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Fullerenes and Nanodiamonds for Medical Drug Delivery

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Abstract

Carbon is a chemical element has the ability of forming long carbonic chain. Due to its special electronic structure, each carbon atom can be linked with another carbon atom or with another element via single, double or triple covalent bonds. The special electronic structure of carbon atom affecting on its properties also affecting on its ability of existing in different forms called allotropes. During few last decades, new carbon-based nanomaterials have been described including fullerene, carbon nanotube, graphene and nanodiamond. These new allotropes attracted the interest of science and industry and became as a new and important class of materials due to its outstanding features which candidate for numerous applications. In parallel with new developments in nanomedicine especially in drug delivery field, the targeted delivery systems became an important to overcome the limitations of the old fashion systems. So, it become very important to translate this idea into reality. Fullerene and nanodiamond have a unique combination of structure, morphology and biological properties that make them as a powerful tools for targeted delivery system. So, this chapter will focus on two major aspects: synthesis routes of fullerenes and nanodiamonds, and their role in nanomedicine as drug delivery systems.

Keywords: Fullerene, Nanodiamond, Synthesis, Properties, Drug delivery

1. Introduction

Since ancient times, materials are the most interesting thing for human. In fact, human deals with different materials to meet life's requirements. Invention of new technologies requires new materials, materials with new physical, mechanical and chemical properties. Therefore, material scientists and engineers made their efforts to produce these required materials by changing their composition, structure via synthesis process [1].

In general, materials development is continuous from ancient time. So, we can notice that each period of times known by specific material's name such as: Stone Age, Bronze Age, Gold Age and Iron Age. So, due to the widespread use of nanomaterials in different industrial as well as biological fields, our current age could know by Nanotechnology Age [1].

Nanocrystalline material is one of the most interesting material with a grain size in the realm of nanometers (1–100) nm. It is not new, it is produced and used in different fields for hundreds of years. For example silver and gold nanoparticle was found in ancient paintings of glasses which gave it the ruby red color, also carbon black which is a nanostructured material was discovered in 1900 s and

used in tyres technology. These materials are bigger than single atom and smaller than a microcrystalline grain. Due to their unique structure, it exhibits unique and unprecedented mechanical, physical and chemical properties that differ from those of single atom or microcrystalline grain, these materials can be synthesized from ceramics, metals, polymers and composites [2].

At nanoscales, materials undergoing to changing in their structure, physical and chemical behaviors, these changes were driven from the several effects such as; increasing their surface area, increasing atoms concentration at grain boundaries, increasing the area of grain boundaries and decreasing the percentage of dislocations within material's structure [1–3].

On the other hand, nanotechnology was presented for the first time in 1959 at the scientific annual meeting of the American Physical Society by Nobel laureate Richard P. Feynman in the famous and classic lecture that titled “There is plenty of room at the bottom”. Nanotechnology can be imagined as umbrella for all different fields and areas dealing with nanomaterials and nano objects. Furthermore, it is worth mentioning that there are several observations related to the behavior of natural nanomaterials became as inspiring and promising ideas for several applications. For example: nanofluids which has been used in different applications was inspired from blood and milk (natural nanofluid) with high dispersion stability for long periods of time [1–5].

Although nanomaterials had been known and used for many years ago, but this science gained its greatest importance after the discoveries of fullerene molecules in 1985 by Kroto's and Smalley's team [3, 6], carbon nanotubes CNTs in 1991 by Saumio Lijima [3, 7] and graphene in 2004 by Andre Geim and Kostya Novoselov [3, 8]. This fact is associated to the nanochemistry of these carbon allotropes, these nanomaterials show stability did not found in any other nanomaterials due to their high activation energy barriers. Hence they attracted a great attention of researchers to employing them in a wide variety of applications even in their non-functionalized state [4].

Nanomedicine-based drug delivery system has a great influence on the targeted therapy field. Via this sector of nanotechnology, the therapeutic drugs can be incorporated into a variety of bio- nanocarriers, hence, their pharmacological behavior were enhanced and leading to high treating efficiency. Nowadays, the most attracted materials in this field is the carbon- based nanomaterials [9, 10].

2. Carbon atom

Carbon, denoted by letter C, is the most interested element in nature due to its abundant in universe. It is 15th most common element on earth's crust [11]. In nature, carbon's ores can be exist in different forms, as carbonates [11], wood charcoal [11], briquette and others. In human body, it is the second abundant element by mass after oxygen. Also, carbon atoms exist in all organic materials. So, it is regarded as the basic building unit for all life [11].

In periodic table, carbon atom exist in group 14, therefore it is a tetravalent. Carbon has fifteen different isotopes, two of them are stable known as ^{12}C and ^{13}C that comprise 98.89% and 1.11% of the carbon on earth respectively. Other isotopes known as a radio-active isotopes, among them ^{14}C is the more stable one [12, 13].

In general, the term of electronic configuration refers to the electronic structure of an atom, with its levels, sub-levels and electrons number that occupying its orbitals. The electronic configuration of carbon atom is: $1s^2 2s^2 2p^2$. Excited configuration is the basis of the hybrid orbital. $1s^2 2s^1 2p_x^1 2p_y^1 2p_z^1$, hence with four unpaired electrons, four L- shell can be hybridize then and forming sp^3 orbital which directed

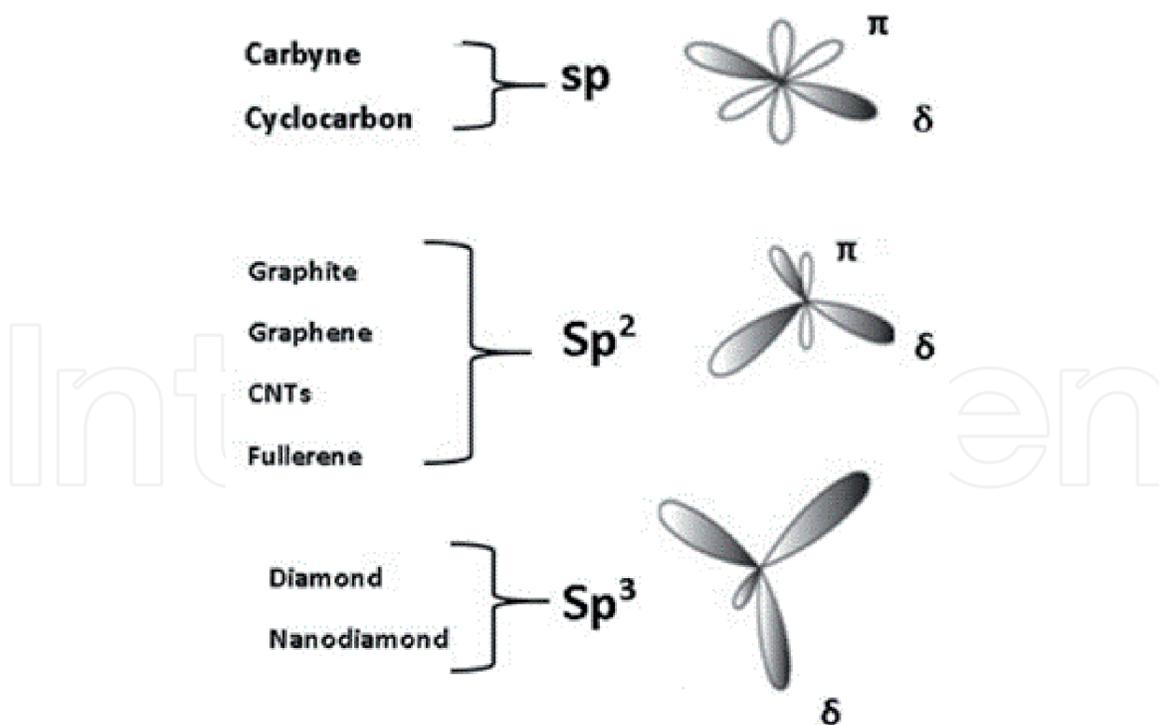


Figure 1.
Representation of carbon structures hybridization states.

in the tetrahedral direction at angles of 109.5° . This electronic structure found in diamond. When 2s and two of 2p orbitals hybridize together, three of the sp² orbital was formed and directed in the trigonal direction at angles of 120° from each in a plane. This electronic structure found in graphite. While in sp hybridization type, there is only one of 2p orbital is used which led to diagonal bonds with 180° apart. This electronic structure found in carbyne. Also it is good to mention that the unused 2p orbital in each sp² and sp hybridization types forming pi bonds [14, 15]. See **Figure 1**.

Carbon atoms have the ability to form long chain with its own atoms via feature called “catenation”. There are three basic covalent bonds between carbon-carbon atoms, single bond (sigma bond) is the most common bond between carbon-carbon atoms, and it is consisting of one electron from each carbon atom and is thus a two-electron bond such as the bond in ethane. A double bond is another type that exist between two carbon atoms, generating the alkene group, also called olefins. These hydrocarbons are exclusively composed of carbon and hydrogen. The third type of bonding between two carbon atoms is the triple-bond which is existing in compounds called alkynes. Due to the flexible chemistry of carbon atom and the strength of the covalent bond, carbon has the ability to create endless chains, sheets and three dimensional structures with different properties [14, 16].

3. Carbon allotropes

The most prominent allotropes of carbon are graphite, diamond and lonsdaleite. Each one has its specific properties which very varying from that of another one [16].

Graphite was named by German mineralogist and chemist A.G. Wenner in 1789 [11]. It is a naturally occurring material found in a metamorphic rocks. Its structure made by holding many layers via weak forces. Each layer consisting carbon atoms arranged themselves in a honeycomb lattice [16]. Graphite is characterized by its

dark opaque appearance with soft texture and well electrical conduction property. Within its structure, three electrons of each carbon atom shearing with another neighbor by single bonds while the fourth electron become delocalized overall the whole sheet of atoms in each layer. The delocalized electrons are not fixed to a specific carbon atom and can be move freely on the sheet's surface leading to induce a temporary dipoles which induced an opposite dipoles above and below each sheet that leads to hold the overall sheets of graphite structure [17].

Diamond was derived its name from the Greek word "adams". Diamond is the cubic high pressure phase of elemental carbon [18]. It is occurred naturally and it's the hardest known material [18], with a transparent appearance [11] or can be exist in different colors depending on the presence of specific elements or some structural defects with a very low electrical conduction [18]. In diamond, carbon atoms forming 3-D lattice structure in which each carbon atom shears its four electrons with another carbon atom by four single bonds [11].

Lonsdaleite, the hexagonal diamond [11], it is named in honor of Kathleen Lonsdale. It is found naturally in a graphite containing meteorites that struck earth. It is a transparent material with hardness much higher than that of diamond [11, 16].

Amorphous carbon [19], is an interested allotrope, in which carbon atoms can be exist with a wide variety of hybridization states. The most familiar form of amorphous carbon is diamond-like carbon (DLC) due to its structure which is amorphous with many fraction of sp^3 bonding so it exhibit some important characteristics of diamond without the necessary for complicated synthesis techniques [20]. It is characterize by its high hardness, low friction property [20] and chemical inertness [20].

Furthermore, there are several allotropes of carbon atom exist in nano- scale featured by their unique structures that led to a great explosion in materials science and technology. Here we will give a summarize description about the structure of some of these materials [21].

Graphene, attractive nano- scale allotrope, is an atomic thick sheet made up of carbon atoms arranged themselves in a honeycomb lattice. So, it is a 2-D allotropic form within carbon family. It is represents the structure of other allotropes of carbon due to its structure flexibility. By rolling its structure, carbon nanotubes is obtained and by warping up a fullerene allotrope is obtained while the stacking of several sheets leads to produce graphite structure. So it is called a mother of all other carbon allotropes, see **Figure 2**. Due to its attractive properties it is candidates for many critical applications in industrial [4] and health care fields [22].

Carbon nanotubes is a cylindrical structure nano allotrope of carbon with a diameter of several nanometers and micro- scaled length, consisting of rolled graphene sheets. Its structure can be vary by its diameter or, its length or its layers number.

There are two main types of CNTs, single walled SWCNTs and multi walled MWCNTs. Several studies had been clarified that SWCNTs have about (1–3) nm diameter and few micrometers in their length, while MWCNTs have about (5–40) nm diameter with length around 10 micrometers. This type of carbon allotropes have unprecedented aspect ratio property due to their unique structure together with high thermal and electrical conductivity compared to other conductive materials [4, 23].

Fullerene and nanodiamond another allotropes of carbon atom, have unique and novel properties due to their unique nanostructure. These two carbon nanomaterials will be discussed later.

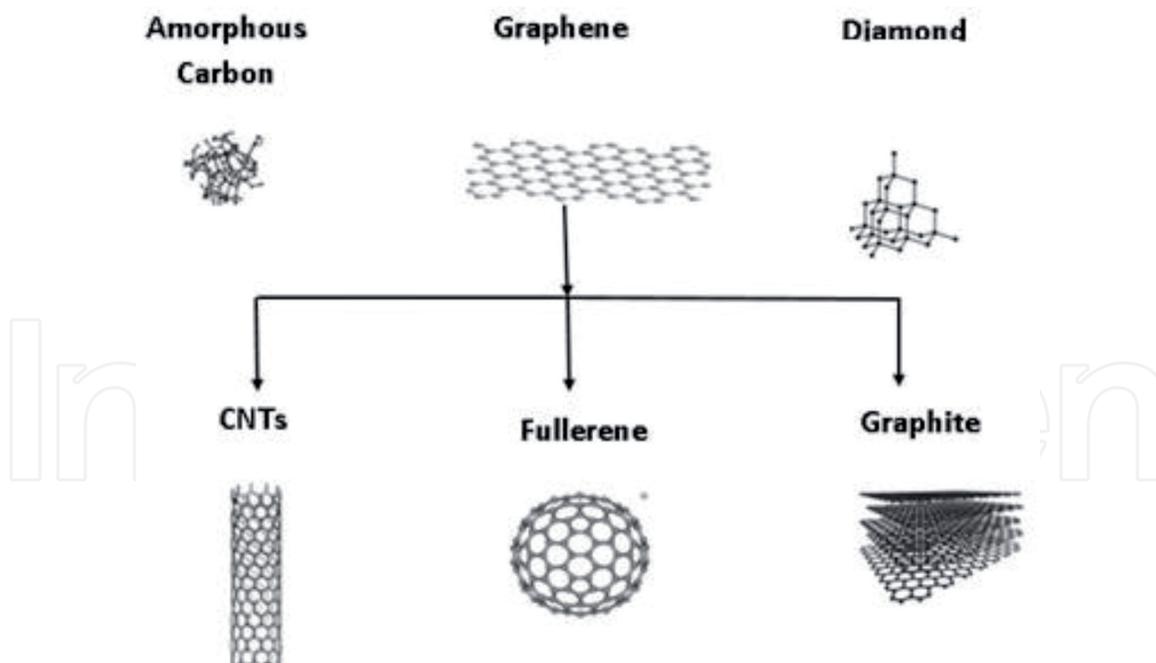


Figure 2.
Representation of carbon allotropes.

4. Hybridization of carbon atoms

The recent materials discoveries at nano scale open new horizons in all science and engineering fields. One of the most important point of view reported in several literatures is depending on classify carbon materials according to their hybridization characteristics [24, 25].

The electron hybridization determines the ability of carbon atoms to arrange themselves in a wide variety of structures with linear, planar and tetrahedral symmetry forming different allotropes, such as carbyne/carbyte, graphene/graphite and diamond. So, depending on hybridization type carbon structures can be classified from sub-molecular to macroscopic scales into three general families: carbyne- general family (sp^1 family), this family includes carbon atoms with sp^1 hybridization state from its nanostructured like carbyne or cyclo-carbon to its macrostructural crystalline form [26]. The second class called graphene general family (sp^2 family), this family includes carbon atoms with sp^2 hybridization state in their nano as well as macro-crystal structures with hexagonal and rhombohedral structures like graphene and graphite. The third class called diamond general family (sp^3 family), the carbon within this family existing sp^3 hybridization state like diamond structure in its nano and macro scales [27].

For more complexation, carbon atoms can be exist with other hybridization states called intermediate hybridizations with different degrees. The degree of hybridization in this case caused by the curvature of the sp^2 hybridized structure, leading to produce strained C–C bonds. Usually carbon atoms with pure sp^2 hybridization state shows an ideal flat structure. While in the case of atoms with curved structure, their hybridization degree should be >2 as in the case of fullerene carbon [14, 27].

On the other side, usually carbon atoms in sp^2 hybridization state arrange themselves in hexagonal rings as well as in a various other polygonal rings. The non-hexagonal rings can leads to curving the flat sheet or keeping its flatness if the polygon arrangement fulfils certain symmetry rules [14].

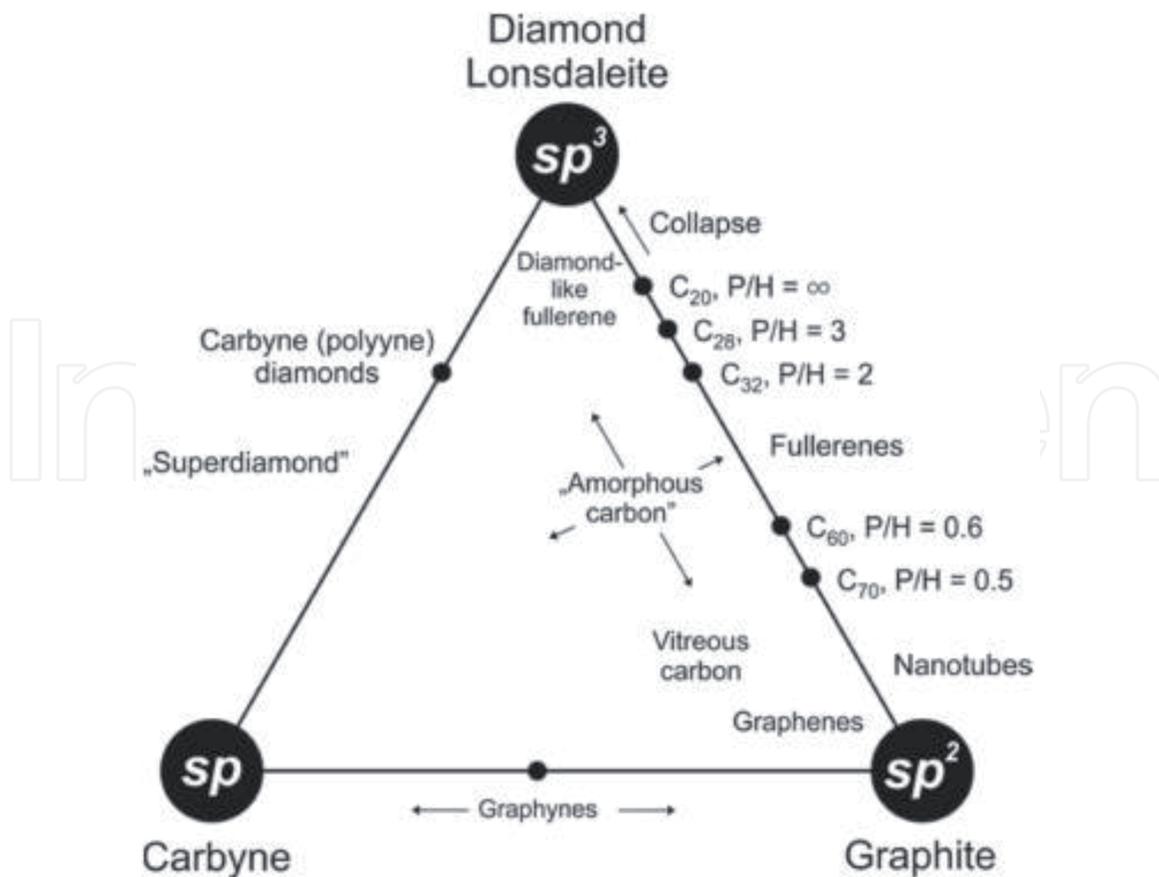


Figure 3. The ternary carbon allotropy phase diagram based on hybridization type (reuse with permission Elsevier [14]).

The pentagon rings induce a positive curvature while heptagon or octagon rings induce a negative curvature. Therefore, carbon materials with sp^2 hybridization state can exist into three types: positive curved fullerene-type, which includes carbon atoms with hexagonal and pentagonal rings and negative curved schwarzite-type, this type includes carbon atoms with hexagonal and either heptagonal or octagonal rings and the last one called zero-curvature graphene-type which includes carbon atoms with hexagonal rings only [14]. This procedure of classification carbon based- nanomaterials had been presented by a triangular carbon allotropes phase diagram, see **Figure 3**. In which, hypothetical carbon allotropes located at the corner of the diagram, and allotropes with intermediate hybridization states located at the edge of the diagram while carbon existing mixed hybridization states located inside the triangular diagram [14].

5. Fullerene and nanodiamond

The recent discoveries of the nano-sized carbon materials leads to expand the list of carbon allotropes. In association with the ability of carbon atoms to form wide range of structures, carbon based- nanomaterials become widespread in the fields of nanoscience and nanotechnology [28].

Generally, Carbon-based nanomaterials possess effective physicochemical properties make them as a powerful tool in medicine. For example, graphene possess many promising properties due to its high surface area and high functionalization ability that make it suitable for drug delivery treatment, along with its high mechanical properties, graphene had been recommended for tissue engineering

field. Carbon nano tubes CNTs had been suggested for different in vivo applications due to its strong optical absorption in the specific wave length and as an active tool for bi0 imaging and drug delivery applications. Recently, fullerene and nanodiamond had been investigated and received much attention to use as a drug delivery carriers [29].

In spite of the promising benefits of using carbon based- nanomaterial as medical tools for the treating of difficult to treat diseases, several challenges are involved within this technology such as, their toxicity, diffusion and distribution abilities throughout the body which may leading to unpredictable effects. So, in-depth and carefully studies around their nature and behavior in human body regarded the most important factors in this field. One of the great promises of nanotechnology in medicine is the local or targeted delivery of drugs. Efficient targeting would allow for a reduced systemic dosage meaning also a reduced toxicity while resulting in relatively higher or more efficient dosage at the desired target site [29].

6. Fullerene

6.1 History and structure

Several ideas, suggestions and observations in addition to physical and chemical experiments of clustered molecules were led to the way for discovery of C_{60} in 1985.

In 1966, David Jones discussed the possibility of creating balloons made up from carbon atoms. Then in 1970, this idea was progressed by Eiji Osawa when he revealed the possibility of preparing molecule made up of 60 carbon atoms known as C_{60} molecule in a condensed icosahedron structure [30]. After that in 1971, Eiji Osawa and Zensho Yoshida enumerated the possible aromatic properties of the structured C_{60} molecule. Later, Bochva and co-worker studied the electronic structure of this molecule. Then in 1980, Davidson characterize the closed- hollow structure of this molecule using different theoretical techniques. Subsequently, in 1985, Kroto and Smalley and their team obtained carbon cluster through scientific experiment to study the suitable conditions at which carbon atoms nucleates in the atmosphere of the red giant star. The mass spectrometer analysis of the obtained clusters indicates that most of them had 60 carbon atoms and some of them had 70 ones [31].

This carbon allotrope become the heart of nanotechnology and attracted significant attention of scientists. For that, in 1996, Kroto, Curl and Smalley were rewarded by Nobel Prize in chemistry for their discovery of fullerene [31].

Fullerene derived its name in the honor of the geodesic domes designer the architect Buckminster Fuller. Fullerene family usually represented by a formula of C_n , where n refers to the existing carbon atoms in the cage structure which can be up to several hundred atoms, the number of the carbon atoms existing within fullerene structure has a great influence on its structural geometry and its properties. C_{60} is the most dominant molecules within fullerene family [31].

The structure of C_{60} has truncated icosahedrons made up of 20 hexagonal rings located at the center of the icosahedral faces and a 12 pentagons located around the apexes. It is the most symmetric molecule. It has 2.fold, 3.fold and 5.fold rotational symmetry. The first one is through the edge center of 2- hexagons, the second one is from the center of 2-hexagons which facing each other, while the last one is through two pentagons centers which facing each other [30, 31].

Furthermore, fullerene molecules can be exist as a spherical, ellipsoid, tubular shapes consisting hexagonal, pentagonal and sometimes heptagonal rings. C_{60}

belongs to the spherical fullerene class which looks like a soccer ball, while C_{70} belongs to the ellipsoidal class which looks like rugby ball. In addition, several efforts have been reported to produce fullerene with high yields, in 1990, a method was discovered for producing macroscopic amounts of this distinctive material and this breakthrough allowed scientists to understand its chemistry and explore its properties [31].

Generally, fullerene can be classified into classical fullerene and non-classical fullerene. The first one containing 12 pentagons and any number of hexagons, while the second fullerene class can have heptagons, octagons, and an additional number of pentagons or squares [30, 31]. Due to the unique structure and properties of C_{60} , scientists showed high interest in synthesis both larger and smaller fullerenes. Therefore, the family of fullerenes has been expanded involving fullerene molecules with a wide range of carbon atoms number. Larger fullerenes that have an icosahedral- symmetry also can be constructed. While, the carbon cages structure smaller than C_{60} consist of adjacent pentagons. These smallest fullerenes are predicted to have unusual physical as well as mechanical properties due to the high curvature of their molecular surface. The smallest fullerene molecule is a dodecahedron consisting of 20 carbon atoms with only pentagon rings. The fundamental understanding of the size dependence of the closed carbon cage structures is important for tailoring these systems for possible nanotechnology applications [31].

Due to the electronegative nature of fullerene, fullerene can form different compounds with different structures. One of the most important fullerene species is derived from the cage- like structure in which there is an ability of trapping metal atom inside the cage and forming specific endohedral fullerene known as metallofullerene. Exohedral fullerene is another type of fullerene with enhanced solubility property, obtained due to the chemical reaction with chemical groups. On the other side, when one or more carbon atoms within cage structure are substituted by specific hetero atom a hetrofullerene is produced [31].

6.2 Synthesis routes

Synthesis of graphenic materials like fullerene have been studied and reported in many literatures. Different techniques have been adopted for fullerene synthesis, such as arc discharge technique [32], vapor deposition of carbon atoms technique [33] and laser technique using graphite [34]. The cage- like structure of fullerene was identified for the first time by Kroto and Smalley in 1985, their experiment depending on applying an intense pulsed laser on a rotating graphitic disk to vaporize carbon atoms in the presence of helium atmosphere, then the condensed material had been collected, some of these routes are shown in **Figure 4** [35].

In 1990, another method was used to prepare fullerene reported by Ajie and co-workers, this method depending on the principle of the resistive heating of carbonic rods in a partial helium atmosphere which leads to evaporating carbonic atoms and then condensing it into fullerene structure [36].

Another method was discussed in U.S Patent in 1991, using electric arc technique, through this process an electric arc is generated between graphitic rods in inert atmosphere leading to produce soot- like product in which fullerene molecules extracted from the soot using suitable solvents [37].

The previous methods were associated with producing fullerene with low yields and there is no temperature controlling zone which is required for graphitization step. To overcome these two limitations, in 1994, Smalley discussed a laser vaporization technique to prepare fullerene from graphite materials using a focused laser beam. This technique involving evaporating carbon atoms and retained it in a

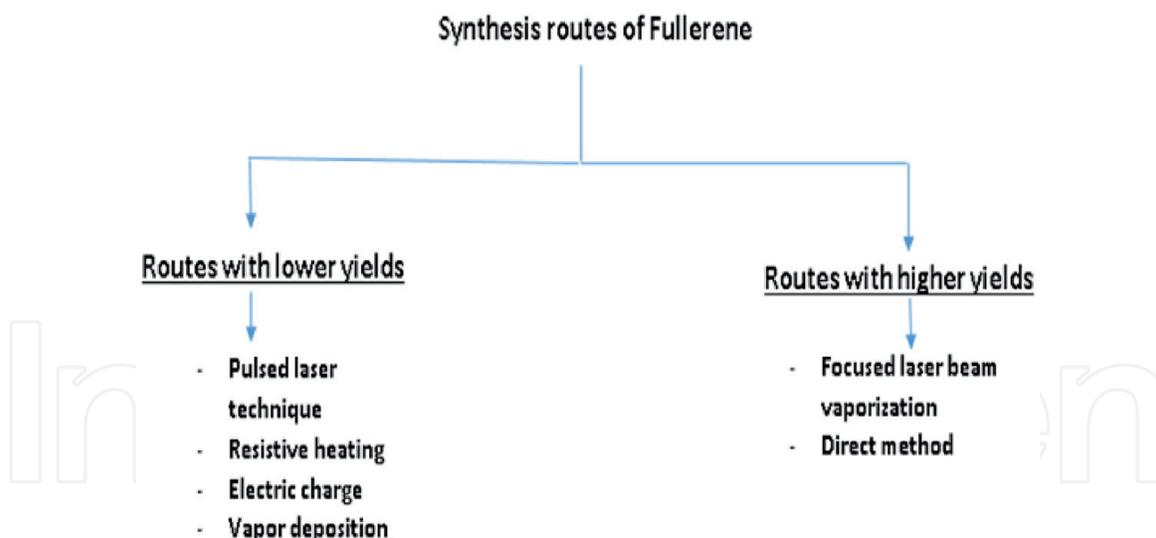


Figure 4.
Some synthesis routes of Fullerene.

temperature- controlled- zone for sufficient time in order to complete the growth and annealing process of the produced structure [38].

Furthermore, another method was reported by Boorm and co-workers in 2001 called the direct method. This method depending on using polycyclic aromatic hydrocarbons with fullerene- like- framework. Through this method fullerene was synthesized directly due to rolling- up of the hydrocarbons structure into fullerene structure via laser irradiation process under flash vacuum pyrolysis conditions [30]. Whereas, in 1993, fullerene has been synthesized in high yields via ablation technique of graphite rod with solar irradiation using solar- furnace. Through this technique graphite was vaporized under the action of direct exposure to high- flux- solar- irradiation. Then, the carbonic vapor was entrained by helium flow and cooled into dark- water- zone to form fullerene structure [39].

Since the discovery of fullerene as an important carbonic allotrope, tremendous development have been made in nanoscience and nanotechnology in order to fill the urgent need for this materials in a wide variety of applications. But, the formation mechanism of the cage- like structure still as a mystery and not well known [36].

One attempt to explain fullerene formation mechanism was reported by Paul and co-workers in 2012. Through their experiment, they depending on the principle of the bottom- up technique to explain the growth mechanism of fullerene by integration with carbon atoms and C_2 using laser irradiation technique. A carbonic target made up from graphite or ^{13}C amorphous carbon with fullerene content exposed to a single laser strike that leads to vaporizing carbonic target into atomic carbon and C_2 while fullerene molecules desorbed into carbonic vapor zone under the action of helium flow. Then an interaction takes place between C_{60} fullerene (98.9% ^{12}C and 1.1% ^{13}C) and enriched ^{13}C carbonic vapor which involves the exchanging of the original ^{12}C atom of fullerene structure with ^{13}C atom of carbonic vapor [40]. Each ingesting of ^{13}C atom into fullerene structure occurs parallel with ejecting ^{12}C atom from its structure and this interaction will spurring bond rearrangement with fullerene structure. Then, the produced species leaves clustering zone and undergo to a supersonic expansion step. Hence, different fullerene isomer such as C_{70} can be formed and the ejected ^{12}C atoms may be ingested or exchanged with another fullerene structure [36].

Furthermore, the growth mechanism of fullerene via different techniques that rely on the interaction between carbon atom and C_2 affected by several parameters such as the density of carbonic vaper, exposure time, the flow rate of

inert gas, therefore, there is a possibility of controlling the growth mechanism by these parameters [36].

7. Nanodiamond ND

7.1 History

Recently, nanodiamond ND with its novel structure opened a new path in the creating and developing materials field. Nanodiamond is a new member of carbon- base- nanomaterials consisting nano tetrahedral network [37]. Naturally, nanoparticles of diamond have been found in meteorites as well as they have been found as inclusions in the old crust fragment of the earth [38].

The history of nanodiamond discovery starts since the second half of the last century via several successful and unsuccessful attempts in the synthesis and analysis of nanodiamond ND or ultra-dispersion diamond UDD begins in 1956 by Yu. Ryabinin using dynamic synthesis approach [39]. In 1961, diamond have been detected in a preserved shock compressed graphite in a plane ampoule by P.J.De Carli and co-workers. Then, in 1962, diamond was produced via shock compression using carbon black and graphite as starting material in cylindrical and spherical storage ampoule with up to 2% yields. Later, diamond was synthesized in explosion chamber using graphite, through this process graphite was placed directly into cylindrical charge containing of a troty- hexogen mixture and the charge was enveloped in a water jacket in order to inhibit graphitization process.

During 1963–1965, the effect of explosion conditions on the produced UDD was studied and indicate that the DP cooling as a result of conversion of the potential energy of diamond particles into kinetic energy of the envelope surrounding the charge plays a decisive role in the UDD synthesis [29]. Then, in 1976, Dupon co. used a cylindrical ampoules to produced diamond micropowder in commercial production rates by compressing a mixture made up from graphite and copper with charge. After that several scientific experiment were carried out to produce UDD with high yields using large mass charges. Another attempts were carried out in 1994 by V.V.Danilenko and co-workers to sintering UDD under static conditions [39].

Furthermore, a wide variety of techniques have been reported and employed to prepare micro and nano diamond particles. But on the other hand, the main drawback of most of these techniques are their requirement for high temperature and high pressure conditions, also, it was found that the produced material is a mixture made up from diamond and nan-diamond phases and some procedures leads to precipitate a amorphous carbon films at the grain boundaries of the produced nanodiamond [40]. After that, several techniques were suggested to produce nanodiamond at lower temperature and pressure conditions [41].

In this area, many researchers compete to synthesis ND with higher yields using advanced techniques in order to use it for a wide range of applications such as in drug delivery, biotechnology and tissue engineering fields [42].

7.2 Structure and properties

ND have unique properties, for this reason it is attracted the desire and interest of scientists and researchers in the physics and chemistry of nano- materials. It is believed that the structure of ND consisting of single or more diamond crystal surrounding by a shell containing graphenic carbons sp^2C , amorphous diamond

sp³C in addition to surface- state- carbons. The latter made up from chains of trans- polyacetylene TPA and graphene/fullerene fragments. In addition, different functional groups have been found, see **Figure 5** [43].

However, some of the existing sp²carbon and amorphous diamond can be discarded by specific techniques such as thermal oxidation technique [44], while some graphene/fullerene fragments of the shell are an intrinsic components formed through the re-arrangement of the diamond surface. So, it is believed that the collected information about the structure is necessary in order to understand the nature of interaction between ND particles on one side and with other compounds on another side [43]. It is worth mentioning that the shell's constituents will have a great influence on the properties of ND particles with smaller sizes [45].

In the last decades, it was supposed that the shape of ND particles were quasi-spherical, but the modern microscope confirmed they are a polyhedral with distinct faceting shape and about half of the presented carbon atoms in ND are located at their surfaces. Hence, ND particles have bonding ability with different functional groups that effecting on its stability [46]. ND particles were required for a wide variety of applications, in lubricant industry, composites, medical therapy and others, this is due to the nature of their surface chemistry which depending on the chemical history of the material and the synthetic process [47]. For example, oxygen- rich- functional groups like hydroxyl, lactone and carboxyl have been found on the ND particle's surface produced via detonation technique [48]. Several efforts were reported about the surface modification process by functionalization with different groups which regarded as an effective strategy for reducing the size of ND aggregations. For example, functionalization with long chains of alkyl leads to reducing their aggregation size and enhancing their dispersion ability in organic solvents. Similar effects have been achieved via functionalization with boran. Furthermore, functionalization with Lysine molecules showed better water dispersion ability comparing carboxylic- ND [48].

Another type of ND is called hydrogenated ND, in which the surface of nanoparticles were wholly hydrogenated, hydrogenation process involves of linking a hydrogen atom with carbonic specie, then hydrogen atom will take its active role in etching of ND particles such as graphenic/fullerene carbon sp² C or amorphous carbon, discarding oxygen-rich-groups as well as forming C-H bonds at ND surface [47, 49]. In fact all these benefits make this type more attracted for the most critical applications.

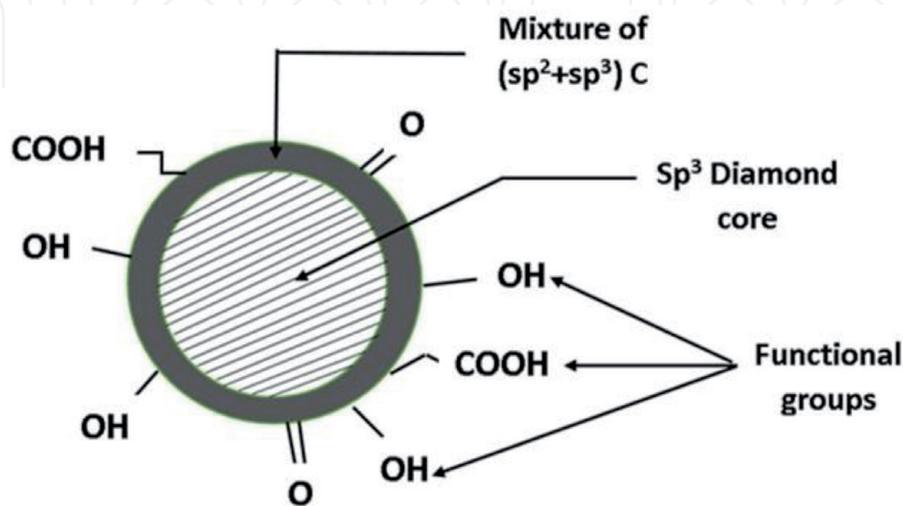


Figure 5.
Representation of ND structure.

7.3 Synthesis routes

Graphite is the most stable carbon allotrope at ambient conditions of temperature and pressure. While, diamond formation requires more severe conditions. For example, the conditions for naturally formed diamond are ($>1000^{\circ}\text{C}$) temperature and (4.5–6) Gpa pressure. After diamond formation, the reverse transition to graphite structure will not occur due to the high- energy- barrier for phase transition. Although, graphite is the favored allotrope from thermodynamic point of view, but about 0.4 eV energy barrier must be overcome to transform sp^2 C structure to sp^3 C structure and this fact makes diamond as a metastable allotrope. But the transition kinetic to graphitic structure is not allowed [50].

Nowadays, a wide variety synthetic techniques for ND are available. In the following a brief description of the main techniques.

1. Detonation technique.
2. Chemical Vapor technique.
3. Laser technique.

7.3.1 Detonation technique

In detonation technique an explosives with a negative- oxygen- balance and a source for carbon atoms (graphite or molecules driven from the used explosive materials) were placed inside the detonation chamber which is a closed metallic chamber. The driving force for diamond formation obtained from the explosion energy. During detonation, carbon atoms released and then condensed and transform into nanoclusters of crystals. In association with the generated high pressure and temperature, a crystallization of nanoclusters will occur and ND particles will form and grow into aggregations with size about (4–5) nm. The used coolant agent can exist as gas (dry detonation) or as water (wet detonation) [38, 39, 49].

The final produced soot-like material is usually consisting of diamond core with sp^3 C surrounded by sp^2 C. The main advantages of this technique is its ability to produce ND with wide range of particle size, structure and surface- functional- groups these features makes this technique useful for a wide variety of applications as polymer filler for nanocomposites, polishing and coating purposes and others. While on the other side, the main associated disadvantage is the contamination of the produced ND with fragments from chamber wall [49]. So in order to eliminate the unwanted sp^2 C, to discard metal contamination and to breakup ND aggregations, a post- treatment step will be an essential to produce pure, de- aggregated ND with sp^3 C [39, 49].

Formation mechanism of detonation ND has been proposed by Danilenko. He suggested that the required temperature to form liquid carbon from its nano scale is lower than that from its bulk scale. So, he is suggested that the liquid carbon region is shifted to low- temperature region while the stability region of ND is shifted to high- pressure. This situation leads to a homogeneous nucleation of ND in carbon supersaturated vapor region followed by crystallization of the produced carbonic liquid [50].

7.3.2 Chemical vapor deposition technique

Till this day, CVD technique is widely used in the preparation of ND as powder or thin film with a wide range of sizes. The required carbon atoms for ND formation

is derived from the decomposition of gaseous phases (usually methane in hydrogen excess) and a carbon-rich species. During decomposition process, the released carbon atoms were deposited on a silicon substrate covered with a detonation nanodiamond DND acting as a seeding sites for nucleation of ND [51].

For further illustration, several sources of energy can be used to activate the gas phase such as hot filament [52], plasma and flames [53]. Due to decomposition of gas phase, radicals will form and then each two adjacent carbon atoms located at the surface of the used diamond-coat are left with the dangling bonds after hydrogen abstraction by H• radical. After that these bonds will be full with CH₃ radicals then the adjacent carbon atoms will bond together and locked within diamond lattice [54, 55].

The main advantage of this technique is its ability to produce ND particle or ND thin film with a wide range of size (10–200) nm, in addition, to the possibility of controlling on the structure and morphology characteristics of ND. Also there is possibility to produce ND doped with different species that can be inserted within diamond structure through growth process. In fact these possibilities enabled this technique to produce ND with modified electrical and optical properties required for many applications [54, 56].

7.3.3 Laser technique

This technique is one of the most attractive used techniques for synthesis ND in liquid [38]. This technique including directing an intense laser beam on the graphite target immersed in a liquid medium, usually water. The directed laser beam with high energy induces target surface melting and turning it into superheated liquid. Due to the highly increased temperatures, a phase explosion will take place and nanodroplets will be formed [57]. At these conditions, the emission of plasma plume with ablation will occur and an extremely high pressure and temperature conditions are created. Then through cooling of the ablation plume with the liquid medium a rapid quenching will take place. In fact this situation of rapid and sudden decreasing in temperature creates the appropriate conditions for carbonic nanodroplets formation within few nanoseconds [49–59].

This technique presents good benefits such as the ability to produce ND with high purity, while the main drawback is the high cost with low production rates [39]. On the other hand, several attempts have been reported to overcome such undesired features one of these attempts is called (Light Hydro- Dynamic Effect) LHDE. This technique used laser beam with higher power cross a fluid with a specific refractive index. The direction of laser beam produces white light flash and generates acoustic waves which leads to form high- power- hydro- shock [39].

This technique produced ND with high yields in association with good controlling on its size and surface functional groups. Moreover, it is found that the produced material possess outstanding thermal property make it suitable for nanocomposites applications require heat dissipation property [58].

7.4 Nanodiamonds at ambient conditions

Nano-sized diamond have been synthesized via different techniques as previously discussed. In spite of the expected stability of the produced material, high-temperature and high- pressure are the main requirements for these techniques. In addition, the produced material is usually consisting sp³ and sp² carbon and some of these techniques leads to produce ND with contaminants which requires additional purification steps and hence the overall cost will be increase. Therefore, several studies have been reported to prepare ND at ambient conditions [60, 61].

Proceeding from the chemical principles, the chemical reaction depending on the energy- materials interaction degree and require specific energy to proceed. Some of these studies suggested the possibility of using ultrasonic irradiation technique as a source for the required energy [60].

So, ultrasonic irradiation technique has been candidate to prepare ND. This technique improves the chemical reaction in solution via production of hole-constituent micro-bubbles [60]. During this process, a liquid media is irradiated with ultrasound and bubbles will be creates and oscillates under the action of the alternating compressive and expansive acoustic waves. Then, these bubbles will grow to a critical size and collapse leading to release an intense- localize energy about (5000 K and 1000 bar) within a very short period of time which is enough for synthesis of nanodiamond particles [61, 62].

The features of this technique were taken by researchers to produce micro and nano diamonds. In 2008, Khachatry and co-workers used graphite organic liquid suspension to synthesis microcrystalline diamond with degree of purity, cubic-structure and size range about (6–9) μm via ultrasound- cavitation process [63].

In 2019, researchers used a suitable method to synthesis nanocrystalline diamond via ultrasound waves. Through their experiment, graphene oxide was synthesized by modified Hummer's method then the prepared GO dispersion is activated by ultrasound waves which impacts its morphology and chemistry leads to produce graphene sheets. On the other hand, the generated shear forces leads to convert some of the produced graphene sheets into graphenic nanoscrolls with Mn2O7 had been inserted within its cavity. After decomposition of the unstable Mn2O7 a localized damage at the nanoscroll structure takes place which then undergoing to self-healing and as a result, ND seeds was formed and warped into nanoclusters of diamond, see **Figures 6** and **7** [62].

Other studies have been shown that the nucleation of ND is preferred inside the structure of carbon nanotubes under the action of surface tension property as a result of the carbon nanostructured curvature [64]. In association of founding some carbonates such as Li_2CO_3 , Na_2CO_3 and K_2CO_3 as inclusions in natural diamond. Kamali and co-workers made their study in 2015 to produce nanocrystalline diamond from lithium- carbonate containing nanostructured carbon by simple heat treatment and at atmospheric pressure. In this study, CNTs produced by electro-chemical process in lithium chlorite melt using graphite material. Through the experiment, lithium ions discharge on the cathode and inserted between the layers of graphene of the graphite structure under the influence of the cathodic which led to initiated enough stress to pulling graphene sheets from graphite structure into the melt and then these sheets will rolling up into CNTs. And after simple oxidation of the produced CNTs at temperatures range (420–550) $^\circ\text{C}$ and at atmospheric pressure, ND was formed, see **Figure 8** [64].

Another methodology was reported by Maia and co-workers in 2015. Their strategy depending on using dynamic compression as a tool for carbon structured transformation process under the action of accumulation of ultra- short laser pulses assisted by the formation of onion-like carbon structure as intermediate phase. Basically, the accumulation of free-electrons with high densities at the grain boundaries of graphite absorbed the applied energy which leads to creation a super excited region and then an ablation takes place followed by the propagation of non- thermal shockwave. After that, heating and thermal equilibrium takes place. In fact, these sequences of effects happened at each strike of laser which leading to destroy the lattice in continuous manner and causes more carbonic order to form. The formation of latter structure considered as intermediate phase with lower energy barrier to allotrope transition while the degree of crystallinity increases at each strike of shockwave [65, 66].

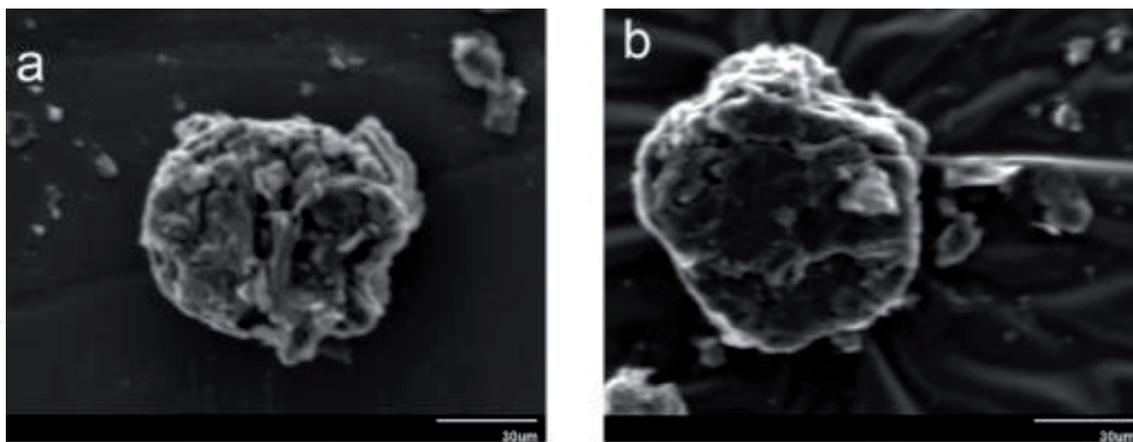


Figure 6.
SEM images of nanodiamond at its cauliflower stage.

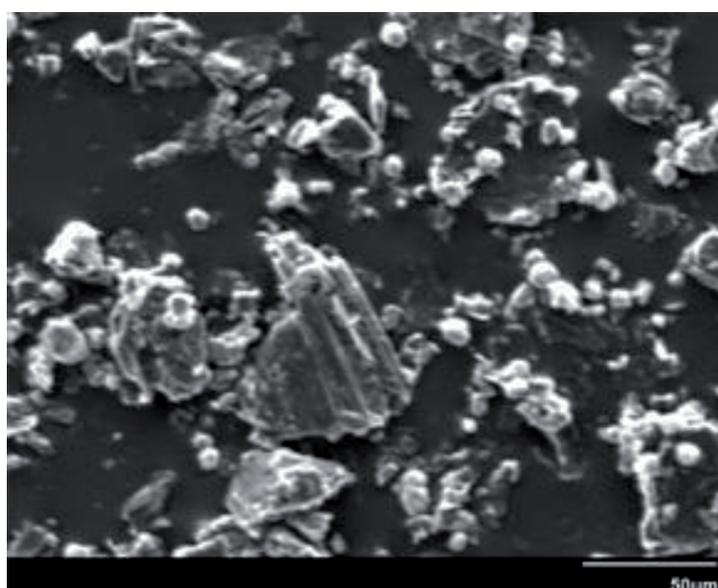


Figure 7.
(a-b) SEM image of Nanodiamond ND.

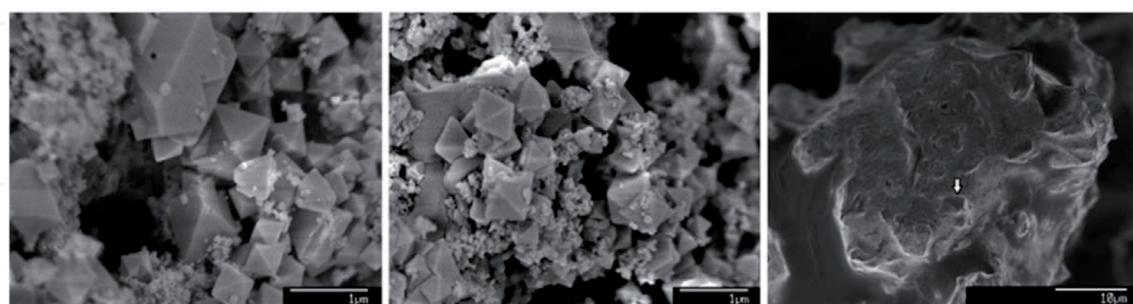


Figure 8.
SEM images of the micro and nano sized diamond particles after heating CNTs to 550°C in air (reuse with permission Royal Society of Chemistry [64]).

8. Drug delivery system

Nanotechnology is the nano-sized materials science, involves materials manipulation at atomic and molecular scale in order to produce materials, systems and devices with unprecedented features. Recently, nanotechnology become the most promising technology in a wide variety of fields, one of these fields is medicine field. In fact, the employment of nanotechnology in medicine field is called

nanomedicine which regarded as a tool enabled doctors to reach the human body at the molecular and cellular levels and treat the damaged tissues [67].

It is believed that this technology will have a great impact on the health care field via its effect on the sickness diagnosing and treating [67, 68]. There are several features of using nanotechnology in medical field, for example, when it is used for drug delivery, this technology will protect drug from degradation within human body before reaching the target also, it is improving drugs absorption into the diseased cells and at the same time it give assurance that there is no any interactions between drugs and the healthy cells [67, 68].

Therefore, nanomedicine is one division of nanotechnology and nanoscience has the ability of treating the diseased and damaged cells or organs within human body at the cellular and molecular levels via nano-devices and nano-structured materials [68]. There are three main sectors within nanomedicine: Nano- diagnosis, which involving detection and analysis of the diseased cell using different devices such as imaging devices. Nano- therapy, this sector involving the direct transfer or delivery of drugs to the diseased cells with the least possible of side effects. And the last one is renovated medicine, which involving fixation and replacement the deteriorated parts within human body using different nano-devices and nanomaterials [67].

In the following we will discuss the role of carbon based- nanomaterials (fullerene and nanodiamond) as a drug delivery systems.

9. Significance of carbon based- nanomaterials in drug delivery

Generally, the suitable choice of nano- drug delivery systems aids to overcome many health issues usually associated with using traditional treatment strategies. For example, in the case of cancer chemotherapy, the traditional strategies leads to several undesired side effects such as suppression of bone marrow, hair loss, gastric and renal damage and other toxicity effects [67].

On the other side, there are many features and reasons related to the nature and structure of nanomaterials make it as an attractive subject for intense bio-studies from one side and as an attractive materials for drug delivery systems from a other side [69, 70]. The most significant features are: their quantum property, their sizes which determine their in vivo and in vitro behavior, their structure and aggregation ability as well as their surface atoms or molecules. In fact, all these features determine their ability for binding, carrying and adsorbing other compounds or in other words these features determine their pharmacology behavior [70–72].

Furthermore, the main characteristics that nanomaterials should have to be use in drug delivery systems are high- solubility, bio- compatibility, bio- availability, bio- distribution and targeting ability, drug incorporation and release ability, their shelf- time, anti- clotting property and bio- degradability [71].

9.1 Fullerene-drug delivery system

Some of the most interesting characteristics of fullerene are their size, electronic configuration, hollow and cage structure, their inertness and surface modification ability that offer the utilization of using fullerene in biological and medical chemistry fields and open new horizons in nanomedicine [73]. The main problems facing the previous possibilities are the insoluble nature in aqueous media with high aggregation tendency [73]. But on the other side, there are several attempts have been done to overcome these problems. One of these attempts involving encapsulation in specific carriers such as calixarenes, micelles and liposomes. Other attempts used chemical functionalization methods with carboxylic acid, polyhydroxyl and

amphiphilic polymers to increase the hydrophilicity property of these structures [73]. Furthermore, fullerene shows a nontoxic behavior which tend to decreasing with increasing surface functional groups, while the circulation and biodistribution property depending on the composition of the existing derivative groups. In addition, the presence of functional groups acts as a flexible interfaces for tuning the required drug delivery and its action besides the size of fullerenes even with their derivatives are still smaller than other types of nanoparticles [73, 74].

Both exohedral fullerene which have additional atoms, ions, or clusters attached its outer spheres structure and endohedral fullerene which have additional atoms, ions, or clusters enclosed within its inner spheres structure, have been employed in nanomedicine field as drug carriers. Endohedral fullerene and its derivatives can be used to deliver atoms or ions in biological systems, for example, metallofullerene can be serve as drug delivery depending on the composition and properties of the trapped metal within its structure [75]. Depending on the type of functional groups, exohedral fullerene can be exist in three main forms. The first one is called surface- derivative fullerene, the biological action of this type is driven from the inherent properties of its structure such as: their size, reactive property and photochemistry property. The candidate application for this type is as antioxidants systems due to its electronegative nature in association with its reaction ability with different radicals. So, this type work as antioxidants radicals' scavenger. Furthermore, surface- derivative fullerene can be used to generate a reactive- oxygen species by light irradiation, so this type is useful as photodynamic therapy for killing cancer cells and other undesired cells [75].

The second type of exohedral fullerene is known as covalently fullerene. In this type, the derivative surface of fullerene is directly connected to the pharmaceutical activated compounds via covalent bonds. This fullerene molecule has unique bio-functions with biological body such as drug release with selective targeting at the same time. For example, C60- paclitaxel fullerene used in lung cancer treatment [76], here the paclitaxel has been conjugated to C60 derivative via hydrolysable- ester- group linker used for slow release of drug to the diseased cells [76]. Furthermore, this type of fullerene has high tendency to attach covalently with different biological relevant like sugar, cholesterol, carbohydrates and others [76].

The third type of exohedral fullerene is called non- covalently fullerene. Here, fullerene and its derivatives tend to form a complex species via a wide variety of interactions. These interactions could be exist as pi-pi interaction, van der Waals interaction, electrostatic interaction, hydrophobic interaction and it could be exist as a hydrogen bonding. An example of using this type of fullerene in nanomedicine is the protease inhabitation of Human Immunodeficiency Virus (HIV) [77] by C60 fullerene of this type. The active catalytic sites of HIV protease enzyme is as a hydrophobic bag with a 1 nm diameter which is very close to the size of C60 molecule. Hence, this fullerene will bind with the active sites and virus inhabitation process will takes place [75].

9.2 Nanodiamond-drug delivery system

Nanodiamonds are one of the most interesting material in nanomedicine have the ability to conjugate with different drug molecules [48]. This fact is born out of their unique structure and properties. High surface flexibility, small size, high surface area and functionalization ability with different molecules besides their biocompatibility which is more than that of other carbon based- nanomaterials like fullerene and carbon nanotubes. All these features make ND as an attractive tool for both in vivo and in vitro applications [38, 50, 78, 79]. Conversely, there are many concerns and challenges related to their structure and nature toward their

interactions with the living cells. Therefore, this situation requires many in- depth studies about the interaction nature between ND particles and the living cells. For example, some types of ND have a strong tendency to aggregate in specific medium which hindering and limiting their applications [48]. In fact, this aggregation tendency is related upon some synthesis techniques leads to produce ND particles with high dangling bonds on their surface such as detonation technique [48]. Hence the free electrons of the surfaces tend to form many functional groups and then these functional groups tend to form covalent bonds with the primary particle forming core- aggregates [48]. On the other side, the existing of sp²C around ND leads to bond these particles together into core aggregate [48].

Several methodologies have been carried for disintegration process, the most attractive one is the beads assisted sonication method which involving the double actions of shear force (induced by using zirconia beads) and cavitation effect (induced by ultrasound waves). The results shows colloid stability for one year after sonication for one hour [80]. While surface functionalization process has been recommended as an active way to reduce the aggregation size of ND. In fact there are several surface functionalization techniques, one of them involving generating specific surface radicals which then will act as a substrate used for synthesis of ND with carboxylic acid and dicarboxylic acid functionalization [48].

From a biocompatibility point of view, several studies have been demonstrated that ND toxicity can be varied and it is affected by surface chemistry of ND, cell- line type and the composition of treatment medium. In this field, the mitochondrial activity and the inflammatory activity of the cell have been used as toxicity indicator. So depending on these keys and the results of many clinical experiments, it was found that there is no manifestation of toxicity with ND dose (100 µg/ml concentration) after 24 hour of incubation period [81]. In addition, ND with high loading capacity, payload with high concentrations is allowed via using less delivery agents in association with the ability of releasing the cargo from the carrier in controlled manner, these two important features of ND developing the bio- applications of them either for small molecules delivery or for bio- technology product delivery [48].

In 2007, the suitability of ND particles as a delivery agent of doxorubicin hydrochloride (DOX) was studied by H. Huang et al. [81]. The study was based on the rationale that the surface carboxylic and hydroxylic groups of ND can interacts with the amine groups of DOX via ionic- forces when dispersing them in aqueous medium. The surface loading of DOX on ND particles was increased from 0.5 to 10 wt% via addition of 1% solution of sodium chloride to their aqueous dispersion, and the removal of salt favored the release of DOX. ND particles loaded with DOX were recommended to assemble in the form of loose- clusters, such that a certain amount of DOX adsorbed on the ND particle's surface resides within the cavity of the cluster [81].

This methodology of drug- entrapment in loose aggregates of ND particles could provide a feature by minimizing the systemic adverse effects of the naked- DOX. Thus, ND-based delivery systems could overcome the problem to the use of high concentrations of chemotherapeutic drugs in cancer treatments. In addition, the lower levels of cytotoxicity of the ND-DOX composites in mouse macrophages and human colorectal cancer cells compared with bare DOX in a 48-hour period could be beneficial in sustained drug release [81]. The potential of using ND particles as a targeted protein-delivery- vehicle was investigated in a pH-dependent system. By means of the physical- adsorption, ND particles achieved a considerable high surface loadings of bovine insulin about 80% in pH-neutral water with a weight ratio of 1:4 of insulin:ND. Also, the aggregation properties of the insulin improved after interacting with ND particles. This propose that ND particles have the ability to

facilitate the formation of a uniform-sized complex. Further, the release of insulin from the ND particle's surface was about 20- times higher when at a pH of about 10.5 than when in a neutral pH medium. Another advantage of using ND particles is the viability of cells, this effect had been observed with sodium hydroxide treated ND-insulin higher than what observed in neutral pH treated ND-insulin. Hence, the inherent and enhanced characteristics of ND particles make them as an active tool in drug delivery systems [48].

10. Conclusion

In summary, fullerene and nanodiamonds have been studied for drug delivery applications. Fullerenes and nanodiamonds are attractive allotropes in the carbon nanomaterials family. They can be synthesized with attractive properties in higher purity, higher surface homogeneity, and different surface functionalization and in controlled sizes that make them essential in nanomedicine fields. Utilization of fullerenes and nanodiamonds in drug delivery systems show higher advantages with enhanced targeted delivery and controlled drug release ability than other traditional strategies. But on the other side, further in-depth research about toxicity concerns are necessary in order to achieve the full advantages of utilization these nanomaterials in human body.

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