4 nm. In other words, at higher

aspect ratio, the reinforcement effect of graphene is increased and the result is in accordance with the mechanism of MWCNTs, as at the higher number of walls, the higher mechanical property could be exposed. However, by comparing the moduli, CNTs show values with the magnitude of GPa in contrast to TPa values for graphene [15]. Graphene oxide nanoparticles as a presence of epoxy and hydroxyl groups indicate the stronger hydrogen bonding between the sheets in contrast to their higher interlayer distance. In opposite to graphene nanoplatelets, fullerene particles could increase the matrix modulus even at small sizes that is due to the spherical particles stand loading forces from all directions [16]. However, at higher aspect ratio with short carbon fibres, the higher strength is developed due to that the uniform particles distributions [17] act likely to the mechanism of graphene noted in before paragraphs. Nanodiamond particles (0 D) after the oxidation reaction show a high tendency to agglomerate making trouble for the mechanical reinforcement and thus, need surface modifications as converting sp^3 into sp^2 [18]. In other words, nanodiamond particles in spite of their higher hybridization number (sp3) may have a large surface activity due to inappropriate surface modifications. Also, these nanoparticles provide highest surface area as a function of unsatisfied surface atoms among other carbon of the nanostructures. The chemical reactive groups improve the extreme hardness, thermal conductivity and electrical resistivity of nanocrystalline diamonds [19]. The higher mechanical property depends strictly to the distribution of fillers. Among them, only functionalized graphene, multilayer graphene with lower layer numbers (<10) and nanometre-scaled carbon black could disperse uniformly and the other carbon nanoparticles including MWCNT made aggregates within polymer structure. The surface-modified graphene nanoparticles increase stiffness, Young's modulus and yield stress exceptionally [20]. Graphene and CNT nanoparticles, which are defect free, are employed to dissipate the generated heat in electronic apparatus. Both CNTs and graphene nanosheets have almost similar thermal conductivity value (3000 W m^{-1} K^{-1}) [21]. It is worth noting that the thermal conductivity shows highly anisotropic performance that would be increased when the heat induction is applied towards the vertical alignment of these nanoparticles. Previous studies approved higher covalent bonds between carbon hybrids could guarantee higher heat transfer [22]. Even, by replacing van der Waals interactions by covalent bonding, the thermal transport is enhanced due to the covalently integration between graphene nanosheets and CNTs [23] as a function of close connection between the particles and also big contact area for heat dissipation. The covalent bonds in graphene oxide structure are made by reduction reactions and binding 2 aromatic hydrocarbons with each other [24]. However, carbon nanofibres could not increase thermal conductivity as a function of lower crystalline perfection, defects on edge terminations and aggregation potency compared to CNTs. However, their mechanical ability and thermal conductivity as 960 GPa and 900–1100 W m^{-1} K^{-1}, respectively, [25] could be compared with the values related to CNTs and graphene nanosheets. Moreover, the expanded graphite, multilayer graphene and functionalized graphene show a strong increase of thermal conductivity on contrary to the slight effect of carbon black particles and MWCNTs. The corresponding properties depend on the ratio of specific surface area to volume in the nanoparticles. Although the functionalized graphene and carbon black nanofillers have the surface area of 400 and 1040 m^2 g^{-1}, respectively, but the layered shape of functionalized graphene could act as a protection barrier against heat transport [20]. Moreover, the mechanism of heat transfer is different from electrical conduction due to essential closer contacts between the nanoparticles that is not provided with carbon nanofibres due to their high aggregation value during heat treatments [26]. Nevertheless, the intrinsic radiation of carbon nanofibres and consequently increasing polymer extinction coefficient, the thermal conductivity does not show larger value after enhancing the concentrations of carbon nanofibres and even could be decreased to some extent. However, when the concentration of carbon nanofibres and CNTs is higher than percolation threshold, the aggregation of these particles could be destroyed. The percolation threshold is decreased after axial orientation of nanofibres and nanotubes in the direction of applied electric current [27]. Also, the combination of different carbon nanoparticles such as carbon nanofibres and CNTs could be useful. The best strategy to avoid the appearance of surface defects is the synthesis at high temperatures. The nanoparticles as a function of large value of surface area to volume could be employed to obtain higher photoluminescence and the particles with larger diameter but the same surface chemical passivation, provide lower luminescent. The mechanism involved in the light activity of carbon nanoparticles have not been ascribed yet, although the quantum confinement of π-electrons in sp^2 carbons have been introduced as a main proof [28]. CDs have photoluminescent property and the strong absorption of UV–visible band. They are extremely biocompatible due to their hydrophilic nature and could be employed for *in vivo* studies. The light absorption of CDs is referred to p–p* of C=C and n–p* of C=O transitions, respectively, for the core and surface of these particles. The property depends on bandgaps in opposite to semiconductor QDs with size-dependent emission. Also, the particles if are modified with noble metals as Au or Pt could be used to drive the synthesis of solar fuels via plant photosynthesis [29]. However, the aqueous solubility of these nanoparticles is fundamental for the reactions and could be provided by surface functionalization [30]. CDs could disperse in water after the surface modification by poly(ethylene glycol) (PEG) [31] as well as CNTs by diamine-terminated oligomeric PEG [32]. The modified CDs by ethyl glycol could be employed to detect Ag+ ions through the quenching effect of the ions on fluorescence intensity [33]. The

photoluminescence activity of CDs is done via fixed single dipoles with quantum emission [34], suggesting them as most useful candidates for imaging approaches. Therefore, the surface-modified CDs that act as molecular dyes, after light absorption, reduce protons to H_2 and CO_2 to CO, hydrocarbons, acids or alcohols by using metal electrons [35]. Another surface treatment had been done for graphene QDs using octadecylamine to obtain amphiphilic luminescent particles [36]. As it is clear that QDs are most famous photoluminescent nanoparticles depending on size, however using heavy metals is a limitation due to their surface defects that make the exciting energy to be quenched. The mechanism of QDs for photoluminescence activity is referred to excitons that possess limitations for the absorption of quantized energy levels. In spite of this, graphene sheets with the confined electron in π-domains show fluorescence activity dependent on electronic energy bandgaps. However, graphene nanoparticles could suffer from the defects and edges for fluorescence emissions, but it did not happen obviously due to less impairment effects as a result of their photoluminescent sensitivity and easy passivation. On the other hand, the passivation of QDs defects using heavy metals such as cadmium led to toxic nanoparticles, while the modified graphene nanoparticles intrinsically remained biocompatible [37]. A simple and economical synthesis method of highly fluorescent crystalline carbon nanoparticles was reported using microwave irradiation of sucrose with phosphoric acid during a single step. The resulting nanoparticles had the diameter of 3 to 10 nm with green fluorescence emission brightly and the particles could be easily modified with organic dyes, such as fluorescein to reduce their possible toxicity as well as increase fluorescent activity. The nanoparticles especially fluorescein-carbon nanoparticles appeared as least toxicity after loaded into erythrocytes of human blood [38]. Hollow carbon nanoparticles, which were produced by mixing acetic acid, water and di-phosphorus pentoxide in the absence of heat crosslinking, had oxygenous groups on the developed graphite particles and indicated strong fluorescent emission. These particles showed biocompatibility for cellular imaging, although they need to be modified to enter the cells and also resistance to photobleaching in opposite to organic dyes and CdTe QDs [39]. Also, laser irradiation of carbon powders produced fluorescent carbon nanoparticles with various surface chemical groups [40]. The more economical synthesis method of fluorescent-active carbon nanoparticles was done by the hydrothermal treatment of strawberry juice until 180°C. The fluorescent property of the prepared nanoparticles is quenched after the addition of HG^{2+}. Thus, these nanoparticles could be employed to detect these ions in aqueous media as water [41]. In a study, fluorescence carbon-based nanoparticles were obtained via the green synthesis of sucrose. The produced nanoparticles could emit green luminescent and also blue light after the surface functionalization with a derivative of PEG [42]. An economical method based on hydrothermal process was used for the synthesis of fluorescent nanoparticles from ascorbic acid as a carbon source, although the emission efficiency of the nanoparticles with diameter of 2 nm was higher [43]. Microwave pyrolysis is another economical synthesis method for the production of carbon-based nanoparticles with fluorescent property that the colour could be changed accordance with the size [44]. The combustion soot of candles was used for the synthesis of fluorescent carbon nanoparticles after oxidative acid treatments. The developed nanoparticles had diameter smaller than 2 nm and used for cell staining due to their hydrophilic property [45]. Moreover, photoluminescence carbon nanoparticles could be obtained via hydrogen peroxide-assisted ultrasonic treatment in a single-step process. The particles had hydroxyl groups on their surface and dispersed easily in water without further surface modifications. The particles could enter through cellular membrane and in contrast to QDs, these particles have easy synthesis methods and they do not have any cell toxic effects. Thus, these particles are better substitutes for biomedical imaging. Table 1 includes the carbon-based nanoparticle types and their properties.

3. Biocompatibility of carbon nanoparticles

The very small diameter particles could escape from the immune system and reach the blood or nervous system, however they deposit in the lungs and act like haptons to change protein structure. Regarding the low particle size as nm, the ratio of surface area to volume enhances surface energy in the following. Also, the reports confirm that the particles with nanometric dimension compared to micrometric materials have more considerable toxic effects on human. Pristine CNTs are insoluble in physiological media and should be modified via either surface adsorption or electrostatic interactions or covalent bonds. A related examination indicated after appropriate surface modifications, water solubility not only could be increased, but also their biocompatibility of toxic particles such as CNTs is transformed. Regarding this, the aggregation of CNTs was reduced after surface occupying chemical groups by using either protein, DNA or phenyl-SO_3H or phenyl-$(COOH)_2$ groups. Among physicochemical parameters involved in nanoparticle toxicity, high surface area and chemical composition are most fundamental. After injection of soluble SWCNTs in water to mice via intraperitoneal, subcutaneous, oral or intravenous routs, the rapid distribution of the particles happened after 3 h in whole body except brain tissue and about 94 and 6% were excreted, respectively, from urine and faces without any tissue damages. When modified SWCNTs by diethylene triaminepentaacetate (DTPA) were injected via the tail vein of mice, the biodistribution occurred after 30 min in whole tissues without toxic effects. The mechanism involves in platelet aggregation after carbon nanoparticles treatment. It was reported that the particles must activate glycoprotein

Table 1. Carbon-based nanoparticle types and their properties.

Carbon NPs	Dimension	Hybridization	Surface area ($M^2\ g^{-1}$)	Electrical conductivity ($S\ cm^{-1}$)	Thermal conductivity ($Wm^{-1}\ K^{-1}$)	Young's modulus (GPa)	Tenacity	Refs.
Graphite	3	Sp^2	10–20	Anisotropic 2 to 3×10^4 to 4000 p,33c	Anisotropic 1500–2000, 5–10	1000	Flexible, non-elastic	[46–48]
Graphene	2	Sp^2	2630	~2000	4840–5300	856.4 to +0.7(z)	Flexible, elastic	[46,47,49]
CNT	1	Mostly Sp^2	200–900	2×10^{-2} to 0.25	3500	240–730	Flexible, elastic	[46,47,50]
Fullerene	0	Mostly Sp^2	80–90	10^{-8} to 10^{-14}	0.4	84.5	Elastic	[10,46,47]
Nano-diamond	0	sp^3	300	Insulator	8.5	560	Elastic	[12,51,52]

integrin receptor to make platelet aggregation. When the size of particles is micro or nano, it activates protein kinas C or integrin receptors. A study approved higher inflammatory potential after the cell treatment by using graphite particles compared to SWCNTs and C60 fullerene particles. The result could occur due to the presence of more dangling carbon bonds with graphite nanoparticles. The bonds activated macrophages stronger at short time and the apoptotic/necrotic bodies in these cells were detected [53]. It has been approved that the interactions between the nanoparticles and biological molecules is strictly related to carbon hybridization number. Accordingly, it is expected that graphene and graphite nanoparticles with the same carbon hybrid of sp^2 expose a similar mechanism about toxicity. A group determined that graphene nanoparticles had toxic effect against U118 glioma cell line [54]. In this manner, graphite nanoparticles with the carbon hybridization number of sp^2 made more pulmonary and systemic toxicity. This toxic potency was repeated again when the lateral size of the nanoparticles was more than 5 μm compared to 1–2 μm due to their higher surface reactivity per unit surface area. Thus, in spite of the cell penetration of graphite nanoparticles with a size distribution between 4 and 5 nm, there was no evidence of cell toxicity. A group studied the impact of graphene oxide modified by using poly sodium 4-styrenesulfonate (PSS) and injected systematically in mice and after 6 months, the toxicity was confirmed with acute liver injury and inflammatory reactions in the lung, liver and spleen tissues [55]. All graphene family members could apply mechanical damages as a function of sharp flake edges with sp^3 hybridized bonds. Also, the effect of oxygen atoms with graphene oxide nanoparticles could augment the toxic impact of sharp surface defects. A study evaluated the toxic effects of graphene oxide nanosheets on A549 cell line and results showed that these nanoparticles could not enter the cells and thus, there was no significant cytotoxicity, of course at low concentration [56]. However, it had been approved that graphene nanoparticles with the size of 11 ± 4 nm could penetrate from cell membrane and made genotoxic effects [57]. However, the oxidative stress resulted from graphene oxides at higher concentration, although a serious oxidative condition did not happened. Further on, when graphene and graphene oxide nanosheets were deposited on a substrate, they could inactivate bacteria through their direct interactions by using sharp edges. A study evaluated toxic effects of graphene oxide with the lateral of 200^{-3} nm and thickness of 0.9 nm on lung epithelial cells, and described that not only there was no toxic changes on cell viability or protein/lipids in cell membrane, but also higher cell proliferation happened. Additionally, graphene oxide and graphite nanoparticles interacted with 3 isoforms of cytochrome P450 and inhibited their enzymatic activity. Also, the related gene expression into these enzymes was reduced at the mRNA level [58]. The exposure of graphite, MWCNT and graphene nanoparticles at equal or higher concentrations of 10,

2.5 and 10 mg ml^{-1} led to start inflammatory reaction in rat pulmonary tissue. Among CNTs, carbon black and graphene, higher chemical reactivity on RAW 264.7 macrophages cell line was obtained in CNTs and graphene nanoparticles as a function of defects with platelet or their fibre-like shape. Also, another study approved that the toxicity of CNTs relates to the fibrous shape and their aggregation status as a main toxic reason in lungs and immunological system. Accordingly, the toxicity of functionalized form of graphene and CNT nanoparticles was reduced due to mask effect of oxidation by using acid treatments. Besides this, the presence of defects resulted from sp^3 carbon hybrid in graphene nanoparticles should not be ignored. A study evaluated the toxicity of MWCNTs on chlorella alga and the results approved cell damage as a function of the particle penetration and agglomerate. Also, the particles indicated shading effects meaning lower phototrophic potency in organisms. CNTs are bio-persistent due to their fibre shape and imitate asbestos via the injuries of granuloma and mesothelioma. When CNTs were modified with a longer molecular weight of PEG, it showed lower toxicity. The energy of sp^2 displacement is smaller than sp^3 approving that the diamond atoms at electron bombardment remain intact compared to graphitic atoms and the sp^2 of graphitic atoms is changed to sp^3 [1]. In addition, the carbon materials with benzene groups such as graphene family or fullerene nanoparticles have also free radical scavenging activity originated from π electrons. However, other study indicated the applied oxidative stress and pulmonary inflammation by CNTs after their surface modification. However, this property could be possible to get some benefits for cancer therapy. SWCNTs possess higher potency compered to C60 fullerene nanoparticles to block cellular channel subunits when mammalian cells are treated. The mechanism of this impact relates to fibrous shape and particle dimension. Regarding to this, fullerenes as a function of spherical architecture act without toxicity. When CNTs with the closed end were employed, the deactivation of cell channels was slow. Because pure fullerene nanoparticles are not hydrophilic, the cellular uptake of these particles is as low as pure CNTs in contrary to graphite nanoparticles. A group indicated C60 fullerenes not only are biocompatible, but also, they could act as antioxidants in rodents although in a dose-dependent manner [59]. In contrast, there was some studies that approved the uncoated fullerenes could localize into the lipid nature of cellular membrane and made peroxidation reactions in the fish brain [60] and embryonic zebrafish [61]. Thus, C60 nanoparticles developed after the modification by cationic chains had hemolytic effects in contrast to neutral or anionic molecules on human red blood cells. Another research approved water-soluble fullerenes generated superoxide anions and damaged cell membrane [62]. Nano-diamonds as a member of carbon nanoparticles with sp^3 carbon hybrid orbitals showed no toxicity effect on glioblastoma cells in spite of their absorption by the cells, although the particles inhibited cell adhesion and migration. On the other hand, graphite nanoparticles containing sp^2 carbon hybrids showed distinct effect with no toxicity on these cell lines. In spite of this, there are some unsaturated carbon bonds on these particles surface and therefore, they possibly apply toxic effects at first glance. In spite of this, in a survey, the cell interactions of diamond nanoparticles were evaluated after the systemic injection in rat. The results indicated that the nanoparticles were bonded to red blood cells (RBCs) and moved with them in the whole body without the activation of inflammatory reactions [63]. Another study indicated the anti-angiogenic effect of nano-diamond particles in *in ovo* chick embryo chorioallantoic membrane model [64]. The combination of nano-diamonds and graphene nanoparticles and their interactions with thiabendazole (TBZ), as a fungicide agent, helped a group to fabricate an application due to its higher bioavailability. The new combined nanoparticle blocks light and finally impaired algal proliferation [65]. CDs as another carbon-based nanoparticles with sp^3 hybrids induced inflammatory reactions in human monocytes and between the 2 size groups including 50and 500 nm. The lower diameter altered phagocytic capacity of monocytes and showed cytotoxicity without any measurable changes in DNA. When CDs with the diameter of around 100 nm were treated on mouse hepatocytes as *in vitro*, cytotoxicity and oxidative stress happened besides lower cell viability percent. The histopathological examinations in *in vivo* phase confirmed the presence of CDs with the diameter of 13 nm in liver tissue and that they induced apoptosis and inflammation [66]. Table 2 gathers the toxicity behaviour of the carbon-based nanoparticles.

4. Blood compatibility of carbon nanoparticles

For the first time in 2008, the biocompatibility term was defined as the ability of a biomaterial to do its specific function in medicine without any undesirable local or systemic impact [77]. In this manner, blood-compatibility or hemocompatibility can be explained as the property of a material facilitating its function in contact with blood without adverse reactions. Regarding this, ISO 10993 is a standard for the examination of medical materials response after interaction with blood [78]. When materials are exposed to blood, they can make various effects such as protein adsorption, complement activation, activation of leukocytes and thrombocytes adhesion [79,80]. However, the interface between macroscopic material and blood has been studied by few groups. They have been employed nanoscale-sized materials and investigated their interaction with blood. In spite of this, the mechanism of these interactions have not been completely known until now. Although it is clear that properties of materials at the nanoscale due to a high surface area to volume ratio and consequently high surface energy in comparison with bulk materials have considerable differences [81,82]. The

significant physical and chemical properties of CNTs such as heat conduction, semiconducting, mechanical strength and thermal stability make them useful in various applications in medicine field [81–83]. Both CNTs of single- or multi-walled types have typical lengths in the range of micrometres with the diameter of a few nanometres [84]. When CNTs are introduced into biological media as blood plasma, they confront with serum proteins and make corona particles [85]. The corresponding blood protein corona layers have a significant influence on circulation lifetime, biodistribution, dispersion/aggregation and size. Also, the shape of CNTs and host–response could determine the fate of nanoparticles and hemocompatibility. Regarding to this, the activation of immune system decreases their circulation time due to the opsonization and consequently the rapid clearance from blood [86]. Moreover, the interactions with blood depends could be related to the chemical properties of nanoparticles such as their hydrophobic/hydrophilic character [87]. As a whole, the CNTs interactions with blood components as serum proteins depends on to the properties of both proteins and nanoparticles such as their aspect ratio and functional moieties, the charge of amino acids and hydrophilic/hydrophobic domains of these proteins [88]. Salvador-Morales *et al* [89] indicated that all types of CNTs have the ability to activate the complement system in a dose-dependent manner. Other study confirmed the platelet activation by 4 types of functionalized CNTs at different concentrations. The results showed that the platelet activation occurred at the highest concentration of MWCNTs. Therefore, the platelet activation is a dose-dependent event. On the other hand, the thrombogenic behaviour of pristine, COOH- and NH_2-functionalized MWCNTs was studied by Burke *et al* [90] and the results of the coagulation cascade was measured by activated partial thromboplastin time (aPTT) assay. This assessment results show MWCNTs have thrombogenic potential, that this, property could be reduced significantly after modification through covalent bonds. Another carbon nanoparticles, nano-diamond particles due to their unique optical and mechanical properties, are well suited for biological applications [91,92]. In a study to evaluate the blood compatibility of nano-diamonds, it was shown that surface-modified diamond nanoparticles with carboxyl groups in sizes (5 and 100 nm diameter) at the concentrations of 10 to 500 μg ml^{-1} showed no any significant difference in the intrinsic coagulation pathway [93]. In another study by Li *et al* [94], aPTT assay was done for the oxidized nano-diamonds in the size range of 35, 100, 250 and 500 nm in the presence of human serum and the result showed that these nanoparticles have a significant lower hemolysis. Also, fullerene nanoparticles have been used mostly in medicine especially as pharmacological agents. However, the blood biocompatibility of fullerenes have not been studied mostly. In an animal study, it has been shown that by using dipolar trimethylenemethane, a radiolabelled and water-soluble fullerene was synthesized to check out how fullerenes are absorbed, distributed and excreted by the body after oral as well as after intravenous administration. The related results demonstrated that fullerene after oral administration to rats was not efficiently absorbed and can be excreted in feces. Also, after intravenous administration, the particles were distributed rapidly to diverse tissues and after 1 week, these nanoparticles were detectable in the body [95]. A research was done to evaluate the interactions between specific types of fullerenes and blood proteins. In this study, the results showed that the proteins react with fullerenol ($C_{60}(OH)_{44}$) without any significant changes on their compatibility and secondary structure [96]. Moreover, other group investigated the hematological activity of surface-modified fullerenes with cationic and anionic chains and the related assays approved that the cationic chains have a greater hemolytic activity rather than the anionic one [97].

5. Applications of carbon nanoparticles in medicine

5.1 *Imaging applications*

Among the applications of CNTs, the electron-based technologies in medicine need more effective electron sources. Future X-ray imaging would be equipped to CNTs cold cathodes leading to miniature X-ray sources for therapeutic applications. Due to the aspect ratio more than 10^3 could spread at the energy about 0.5 eV with the spread angle of less than 5° and the current of 1500 mA cm^{-2} [98]. It has been confirmed that the resultant beam makes the focal spot of smaller than 50 μm when the tradeoff of current will be the highest value [99]. In a study, a sensitive micro-spring was prepared using MWCNTs coated on via two-photon polymerization (2PP) method for real-time force sensing. These micro-springs could be employed to detect arterial pulses through skin and force sensing during surgeries. Also, the conductive substrates with numerous usages get benefit from carbon-based nanoparticles such as CNTs and graphite family to obtain composites with high durability and also highly sensitive. A study fabricated a sensor to detect rapid human moves, breathing and speech recognition. CDs with the diameter less than 10 nm compared to QDs show higher biocompatibility and also their synthesis is inexpensive and easy [100]. These nanoparticles are potential photoluminescence materials that could be recruited for high-resolution bio-imaging approaches; however, there are some problems about their toxicity when used for a long term. Regarding this, a group evaluated the biocompatibility of carbon particles after intrapulmonary injection in mice and showed that they acted better than functionalized SWCNTs [101]. Also, CDs have stable fluorescence intensity, water solubility and high cell penetration. These characters are required for bio-imaging applications [45]. These nanoparticles were used for two-photon sensing at the physiological pH of cells and tissues and the results illustrated the uniform dispersion of

Table 2. Toxicity of carbon-based nanoparticles.

Type of materials	Particle size	Animal and cell line	Biological toxicity	Refs.
MWCNT	10–20 nm	Alveolar macrophage in lung	Cytotoxicity in alveolar macrophages at high dose	[67]
SWCNT	1.4 nm	Rats	Cytotoxicity in alveolar macrophages at high dose and inflammation	[67,68]
SWMT	1.4	Male rats	Inconsistent but no lung toxicity	[68,69]
MWNT	40–60 nm	Male rats	Toxicity dependent on dose and time	[70]
MWCNT	—	Chlorella vulgaris	Generation of ROS and agglomeration	[71]
Reduced grapheme oxide (rGO)	11 ± 4 nm	Human mesenchymal stem cells (hMSCs)	Induced DNA fragmentations and chromosomal aberrations	[57]
RGO	Lateral size 100–1500 nm	U118 glioma cell line	Reduction of cell proliferation and induced apoptosis	[72]
GO	0.9 nm	Human lung epithelial A549 cells	Dose-dependent, oxidative stress and low cell viability at high concentration	[56]
Pristine grapheme	500–1000 nm	Murine RAW2647 macrophages	Depleted of the mitochondrial membrane potential, high ROS and triggered apoptosis	[73]
FBS-GO	40–180 nm	A549 cells	Low GO cytotoxicity	[74]
PEG-GO	1–2 nm	Human fibroblast cells	Cytotoxicity and genotoxicity	[75]
Graphene-dextran	50–100 nm	HeLa cells	Low cell toxicity	[76]
CDs	50 nm	Hematocytes	Cytotoxicity	[66]
CDs	500 nm	Mouse hepatocytes	Oxidative stress	
CDs	13 nm	Liver	Apoptosis and inflammation	

nanoparticles. When pH was changed from 7.8 to 7.1 and then 6.4 in cancer cells, the photon intensity was intensified and at the depth of 65–185 μm in tissues, again CDs could detect pH fluctuations [102]. CDs can absorb near-infrared (NIR) region and make phototherapy under laser irradiation, although as a function of their photoactivity, real-time monitoring was possible. These nanoparticles favoured to remain in the acidic media of cancer facilitating a higher resolution for imaging [103]. The diagnosis of early blood−brain barrier (BBB) damage following ischemic cerebral thrombosis is important. In this application, the combined CDs with a targeting thrombotic protein showed the traceability of intracranial hemorrhage [104]. Additionally, CDs helped to transfer doxorubicin to breast cancer cells and also detect the region of tumour cells by *in vivo* and *ex vivo* imaging [105]. If CDs was labelled with a radiotracer such as Beryllium 7, the radio-detection of biological samples could be impossible [106]. The reduced particles could be employed for cellular imaging as a function of photoluminescence activity and also for the delivery of doxorubicin through π-stacking between graphene particles and anticancer drug [107]. The particles were used for the treatment of gastric cancer cell line and two-photon luminescence of these cells were better than the group treated with molecular dye fluorescein isothiocyanate (FITC) [108].

5.2 *Biosensor applications*

A study fabricated a sensor to detect rapid human moves, breathing and speech recognition. The sensor with the thickness of 1 mm was stretchable in a matrix of poly(dimethylsiloxane) (PDMS) in the presence of aligned SWCNTs. The high elastic manner of the obtained film approved better deformability of SWCNT films compared to other conductive materials [109]. The higher elasticity of SWCNTs may be related to carbon chirality making higher elongation with armchair conformation compared to zigzag CNTs. In contrast, Young modulus of MWCNTs is strictly dependent on layer number and their distance [110]. Carbon fibres as a function of remarkable sensitivity of 1.41 kPa^{-1} to pressure were employed to produce a sensor to detect physiological signals [111]. Graphene oxide derivatives as a function of epoxy, hydroxyl and carboxylic groups could be easily functionalized with biomolecules, such as enzymes for the fabrication of biosensors. New sensors based on DNA-wrapped SWNTs provide high-quality spatial and temporal information about cellular signalling and proteins, with analyses including nitric oxide (NO), hydrogen peroxide (H_2O_2) glucose, dopamine, norepinephrine, serotonin, lipids, oligonucleotides and integrase proteins. The advantages of SWNT over other sensors in the fluorescence signal in the near-infrared (nIR) tissue transparency window are no blinking or photobleaching, and its small size. In current methods of deposition of DNA–SWNT complexes on cell culture media, they are completely limited to nonspecific or electrostatic interactions. The most common method of SWNT deposition uses aminopropyl silane chains attached to a glass substrate that has a positive charge. On the other hand, a negatively charged DNA strand is complexed with a SWNT sensor, creating a functional level of SWNT through electrostatic interactions. The scatter of data collection for the unique SWNT limits the investigation of large-scale signalling events. Also, the high intensity of the laser causes overheating and has a negative effect on the sample, and also limits the time of data collection. A new method called the sensor immobilization has been proposed that can increase the amount of SWNT present on the surface and subsequently increase the total fluorescence output. The basis of this method is the avidin–biotin interactions, in which an epoxy silane binder is used to covalently bind avidin to a glass substrate, and a biotin is added to the end of the DNA oligo that wraps the SWNT [112]. In one study, flexible strain sensors were developed that convert mechanically dependent variables (such as traction, bending and torsion) into electrical signals. Their applications include the use as wearable and soft sensor joints on the surface of the skin that measure the user's biological and physiological activities. It has brought health. However, the pressure sensor must have sufficient flexibility, high sensitivity, large measuring range, fast response capability, excellent durability and low volume, easy integration with an external circuit and low production costs. In addition, the comfort and convenience of wearing are also the main factors that should be considered. This sensor, which was designed in combination with a porous structure consisting of black CNTs and multi-walled, was successfully installed on various joints of the human body and provided the potential to control human movements and respiratory changes [113].

In one study, silver nanoparticle-coated carbon dots (Ag-CD) were used to detect lactate using colorimetric and fluorometric methods. When Ag-CDs were produced by H_2O_2, the solution of Ag-CDs changed from yellow to clear and the fluorescence of the extinguished CDs was recovered simultaneously. This sensor specifically detects lactate even in the presence of active interfering biomarkers. The sensor is made with high sensitivity and selectivity, with a low detection limit of 0.6 and 10 μM for H_2O_2 and lactate, respectively. On the other hand, this sensor is used to determine lactate in the intracellular imaging in 4T1 (a breast cancer cell line) cells using a confocal microscope [114]. In a study, the latest developments in fluorescent and nanosensor-based CDs for biotiol detection are presented. Fluorescent carbon-based nanomaterials such as CD and graphene quantum dots (GQDs) have received much attention in biotiol assays due to their high water solubility, stable luminescence light and high biocompatibility. Biotiols, which include glutathione (GSH), cysteine (Cys) and homocysteine (Hcys), are considered important tools in clinical diagnosis [115]. GQDs are small semiconductor

fragments of less than 20 nm that limit electronic transport in all three spatial dimensions. CDs show spherical nanoparticles with a diameter of less than 10 nm that are biocompatible and non-toxic and have high solubility in various solvents. It creates hydrogens as a result of high solubility in aqueous environment. Even in combination with PEG or other functional groups, their biocompatibility would be increased [116]. CDs and GQDs interact strongly with biotiols in competition with substances previously added to the system. The interactions between fluorescent nanomaterials and biotiols not only alters the spectroscopic properties of the nanomaterials, but is also coordinated on the basis of reversible (non-covalent) molecular interactions and electrostatic or irreversible covalent bonds. Therefore, the main challenge in designing fluorescent probes is to identify reactions that combine more rapidly with high chemical selection [117]. In a study by infrared (IR) calculations, natural band orbital and frontier molecular orbital were used to estimate the function of fullerene (C20) as a sensor and the absorbent of picric acid that is well known as an environmental pollutant nitrophenol. The absorption of picric acid at the fullerene level is an exothermic and spontaneous reaction. Due to the adsorption of picric acid on the surface of fullerene, its thermal and electrical conductivity is significantly increased. Therefore, this nanomaterial is suitable for making thermal and electrochemical sensors. The results showed that the interactions of picric acid with C20 is more favourable at low temperatures. Natural band orbital calculations state that the interactions of picric acid with fullerene is a chemical reaction. Fullerene (C20), on the other hand, has unique properties due to its highly curved structure consisting of pentagonal rings. In terms of high conductivity, excellent surface/volume ratio and excellent reactivity, it becomes an outstanding measuring material [118]. Because it is important to identify alternatives to flexible materials in the construction of sensors, recently highly flexible traction sensors have attracted a great deal of attention. In one study, a carbon material consisting of three compounds including CNTs, graphene and fullerene was used due to its dense bonding and strong mechanism. In addition, ethylene butylene styrene (SEBS), which has inherent elasticity, was used to induce high tensile strength tolerance in this sensor. SEBS-based flexible substrates were mixed with liquid paraffin and heated. This substrate with strong adhesion properties causes strong interactions with the composite materials of the sensor structure. The CNT/graphene/fullerin-SEBS sensor has high conductivity, medium measurement coefficient, optimal tensile range, and adaptive speed reproducibility, with high potential for human movements monitoring and scalable applications [119]. In a recent study, a new electrochemical sensor based on platinum nanoparticles (Pt NPs) and fullerene (C60) in combination with Pt/C60 modified on the surface of pyrolytic graphite electrode (PGE) was employed to selectively select two phenolic isomers, including catechol (CC) and hydroquinone (HQ). Pt/C60 composites are used in the preparation of counters in QD-sensitive solar cells that show high power conversion potential. This sensor has high oxidation capacity in CC and HQ and showed increased catalytic activity. Isomers are important constituents of dihydroxybenzene, which are produced as pollutants in tanning, cosmetics, pesticides and medical procedures in many chemical and pharmaceutical industries. In a study of sensors, it was reported that C60 acts as an electron mediator in electrocatalytic processes towards target analytes. Another study prepared a new electrochemical sensor based on C60 and tetraoctylammonium bromide (TOAB) to detect hydrogen peroxide (H_2O_2). Herein, H_2O_2-C60 is an intermediate with excellent intrinsic electrochemical activity. A non-enzymatic electrochemical sensor is also fabricated using one of the C60 derivatives, which not only exhibits reduced oxidation processes but also exhibits strong electrocatalytic oxidation of nitrite and reduction of H_2O_2. Metal oxides, carbon nanomaterials and polymers also offer efficient electron transfer property, high electrocatalytic activity and increased stability and sensitivity due to the synergistic effect of their chemical properties [120]. The first method of using a diamond quantum sensor to measure these potentials in *in vitro* by using mouse muscle was examined optogenetically with blue light. In this work, the alternative method of detecting the conversion of action potentials to magnetic fields in living tissue was demonstrated by using nitrogen vacancy centres in diamonds. Because the use of electric probes to measure activity in tissues is difficult and carries a high risk of injury, so the magnetic field is considered an alternative to non-invasive, high-resolution and high-velocity sensing. Tissue depths can be accurately detected and spatially localized without contact or without the need to place invasive sensors. So far, biological magnetic field sensing techniques have been based primarily on superconducting quantum interference devices (SQUIDs), the disadvantages of which are the need for large magnetic shielding and cryogenic cooling, which prevents studies on living tissues and provides poor clarity [121]. Alternatively, ZnO which is used as a coating for the fibre optic sensor to increase the amplitude, improves the sensitivity of the measured parameter, and the measurements are performed in an environment with a refractive index close to the fibre optic core (n = 1.4). However, disadvantages such as the negative impact on the environment cause that the nanocrystalline CVD diamond sheet must be attached to ZnO to protect the sensor head and the measuring medium in the event of an adverse reaction [122]. Flexible pressure sensors are another device used in industries, which is one of the basic components of a wearable device. Graphene is an ideal material for wearable mechanical sensors due to its unique mechanical properties, conductivity, stability and flexibility. Among the flexible materials for pressure/strain sensors, which include piezoresistor, capacitor and piezoelectric, piezoresistor sensors are widely used due to their low cost, ease of

construction and high signal transmission ability. In one study, it showed a triode-mimicking graphene positive pressure (TMPGPS) sensor enclosed by a long-lasting Ecoflex. This device has a positive dissociation property whose resistance is positively related to external pressure. In addition, the device accurately understands both the physiological signal and the detection of large motions. TMPGPS was also used to measure plantar pressure during various movements and blood pressure [123]. A relatively high flexible pressure sensor based on flexibility by combining PDMS micron conical structure with bilayer graphene was also investigated. This sensor with local deformations, converts vertical force into resistance changes. The results show that this sensor can operate in the pressure range of 20 kPa, while sensitivity maintains 0.122 $\pm$ 0.002 kPa^{-1} (0–5 kPa) and 0.077$\pm$ 0.002 kPa^{-1} (5–20 kPa) during a response time of about 70 ms. In addition, the sensor shows high repeatability at different pressures and temperatures. It can also bend joint movements well (index finger bending), a feature is used in an electronic skin, flexible electronic devices and other fields [124]. The production of another new pressure sensor based on MoSe2 nano-sheets coated on cellulose paper is done, which has high performance for detecting insignificant vibrations such as wrist pulses. This sensor shows a combination of a high-pressure sensitivity of 18.42 kPa^{-1} in the pressure range of 0.001–0.5 kPa, 7.28 kPa^{-1}, 1–35 kPa, 2.63 kPa^{-1} and 40–100 kPa. On the other hand, it showed good results in detecting vibrations in mobile phones, compressors, etc., and also includes very good environmental stability and the response of the piezo-safety resistance to temperature changes. These sensors are produced using available substrates such as cellulose paper, sponge, PDMS, PET (polyethylene terephthalate), nickel foam, cotton yarn, silk fabrics, etc. Finally, this versatile sensor monitors wrist pulses well and is used to diagnose cardiovascular disease and arterial stiffness [125].

5.3 *DNA binding applications*

Carbon nanoparticles could be recruited for the applications of gene delivery and diagnosis approaches. For these applications, their interactions with DNA seems too essential. Carbon base nanoparticles such as CNTs and fullerenes due to some unique properties such as high electrical conductivity, high electron transfer rate and hollow cage-like structure have been used for variety of applications including in gene therapy, small molecule delivery and also, electrochemical and optical sensors [126–129]. Pristine carbon nanoparticles are insoluble and difficult to disperse in aqueous media, therefore their surface modifications including chemical and physical adsorption methods improve solubility and biocompatibility and reduce cytotoxicity [130]. An effective parameter in increasing of DNA binding efficiency and gene therapy with carbon nanoparticles is the ratio of length to diameter [130]. The corresponding ratio can create appropriate surface area as a result of surface modification by amino and carboxyl groups [131,132], PEI polymer, PAMAM, chitosan and polyamidoamine. These modifications could improve the efficient of DNA delivery into different cell types [133–135]. Interfacing mechanisms of CNTs with DNA occurs due to hydrophobicity CNTs surface and DNA bases via π–π stacking and forms DNA–CNT complexes [136]. For example in a study, the combination of PEI and polyacrylic acid (PAA) with MWNTs compared to the pure DNA and PEI/PAA separately, increases the efficiency of DNA delivery significantly [137]. Also, graphene oxide particles were modified with PEI and used as a gene vector. The results approved higher transfection efficiency with the complex of PEI-graphene oxide-DNA compared to pure PEI with DNA [86]. A study used fullerenes, which were highly oxygenated by diepoxide compound namely D-mannitol. Thus, DNA binding with the modified fullerene was done through the interactions between the hydrophilic oxygenated moieties and DNA grooves. Then, NIH 3T3 cell line was treated with the particles and green fluorescent activity confirmed the transfection capability of the particle [92]. Gold nanoparticles because of their unique properties such as optical and magnetic properties are very important in nanotechnology and nanoscience. Also, the absorption ability of these nanoparticles to DNA makes it possible to use them in gene transfer and other therapeutic substances such as proteins and drugs [138]. A group functionalized gold nanoparticles by using cationic-capping polymers such as chitosan and poly-L-lysin and cysteine. The results showed that the cationic cap due to the high-affinity and stronger electrostatic reactions with nucleic acids causes higher efficiency in gene delivery [139]. The attachment mechanism of the cationic cap, L-lysine, to the surface of gold nanoparticles occurs through the covalent attachment of amine groups. These chemical groups improve cell binding and adhesion by playing as a mediator between these nanoparticles and other cellular molecules [140]. Also, gold nanoparticles were functionalized with chitosan as chitosan/DNA complexes and they showed a high cationic charge density through electrostatic interactions with the negative charge of cell membrane [141]. These nanoparticles were trapped with cysteine as a capping agent using the thiol moiety of cysteine that acts as an effective site to interact with gold nanoparticles. The result shows that the decorated gold nanoparticles by cysteine in comparison with the pristine gold nanoparticles are more stable in aqueous medium for a long time [142].

5.4 *Tissue engineering applications*

For tissue engineering applications, it seems that nanoparticles with better mechanical property for scaffolds, being

useful to inhibit inflammatory reactions, acceptable cell attachment activity to carry cells efficiently and easy surface modification to bond cell biomolecules are vital. In this manner, if carbon nanoparticles as CNTs have defects such as topological defects, rehybridization and incomplete bonds, the mechanical properties will reduce accordingly [143]. Thus, carbon nanofibre is a better candidate besides their cost-efficient synthesis and long length that they even could be aligned axially. A conductive composite by utilizing carbon fibres and PDMS was prepared to more comfortable electroencephalography and after addition of carbon fibre, electrical impedance was reduced without any significant influence on the device performance. In contrast, the mechanical property of composite was increased against lower deformation potency [144]. The conductivity of carbon nanofibre is similar to graphite and consisted from an amorphous core with a graphitic skin [145]. Thus, carbon nanofibre could enhance conductivity of PLGA scaffold for myocardial tissue engineering [146] or mechanical property of PCL-hydroxyapatite (HAP) without the contraction of HAP osteo-activity [147]. Moreover, carbon nanofibres increase surface energy due to their higher substrate roughness and finally the more protein adsorption develop cell attachments [146]. Also, carbon fibres as a function of fibrous structure disperse better in polymeric matrix helping them to improve in mechanical, cytocompatibility and thermal stability of polypropylene (PP)-HAP scaffold [148]. A group fabricated a nonwoven network of polyacrylonitrile (PAN) and then converted it to carbon fibre via the carbonization of PAN at 1200°C. Then, the fibres was used to induce HAP growth on the surface of the carbon fibres for the application of osteogenic differentiation [149]. Another applicable nanoparticle in tissue engineering is the nanoparticles, which is classified as graphite family. The reduced graphene oxide nanoparticles are hydrophobic that limits their employment in biological media. By covalently combining PEG onto the reduced graphene oxide sheets, their dispersion in physiological environment would be improved. Moreover, graphene oxide nanosheets need to be modified to dominate the quick clearance from blood and accumulation in the liver and lungs [150]. In a study, β-galactosidase was immobilized on graphene oxide particles for better galacto-oligosaccharide (GOS) production. The results confirmed that the production of GOS was increased significantly [151]. In a study, graphene oxide was conjugated with PEG and under laser excitation, these nanoparticles showed two and three photon absorption coefficients. The grafted nanoparticles had high chemical stability at different pH conditions and after intravenous injection in mice, the nanoparticles distribution was confirmed uniformity by deep penetrating two photon imaging [152]. Again, another investigation modified graphene oxide nanoparticles with transferrin and PEG for targeting cancer cells and stability of the particles in blood circulation, respectively. Also, the reduced graphene oxide nanoparticles were modified with chitosan and loaded with Ibuprofen and 5-fluorouracil. The release of Ibuprofen and 5-fluorouracil were 10 and 50%, respectively. Both drugs acted differently at pH = 1.4 and 7.5 due to the hydrophobic nature of Ibuprofen with stronger π–π interactions with the modified graphene oxide [153]. A similar study was done for another anticancer drug namely chlorogenic acid (CA) and the interactions between graphene oxide and a drug were again via hydrogen and π–π bonds. The obtained hybrid particles could preserve the drug against thermal inactivation [154]. A reduced graphene oxide membrane was prepared by casting method and used for ocular implantation. Moreover, the membrane had antibacterial property and without sterilization process, there was no bacterial contamination. Although the membrane was not optically transparent making that into an improper candidate for corneal applications. Related to this issue, there are some studies that tried to fabricate a transparent film of graphene nanoparticles getting help from the polymers such as chitosan. Also, graphene members are classified as conductive materials, which could be used to fabricate conductive composites. In a report, graphene oxide after incorporation with acetyl chloride was used to polymerize 2-hydroxyethyl methacrylate as a function of atom transferring activity of acetyl chloride. The biocompatible, biodegradable and conductive scaffold was cultured by human osteoblast MG-63 cells [155]. However, a preclinical study in rats related to graphene oxide nanosheets confirmed that these nanoparticles at higher concentration of 500 mg kg^{-1} inhibited body weight in contrast to 150 or 50 mg kg^{-1}. Thus, graphene nanoparticles have toxic activity as dose-dependent manner and at higher concentrations, the toxic effects are inevitable and accordingly make injuries in the liver, kidney, spleen, lung, intestine and brain after 21 days [156]. Fullerene nanoparticles are another group of carbon-based nanoparticles with a closed cage structure. When C60 fullerenes were modified with three dimethylpyrrolidinium groups, the nanoparticles showed antimicrobial activity in the infected injuries of mouse. The significant antibacterial result had been synergically obtained when tobramycin was treated in the presence of C60-contained dimethylpyrrolidinium groups. On the other hand, C60 fullerene nanoparticles have been reported that they act as an antioxidant agent when pretreated at the dose of 2 g kg^{-1} body weight in rats. However, these nanoparticles must be as a soluble suspension to scavenge radicals confirming C60 fullerene nanoparticles need unsaturated bonds to function [59]. Another study approved fullerene gel to remove acne resulted from oxidative stress with lower inflammatory reactions. The phenomena occurred via reducing neutrophils diffusion into skin tissue and also sebum production. Indeed, the noted property depends on chemical modification of fullerenes or their solubility in organic solvent to prevent particles aggregates. About the optical activity of fullerene nanoparticles, as a presence of π-bonds, they produce reactive oxygen compounds for photodynamic therapy. A group modified C60 fullerenes into water soluble

using iodine atoms, although hydroxyl groups of C60 nanoparticles must be protected before. The final nanoparticles dispersed highly in water and thus, they were employed for X-ray imaging successfully [157]. Regarding to this, when fullerene nanoparticles are converted into hydrophilic materials, the modified particles would be an appropriate candidate for cancer therapy due to the emission of 0.346 MeV β-rays. The hydrophilic fullerenol particles were resulted from the reactions between fullerene nanoparticles contained Xenon-133 with OH groups. If fullerene nanoparticles are modified by polar functional groups, they could be employed for gene delivery approaches. The applications of fullerene nanoparticles are limited due to their lower water solubility and the protocols are required to remove this obstacle. A study suggested the fabrication of fullerene-substituted amino acid by using oxocyclohexano-fullerene derivative or by pristine fullerene nanoparticles. A β-alanine C60 fullerene was prepared in a study to scavenge reactive oxygen species. Another water-soluble fullerene derivative was model with inhibitory effect against HIV virus. The particles had ammonium groups on their surface [158]. Also, a targeted fullerene nanoparticle type was designed by a group. These nanoparticles were functionalized with bisphosphonate via the hydroxyl groups of fullerene surface and the resultant particles had high affinity to adhere calcium phosphate hydroxyapatite of bone. It was found in a study that after doxorubicin and fullerene nanoparticles were bonded each other as a complex, the efficiency of drug delivery was increased to 1.5–2 times and the tumour volume was decreased about 2.5 folds lower than untreated tumours. The interactions among fullerenes and doxorubicin was noncovalent and could increase the lifespan in mice to 63% compared to control group. Nano-diamond particles are a member of carbon-based nanoparticles consisting of sp^3 hybridization carbons and it was found that these particles are highly biocompatible. Diamond nanoparticles are stable fluorescence, while their nonspecific interactions with biomolecules in spite of their nontoxic effects, it seems that the surface modification is apparently essential. Regarding this, the nanoparticles were utilized to make subcellular spatial resolution during neural activity and the successful imaging was done in the presence of magnetic field and nano-diamond particles in a detection system of an axon transmembrane potential. These nanoparticles, which were modified with octadecylamine, were used to fabricate a film with PLLA for the evaluation of mouse osteoblast cell line. Not only the mechanical properties of the scaffold were improved after addition of the nanoparticles, but also the film had blue and red fluorescence by excitation at 360 and 555 nm. The obtained image coincided with the porous architecture of the scaffold under scanning electron microscopy [159]. Also, diamond nanoparticles were deposited on positively charged glass by poly-L-lysine as a film. The corresponding nanofilm was functionalized with an anti-inflammation drug and the results approved the inhibition of cytokine release confirming that these nanoparticles not only are biocompatible, but also could be employed for drug delivery aims.

6. Economical synthesis of carbon-based nanoparticles

The synthesis methods of carbon-based nanoparticles have different results such as geometrical properties and even, crystallinity degree. These attributions extremely determine the intrinsic characters of the resulted nanoparticles. Mostly, plasma-based method such as CVD could produce a large amount of graphene. However, the process requires the unzipping of CNTs through chemical and thermal reduction methods. On the other hand, it is also common that graphene nanosheets have been synthesized via the mechanical exfoliation and chemical oxidation of graphite or scotch tape, although the production of last method is low and accompanies with defects [160]. Also, multiple graphene sheets could be produced via periodic pulsed laser irradiation. Their average diameter was from 83 to 18 nm with onion-like structure [161]. Herein, we want to focus on the methods done in the absence of strong energy source and also in the presence of most available carbon precursors. In a study, a yellow luminescent carbon-based nanoparticle-type similar graphene sheets (sp^2 hybridization number) was synthesized by using phenylenediamine (PD) and ammonium persulphate (APS) without any condition requirements. The resultant particles due to the presence of aromatic groups could chelate metal ions and detected them at the concentration of lower than 0.5 μM [162]. Other graphene nanoparticles were produced through molten salts assisted method as n-doped type. The particles were obtained by the interactions of alanine and sodium carbonate after the pyrolysis at 1100°C [163]. Again, another graphite nanoparticle with sp^2 hybridization was synthesized via an easy and green method. The obtained nanoparticles had a foam shape and was doped with Ni could make a magnetic material. This method was enough to obtain the microspheres of alginate/Ni by only two-step thermal treatment. Graphene oxide nanoparticles could be doped easily to such as Co_3O_4/Co. The method required the thermal shock exfoliation of graphene oxide sheets at 400°C and then was stirred with cobalt and zeolitic imidazolate framework-67 solution in ethanol to obtain the particles with the property of oxygen reduction reaction (ORR) electrocatalysts [164]. Another graphitic nanoparticle was synthesized by using phloroglucinol and formaldehyde as raw materials of carbon particles. The corresponding method needed an acidic treatment with the autoclave condition and in the last, carbonization at 180, 400 and 850°C [165]. Moreover, a simple method with scale up potential is reported by a group. In this research, iron oxide crystals, which was used as catalysts, poured into a quartz glass tube and then, it was reduced by an electric furnace. Then, methane and nitrogen was gradually injected and the

temperature was increased from 850 to 1050 °C. The graphene nanoparticles were obtained [166]. About CNTs, CVD process is used mostly, but this method requires iron-based nanoparticles as seeds for growth step. Three classes of iron nanoparticles (3.9 ± 0.8, 3.3 ± 0.6 and 2.8 ± 0.4 nm) were obtained to evaluate their size effect on controlling the diameter of CNTs. The resulting nanotubes had the diameters 3.1, 3.6 and 4.5 nm, respectively, although after changing the growth temperature, the diameters increased [167]. Common methods for the synthesis of nanotubes is high temperature-based method as CVD that needs to evaporate pure carbon during to develop CNTs, however it belongs to MWCNTs. CVD or catalytic growth processes is also used to produce carbon nanofibres in the presence of catalysts. Also, CVD method could control the diameter of MWCNTs by using the size of catalysts such as nickel nanoparticles. For obtaining the smaller diameter of CNTs, the size of catalysts must be lower. Also, CVD technique to produce SWCNTs needs catalyst particles such as iron-molybdenum nanoparticles with a specific size to nucleate SWCNTs. The size of catalyst, its concentration and time of reaction strictly change the size of the produced SWCNTs. Compared to CVD with high-pressure, high-temperature conditions and high level of impurities, there was reported a low-cost process for the production of high-purity SWCNTs using alcohol at the low temperature lower than 700°C. For this synthesis profile, the resulted OH radicals ruined the side products as MWCNTs, metal particles and carbon nanoparticles after washing with H_2O_2 and removed the seeds of amorphous carbon compounds [168]. Also, the modification of CNTs could be facile and ecofriendly process. It was reported that only after addition of $CuFe_{12}O_{19}$ nanoparticles, the acid treatment was only step to modify CNTs particles [169]. Another study reported a method that would be scale up for the synthesis of MWCNTs. In this method, metal salt $Ni(NO_3)_2{\cdot}6H_2O$ as catalyst was dissolved in di(ethylene glycol) (DEG), glycerol and ethylene glycol and heated up to 190°C and then, it was transferred separately into quartz crucibles with lid. The calcination process was done at 800°C under N_2 atmosphere and the final precipitates were washed with acid-water and finally, CNTs were obtained [170]. Also, it was found by using nanoscale diamond powder, CNTs could be produced by using CVD method, although the diamond nanoparticles must be salinized prior to the synthesis method. In few previous studies, iron chloride was chosen as a catalyst and the gases were C_2H_2, H_2 and N_2 at the temperature of 700°C [171]. C-dot nanoparticles were fabricated by the electrochemical carbonization of ethylene glycol and after electrolyzing under 30 V, the obtained nanoparticle electrolyte was neutralized with hydrochloric acid to remove sodium hydroxide [172]. However, hydrothermal methods due to lower toxicity and higher solubility of precursors in this method was chosen mostly to fabricate CDs. The thermal condition of this method is usually in the range of 300–800°C for the synthesis of most of carbon-based nanoparticles, although the temperature lower than 300°C was enough for CDs [173]. Another report explained the soot-based method that seem to be easy but with lower synthesis yield. The diameter of nanoparticles was about 2–6 nm with green fluorescence under UV exposure and ability to enter cells for imaging approaches. The soot was mixed with nitric acid and then, acetone and water was added, respectively. The solution was refluxed for few times to obtain the nanoparticles. A step to separate the produced nanoparticles accordance with size was needed in the following. Another similar synthesis method was carried out by a group. Again, the soot was employed as a carbon source and refluxed in nitric acid and filtered to obtain the particles with the diameter lower than 50 kDa. The particles were purified using high-performance liquid chromatography with UV detector coupled to a Picometrics Zeta laser-induced photoluminescence [174]. The precursor of the soot for the fabrication of CDs was repeated by another study with brief modifications. The soot was dispersed in triton X-100 and ultrasonicated in the following. CDs were obtained after refluxing and could be used for further functionalization steps. Sometimes, carbon fabric was used as a carbon source to fabricate carbon-based nanoparticles. Afterwards, the fabric was located in the flame for 30 s, ethanol/propanol was dropped on the fabric. Finally, the electrodeposition of MnO_2 was done in a solution of manganese acetate-ammonium acetate-dimethyl sulfoxide (DMSO) at the current of 0.5 mA cm^{-2} [175]. Also, another study used sodium oleate complex as a precursor of carbon-based nanoparticles. Herein, after obtaining Cu–oleate complex, the ammonia solution was added as a base catalyst and ultrasonicated. The emulsion was transferred into a solution contained dihydroxybenzoic acid-formaldehyde-water and autoclaved for 4 h to obtain the carbon nanoparticles with the carbon shell and Cu as cores [176]. The spherical shape of carbon-based nanoparticles was produced by an ecofriendly method. For this process, capsicum and chilli were the source of the carbon nanoparticles. The ground mixture was ultrasonicated and heated in microwave and then in a hydrothermal reactor at 150°C. Finally, the solution contained carbon nanoparticles and was centrifuged and dialysed. Interestingly, biomass could be as a raw material for the synthesis of carbon-based nanoparticles. Bacterial cellulose makes a 3D network of carbon nanofibres with the diameter of 20–100 nm. When the material was treated in the high temperature at 2900°C, it could convert to a carbon-rich conductive compound [177]. If the pyrolysis was performed under Ar atmosphere at 1300°C, the obtained aerogel would have the highest value of carbon and carbonization degree. However, previous studies showed that the carbon nanofibres could be produced by using glucose as a precursor. Magnetic carbon nano-onions were easily produced by using a candle as a carbon precursor. The candle was calcinated at 800°C under N_2 atmosphere and then, dodecylamine and iron (III) acetylacetonate were added and lighted in the following.

The temperature was increased up to 900°C [178]. For fabrication of a nanoscale diamond film in older methods, CVD method was used mostly in the presence of Ar and CH_4. Herein, tungsten filaments were heated to about 2000°C for the activation of the gas mixture and the film grown on the tungsten filaments. Although it was reported in the presence of graphite nanoparticles as a carbon source, the temperature could be reduced to 950–1000°C [179]. Similar method was done by using the mixture of H_2, Ar and CH_4 on a pure titanium, however at the temperature of 550–600°C. A study used a silicon wafer as a substrate to deposit nano-diamond film with temperature reduced to 150–600°C in presence of H_2 and CH_4 with the pressure of 70 Torr [180]. In a newer study, the film was deposited on tungsten carbides, which was pretreated by boron atoms to increase the adhesion of diamond particles and the temperature was reduced to 800°C [181]. Also, another method explained that, the process was done by a gas mixture of CH_4 and N_2 and with the silicon substrate. The temperature and pressure were, respectively, reduced to 450°C and 50 Torr [182]. For the large-scale synthesis of nano-diamonds, a protocol was suggested with a less hard synthesis condition. In this method, the detonation of soot happened in acidic media and the annealing was started at the temperature of 1300°C and pressure of 1 Pa. The temperature was cooled down and the particles were gathered by $MgAl_2O_4$ + MgO octahedron. In an age-old study, it was reported that fullerene nanoparticles were prepared by using nickel phthalocyanine as a material with considerable electrical conductivity and also optical property. The protocol took relatively a long time [183]. Arc reactor had been employed mostly for the synthesis of C60 fullerene, which was analysed numerically by a study. In such a model, carbon vapor transfers from an electric arc and is blended with helium gas to be cooled down. Carbon vapor starts to condensate and fullerene molecules are formed.

7. Limitations of carbon-based nanoparticles

Carbon nanoallotropes such as CNTs, fullerenes, graphene sheets, graphene oxide, CD and nano-diamonds have been used in various nanotechnology fields. Since the beginning of 21st century, CNTs have been shown as a powerful tool in pharmacy and medicine for drug delivery system in therapeutics, cancer therapy [184], neurodegenerative diseases [185], antioxidants [186,187], biosensor vehicles [188], biomedical imagining and nanoscaffold for tissue engineering, due to their high surface area, excellent chemical stability, rich electronic poly-aromatic structure, their high electrical and thermal conductivity properties [185,189]. Although carbon nanomaterials *in vitro* and *in vivo* studies showed that these nanoparticles have some disadvantages unfortunately, for example, toxicity, physiological barrier and their immune response [190]. One of the most important limitation of pristine carbon nanoparticles is their toxicity. However, the toxicity of these nanoparticles could be reduced by their surface modification [191,192]. Another problem related to the usage of carbon nanoparticles in medicine as CNTs is their insolubility property, due to which they cannot be used directly in biomedical applications. Another limitation is their inhomogeneity in size (both diameters and lengths), as the homogeneous size is very important for reproducible clinical applications. Also, nanoparticle defects are another issue that should be considered during scale-up phase. Even the defects reduce the quality of surface modification, which are done to reach higher blood circulation and biocompatibility. Another important limitation is that the stability of these nanoparticles needs to extra-steps for steric/electrostatic stabilization. Moreover, the employment of toxic solvents and exhausting synthesis protocol for some carbon nanoparticles are unsolved problems.

8. Conclusions and future directions

Carbon-based nanoparticles have attracted attention in recent years due to their considerable ability to remove the gap between disease diagnosis/drug delivery approaches and new facilities for critical diseases as cancers or virus infections or severely damaged tissues. Among nanoparticles, carbon-based types have dedicated themselves to fabricate and optimize medical systems with stable thermal, electrical, optical, electrochemical, electrochemiluminescence and mechanical properties. Also, their higher surface area along with an easy chemical modification could introduce them as more appropriate nanoparticles compared to metal and ceramic nanoparticles, QDs, magnetic nanoparticles, polymeric nanostructures and silica-based family. Moreover, carbon nanoparticles especially oxide types have high capability to integrate with other molecules/biomolecules easily. On the other hand, the higher surface activity of carbon-based nanoparticles leads into pulmonary and systemic toxicity along with higher potency for making aggregations. Thus, carbon nanoparticles for better drug/biological molecule loading compared to polymeric nanocarriers should be modified [193]. However, it seems drug vehicles in the future would be capable to discriminate target cell/tissue accordance with the metabolic differences between them. In other words, for successful drug delivery into cells, it will be necessary that in the future, chemical properties of new drugs such as zeta potential should be switched after their deposition at the target site. In spite of this, it was discussed that gene delivery by using carbon-based nanoparticles could be compared with PEI, which is employed as a gold standard in nonviral gene delivery. Regarding this, the shape, size and surface properties of carbon nanoparticulates make them to be interested for drug delivery approaches. In cancer treatments, carbon nanoparticles-drug complex that are

conjugated to a targeting ligand and at the same time could make possibilities for tumour imaging with high resolution. Also, continuing research into novel drugs are trying to find more effective cures and on the other hand, could increase detailed insights to develop future delivery systems. It is interesting for patients wherein a lower drug dosage is applied during their disease therapy. Also, lower contrast agent by imaging techniques and lower blood sample at laboratory assays are inevitable. Carbon nanoparticles due to their higher surface area and subsequently higher surface interaction power could provide better facilities in near future [194]. Moreover, the hydrophobic drugs get new chance to be evaluated on diseases therapy, besides their higher lifespan after delivery to bio-environments [108]. In such a field, carbon-based nanoparticles have been provided appreciated efforts, but they are in their fancy. Regarding imaging process, ongoing devices those take advantage of conductive carbon nanoparticles are emerging to detect tumour margins [195] or even single cancer cells. Although some carbon nanoparticles could not help to the apoptosis of cancer cells, their anticancer activity was improved when they act simultaneously with approved drugs. In such a case, this synergic mechanism of carbon nanoparticles with multiple components has been not explained thoroughly until yet. In this review, the literatures were focused mainly on nanoscale carbon materials. The corresponding particles were listed and introduced their substantial properties. Herein, it has been tried for the first time, the underlying mechanisms that make them special for medical approaches and were explained to understand better the meaning of 'there is plenty of room in the bottom'. Also, their toxicity strategies were noted as far as researchers have involved in this area. There was an essential effort in this review to cover all biomedical applications of carbon nanoparticles and their employment in combination therapy methods. Furthermore, their different nano-manufacturing methods were reviewed, although this part was concentrated on the new methods trying to resolve the issues belonging to old synthesis methods. In spite of carbon nanoparticles that hold great hope for new therapeutic and detection methods, the current medicine suffers from possible undesired side effects of carbon-based nanoparticles. CNTs nanoparticles with similarity to asbestos and graphite family due to their sharp flake edges have high possibility to make toxic effects. Surface modification for all carbon-based nanoparticles were recommended not only to obtain water-soluble particles with low clearance from blood and lower immune system induction, but also it helps to absorb particles by cells and inhibit particles aggregates [196]. However, it should be noted that when surface modification is not appropriate, the particles are converted to the particles with higher toxic activity. The future medical acceptance of carbon-based nanoparticles needs deeper insights about immune system response and new modalities should be developed to remove the related concerns about toxicity. It seems that here is a variation between the coming results of *in vitro* and *in vivo*. Thus, new methods related to the biocompatibility of these particles would be exposed, such as microfluidic systems with a higher simulation to biological environments [197]. The main advantages of this system is to study the novel disease detection and therapy, with high rapidness, economical production and the low value of sample needed, and more importantly, they are point of care capability. Additionally, this review could be numerously helpful for researchers to obtain basic and updated knowledge about carbon nanoparticles with emphasis on their medical applications. As a whole, in our report, the impact of carbon-based nanoparticles is likely to grow in near future into more biocompatible and potential nanoparticles and become more tightly coupled to medical systems, including drugs or detection devise. Clearly, it is worth noting that the clinical translation of these particles still needs to be considered in near future. Also, ongoing review articles would have more chance to discuss clinical studies, which get benefit from carbon-based nanoparticles and cover a new generation of developed carbon nanoparticles in future.

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