Functionalized Carbon Nanomaterial for Artificial Bone Replacement as Filler Material

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1 Introduction

The human race is witnessing lots of remarkable advancement in the field of Science and Engineering. Nanotechnology is one of that remarkable advancement accomplished by mankind. According to Dr. Richard Smalley (Late), "Nanotechnology is the art and science of building stuff that does stuff at the scale of nanometer". In general, nanotechnology is specifically an engineering of human-made structures starting from a range of 1–100 μm [1]. It is an interdisciplinary field that comprises biomedical engineering, chemical engineering, chemistry, physics, and material and particle science. At present more than 600 products available in the market globally which uses nanomaterials for their products [2]. Furthermore, United States National Institute of Health has referred the assistance of nanotechnology for systems like diagnosis, treatment, monitoring, and control of biological as nanomedicine [3]. Nanotechnology is continuously promoting positive impacts on healthcare and making life more convenient than ever imagined

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before. In addition, nanomaterials are significantly getting attention for the applications related to bone engineering as it holds properties that have the strength similar to natural bone. However, construction of artificial bone with uniqueness, identical properties likewise natural bone is a strenuous task. Therefore, most of the researchers rely on nanotechnology and nanomaterials when it comes to constructing artificial bone.

Carbon nanomaterial is one of the remarkable outcomes from nanotechnology. Carbon-based nanomaterial considered more accentuated and promising when it comes to the application based on the bio-medical field. Carbon nanomaterials are categorized as low-dimensional materials, having sp^2 and sp^3 carbon atoms arranged into a continuous network [4]. Since the discovery of the first well-known carbon nanomaterial i.e. fullerene, have significantly aroused the interest around the globe. Carbon nanomaterial holds tunable physical, chemical, electrical, optical, thermal, and mechanical properties, and its related composite provides remarkable usage in sensors, biomedicine, electrodes, electrocatalysis, energy storage as well as conversion. One of the main features of carbon nanomaterial i.e. biocompatibility [5] increased its demand in the field of bio-medical. Carbon nanomaterials are one of the highlighted topics when it comes to the modern medical field. Out of all carbon-based nanomaterials, carbon nanotubes (CNTs) are considered more suitable and promising for applications related to bio-medical e.g. nano-electronic bio-sensing [6], drug delivery [7], and bone tissue engineering [8].

Carbon nanomaterials are dimensionally categorized as fullerene (0-D), carbon nanotubes (1-D) and graphene (2-D). The origin of carbon nanotubes is from the synthetic carbon allotropes and categorized as sp^2 hybridized network of carbon atoms. At first, Sumio Iijima discovered the CNTs structure as helical microtubules of graphitic carbon in the year 1991 through an arc discharge process that was initially designed for fullerene production [9]. Since the discovery, significant researches took place on this extraordinary nanomaterial. Theoretically, carbon nanotubes synthesized by rolling the sheets of graphene with connecting hexagonal rings seamlessly. Vapour phase growth, corona-discharge, catalyst-supported growth, hydrocarbons pyrolysis and laser ablation are the conventional techniques for carbon nanotubes synthesis [10]. At present, plasma-enhanced chemical vapour deposition and chemical vapour deposition are the most recent synthesis methods for carbon nanotubes [11] (Fig. 1).

Carbon nanotubes are categorized generally as single-walled carbon nanotubes (SWNTs), multi-walled carbon nanotubes (MWNTs) and double-walled carbon nanotubes (DWNTs) [12]. Major making of MWNTs and DWNTs were testified via arc discharge process. And SWNTs synthesis was primarily described independently by Iijima and Ichihashi (Tokyo, Japan), and Bethune's IBM group (California, USA) in the year 1993 [13]. Furthermore, compared to all other inorganic nanoparticles in which heavy toxic metals are present, for example, quantum dots (Qds); CNTs are mainly composed of pure atoms of carbon that are relatively non-toxic [14]. Thus, carbon nanotubes direct use is restricted due to its biological toxicity in application related to bio-medical. The toxicity of carbon nanotubes are affected due to the metal impurities; shape, structure and length of the

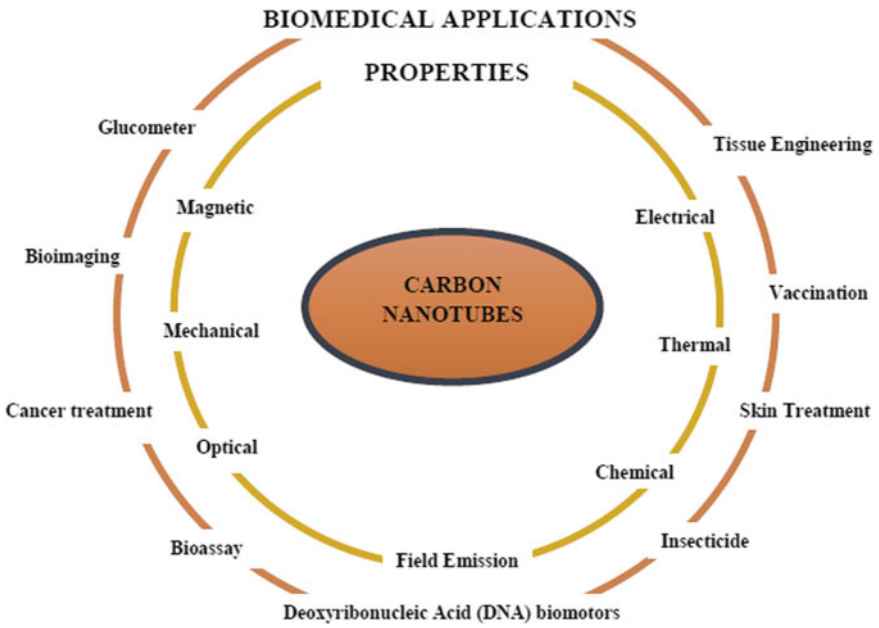

Fig. 1 Properties and biomedical applications of carbon nanotubes

tubes; layers thickness; aggregation degree; etc. Moreover, key factors for the toxicity of nanotubes include metal catalyst residual; length and hydrophobic surface of carbon nanotubes [15]. The metals catalyst (Fe, Ni etc.) containments in nanotubes support free radical generation in cells and are introduced through the process of synthesis and purification which lead to cytotoxicity [16]. In addition, experimental results as evidence clearly show that shorter length of nanotubes, i.e. less than 200 nm, compared to normal length (up to tens of micrometres) is more suitable to enter the cells [14].

Furthermore, synthesized carbon nanotubes hold hydrophobic surface, and are insoluble in many aqueous solutions. Due to the strong hydrophobic interactions, carbon nanotubes stick together and form as bundles that later make it difficult to apart. The formation of bundles trend makes the processability of carbon nanotubes complicated as well extremely difficult their integration into aqueous based biological media, which considered essential for the applications based on bio-medical [17]. Biological behaviours of the tubes precisely based on the surface chemistry. Furthermore, the experimental study proved that raw carbon nanotubes avoid the growth of ovary cells in Chinese hamster [14]. Table 1; listed the theoretical and experimentally calculated properties of carbon nanotubes.

Biomedical refers to the living system; therefore, modification of carbon-based nanomaterial is an important step, like biocompatibility and bioactivity, can be enhanced with chemically modified carbon nanotubes [18]. The modification of carbon nanomaterial includes surface modification as well as chemical alteration

Table 1 Properties of carbon nanotubes (CNTs)

Parameters	Carbon Nanotubes	References
Lattice structure	Nanotubes: ropes, tubes organized in the triangular lattice by parameters of a = 1.7 nm, tube-tube = 0.314	[78]
Elastic modulus	SWNTs and MWNTs ~1 and 1.28 terapascal (TPa), respectively	[79]
Maximum tensile strength	100 gigapascal (GPa), approximately	[79]
Specific gravity	0.8–1.8 gcc^{-1} (theoretical)	[78]
Thermal expansion	Insignificant (theoretical)	[78]
Thermal conductivity	2000 W/m/K	[79]
Oxidation in air	Greater than 700 °C	[78]

steps. Furthermore, stable dispersion helpful for biomedical use, for example, functionalized graphene make it easier for chemotherapeutics and image agent delivery [19]. At present, a countless number of natural and synthetic biopolymers and bio-ceramics are being used for designing artificial bone prosthetic but their usage remained until laboratory. Therefore, designing an artificial bone prosthetic that holds similar properties to that of human bones is a challenging task for the researchers. Furthermore, researchers keeping in mind of getting the radical benefit of nano-technology, nano-materials scaffolds and cell-based biomaterials for constructing artificial bone [20].

2 Bone Structure and Mechanics

Bone is the primary component of the skeletal structure and varies from the connective tissues due to the properties of rigidity and hardness. These properties help the skeleton to keep the shape of the body, cover the main organs, as well as transfer force of muscular contraction at the time of movement [21]. Bones are actually made of the fibrous protein collagen and soak with calcium phosphate like mineral [22]. The content of mineral serves as a reservoir for ions, more generally calcium as human body stored approximately 99% of calcium, which helps in circulating extracellular fluid composition [21]. In addition, bone contains water too, and it is very vital according to mechanical perspective. The organic matrix of the bone composed of collagen and non-collagenous proteins, 90 and 10% respectively [23]. In fact, the collagen proteins especially form-I act as storage for hydroxyapatite, and the mineral phase helps to generate the rigidity of the skeletal structure. However, according to mechanical perspective, bone is considered as an aeolotropic and non-homogeneous material. Furthermore, spongy and cortical bones can be assumed as an orthotropic having 9 and 5 independent material constants, respectively. Bone

is possibly imagined as a linear elastic material with significant viscoelastic effects, in terms of the physiological range of loading [24]. Bone is stronger in compression and retaining higher Young's moduli of elasticity [25].

State to the term composite and structure of the bone; it proves that bone is a composite material. Moreover, considering bone as bio-composite, the hierarchical structure is seen at various level. For example, at microstructural level, cortical bone shows osteon (large hollow fibers with an outer diameter of 200–250 μm) fibers which are made up of concentric lamellae and pores. The fibers are comprised of hydroxyapatite mineral and collagen at nano level [26].

Bone is an internal part of the body and is surrounded by cells entire life. Because of having no-expendable nature, the process of resorption and formation for every bone take place at the surface compared to soft biological tissue which can have growth at both interstitials as well as oppositional. Bone is holding varies values of porosity and it mainly depends on bones macrostructure as it has a porous structure. However at the level of macroscopic, cortical and cancellous are two types of bone structure. Cortical bone (compact) covers 80% of the mass in a mature human and is mainly in charge of the protective function of the skeleton [27]. Osteon is a large hollow cylinder and a primary structural unit of compact bone. However, the spongy bone which is a network of narrow rods and plates of calcified bone tissue. This calcified bone tissue is known as trabeculae, covered by the bone marrow. The function of bone marrow is to provide nutrients and discard disposal for the bone cells.

In comparison with cortical bone, the content of mineralization in spongy bone is less. However, experimental studies as evidence show that spongy bone is significantly active in remodelling compared to cortical bone [28]. Furthermore, the primary cellular elements of the bone are osteoclast, osteoblast, osteocytes and bone lining [29]. Osteoblasts and osteoclasts origin are different for nurturing and categorize as temporary cells because of short life length [30].

3 History of Artificial Organ

An artificial organ is a human developed device that is an alternative to natural organ and holding bit identical but not exactly similar properties. The function of developing such devices is to make the life of patient's as convenient as possible. Referred to artificial organ definition, the device is not required to attach to any sources like filling or chemical processing units. Any kind of stationary resources, chemical refilling, exchanging of fillers, attached to the device will not categorize under the artificial organ. For example, dialysis machine, an extraordinary technology to support kidney patient's life is not an artificial organ. However, developing and installing an artificial organ is significantly expensive, and required years of experimental researches compared to the natural organ. The experiments for artificial organs mostly conduct on animals or people who are close to death. As a matter of fact, the word artificial organ rarely heard because mostly it refers to as the

replacement of human or animal bones and/or joints. At present, an immense number of artificial organs has been implanted with a high range of success. Some of the remarkable studies on different types of artificial organs have been done by scientist all around the world which include brain pacemakers, cardia, corporta cavernosa, ear (cochlear implant), eye (visual prosthetic), heart, limbs, liver, lungs, bladder, ovaries and many more [31].

The first-ever bone defect treatment was trephined prehistoric skull. However, in the year 1668, a Dutch surgeon Job van Meek'ren named himself first for operating a successful bone defect treatment. He used a dog skull to fill the defect of a soldier's cranium which was taken off after 2 years on soldier's wish. Furthermore, in the scientific era, the interest on osteogenesis and bone transplantation was begun in the year 1739 by Du Hammel. But significant numbers of patients with autogenous bone transplantation were already recorded 200 years earlier [32]. Some of the successful artificial organ transplantation is listed below (cited from 33):

- In the year 1857, Eduard Zirm conducted first successful cornea transplantation (Czech Republic).
- In the year 1954, Joseph Murray operated first successful kidney transplantation (Boston, Massachusetts).
- In the year 1966, Richard Lillehei and William Kelly named themselves first for successful pancreas transplant (Minneapolis, USA).
- In the year 1967, Christiaan Barnard operated first heart transplant successfully (Cape Town, SA).

Moreover, bone transplant referred to fix fractures and joints and to treat skeletal defects. However, there are possible side effects for the transplantation of autogenous bone material like the surgical cut on the skin, low strength bone of donors, and inclined postoperative morbidity. As a matter of fact, not only the amount of autogenous bone is limited but also bone graft has insignificant properties too, like mechanical, biological and physiological [32]. The bone transplants or implants are classified into four classes as:

- Autograft: Engraftment of organs within one individual [33].
- Isograft: Transplantation of organs between genetically similar individuals [34].
- Allograft: Engraftment of organs of genetical individuals of the same species [35]
- Xenograft: Engraftment of organs of individuals of dissimilar species [36].

For bone treatment, two well-known procedures are autograft and allografts in the field of orthopaedic. Due to the limited donors, disease transfer (hepatitis), structural problems, pain etc. [37], autograft and allograft methods are no longer preferred and replaced by artificial bone replacement. Table 2; illustrate the tensile strength, elastic modulus, and ultimate strain of the human bone tissue.

As a matter of fact, strength itself not considered enough for artificial bones to fully integrate with natural bones. In order to compete with natural bone, there are

Table 2 Human bone mechanical properties

Tissue	Tensile strength (MPa)	Elastic modulus (GPa)	Ultimate strain (%)	References
Cortical bone (longitudinally)	130	12.0	3	[80]
Cortical bone (transverse)	60	13.4	1	[80]
Cancellous bone	2	0.39	2.5	[80]

certain characteristics that an artificial bone requires which include good handling, suitable mechanical capability and excellent bio-degradability and bone- regeneration [38].

3.1 Artificial Bone Materials

Biomaterials mainly used to construct devices that are associated with the biological system to co-exist for long-lasting use with limited chance of failures. In 1981, Williams express biomaterials as "*non-viable materials with the application of making medical devices, intended to associate with the biological system*" [39]. For the past few years, the demand for biomaterials has rapidly increased. In the USA, biomaterial industry is generating more than $300 billion annually, and it kept inclining [40]. For many years' medical specialists have been working on finding a substitute for the treatment related to bones like bone repair or replacements. In past, a substance like leather, metals (gold, silver and platinum), bones from other species for direct transplant had utilized for bone repairing treatment. However, alternative materials for bones are categorized as natural and artificial (chemical composition) depending on the source of origin. Natural materials have some remarkable advantages, and due to that popularly used. Additionally, chitosan, collagen, fibrin, and chitin are named as natural materials [39]. And artificial materials are further divided into metal, ceramic, polymer, composites and biological origin substances [40]. Based on host reaction, biomaterials classified as:

- Bio-tolerant: It is in the body, and mainly surrounded by the fibrous membrane, for example, bone cement.
- Bio-inert: These biomaterials are not associated or interact when exposing to biological tissues, for example, titanium oxide.
- Bio-active: These biomaterials integrate with the bone, for example, hydroxyapatite.
- Bio-resorbable: These biomaterials indulge in the bone, for example, calcium.

Furthermore, features such as biocompatibility, elasticity, toughness, corrosion, fatigue resistance and allergic diathesis are vital in bone surgery [41].

4 Carbon Nanomaterials

Carbon nanomaterial is one of the remarkable outcomes from nanotechnology. Carbon nanomaterials are categorized as low-dimensional materials, having sp^2 and sp^3 carbon atoms arranged into a continuous network [4]. Since the discovery of the first well-known carbon nanomaterial in the year 1985 by Sean O'Brien, Richard Smalley, Robert Curl, Harry Kroto, and James Heath, i.e. fullerene, have significantly aroused the public's interest. Carbon nanomaterial tunable physical, chemical, electrical, optical, thermal, and mechanical properties and its related composite provide remarkable usage in sensors, biomedicine, electrodes, electrocatalysis, energy storage as well as conversion. One of the main feature of carbon nanomaterial i.e. biocompatibility [5] that increased its demand in the field of bio-medical. Out of all carbon-based nanomaterials, carbon nanotubes (CNT) consider more suitable and promising for applications related to bio-medical e.g. nano-electronic bio-sensing [6], drug delivery [7], and bone tissue engineering [8].

5 Carbon Nanotubes

1991, an exciting year for carbon science as Sumio Iijima of Nippon Electric Company (NEC) discovered a thin material identical as needle under an electron microscope while analyzing carbon nanomaterial, and named it carbon nanotubes [42]. In the same year, the scientist made the availability of fullerene as a compound too. However, fullerene was first-ever discovered in the year 1985 by researchers from the University of Houston and University of Sussex. Due to the identical shape of this element to football holding thirty-two faces, fullerene was first named as Buckminster-fullerene or Bucky-ball [43]. Carbon nanotubes display as one dimensional with the tubular structure, resemblance to rolled G nano-sheets with minute nanometer thickness. Initially, carbon nanotubes were discovered as multi-walled carbon nanotubes (MWNTs), and later as single-walled carbon nanotubes (SWNTs). Earlier applying electric discharge, laser ablation, and similar techniques used for the synthesis of fullerene but with the addition of some catalyst made the availability of carbon nanotubes in bulk form. CNTs generally have the diameter similar to fullerenes i.e. 1 nm but 1000 time longer than fullerene. These tubes even referred as macromolecules, poly disperses in size and having a molecular weight of 1,000,000 Daltons [44]. Table 3; list the discoveries and development of carbon nanomaterials, mainly carbon nanotubes:

In addition, carbon nanotubes have been studied extensively by researchers due to its promising properties [4] such as electrical, mechanical, conductivity, and chemical which help to assist in the application like bio-sensors, nano-oscillators, drug delivery systems or pure structural components in nano-devices [45].

Table 3 Discoveries and developments of carbon nanotubes (CNTs)

Year	Discovery	References
1889	Discovered carbon filaments (thermal decomposition of gaseous hydrocarbons)	[81]
1890 & 1903	Hydrocarbon (thermal decomposition), results in production of carbon-fibers	[82, 83]
1939	Transmission electron microscopy (TEM) became commercialized which help to research in-depth of carbon fibers	[83]
1952	TEM evidence was printed which display the nano sized diameter of hollow graphitic carbon fiber	[10, 84]
1958	Carbon fibers of bamboo texture were discovered with the help of electron diffraction	[83]
1976	Technique of vapor growth generated carbon fibers	[85]
1979	Arc discharge method synthesized hollow carbon fibers	[86, 87]
1987	In USA, graphitic (hollow carbon fibrils) patent were published	[83]
1991	Arc discharge synthesized carbon nanotubes, and brought into hot spot under scientific society.	[10]
1992	Discovered SWNTs	[46]
1993	Iron catalyst was used to manufacture single walled carbon nanotubes; Cobalt catalyst were used to produced SWNTs	[83]
2004	Templates were applied for carbon micro tubes synthesis	[88]
2007	Carbon nano-buds were manufactured	[83]

Carbon nanotubes properties lead them to applications related to bio-medical. SWNTs and MWNTs consider more suitable for bio-medical applications. Extensive researches have been particularly done on both SWNTs and MWNTs.

5.1 Structure and Properties of Carbon Nanotubes

5.1.1 Single-Walled Carbon Nanotubes (SWNTs)

Single-walled carbon nanotubes (SWNTs), manufactured in 1993 [46], having a diameter and length range from 1 to 7 nm and 20 to 40 nm, respectively [45]. This carbon nanotube type has generated some remarkable properties as well as the capability to apply successfully in a wide number of fields. SWNTs described as a single layer of a graphite crystal, rolled up into a continuous cylinder and capped with hemisphere (carbon rings in hexagonal and pentagonal) at both sides [46]. Since SWNTs hold some impressive properties, therefore, the synthesis of SWNTs has significantly become a matter of global studies. At present, many methods have been designed for the synthesis of SWNTs but electric arc discharge, laser ablation, and catalytic chemical vapour deposition are popular among all [47]. Catalytic chemical vapour deposition abbreviated as CCVD method generates a significant

amount of SWNTs at the economic cost compared to all other methods [46]. Moreover, in the market, the vastest method used is laser ablation for SWNTs [48].

5.1.2 Multi-walled Carbon Nanotubes (MWNTs)

In 1952, Radushkevich and Lukyanovich were the original discoverers of MWNTs. Thus, the present carbon nanotube boom in material science without any doubt was instigated by Sumio Iijima in 1991 [49]. Multi-walled carbon nanotubes (MWNTs), extended hollow cylinder, are composed of sp^2 carbon with a diameter range from 2 to 100 nm and growing length up to 10 microns as well as aspect ratio ranges from 10 to 10 million. However, the thickness of MWNTs's wall along the axis remains constant and inner channel is straight. The ends of MWNTs covered by half fullerene spheres due to the channel which is not accessible directly from the outer side but by expanding the nanotube it can be accessed, for example, oxidation, milling or ion beam treatment [50]. However, based on larger diameter and Raman spectrum of MWNTs, clearly differentiate them from SWNTs and double walled CNTs [51]. The techniques to manufacture MWNTs and SWNTs are generally same. Likewise, SWNTs synthesis, a wide variety of methods has been discovered for MWNTs synthesis but the well-known are catalytic chemical vapour deposition, arc discharge, and laser ablation. Likewise, SWNTs, catalytic chemical vapour deposition is the most efficient and most widely used process (Table 4).

Table 4 Single-walled and multi walled CNTs comparison

Single-walled carbon nanotube (SWNTs)	Multi-walled carbon nanotubes (MWNTs)	References
Mono-layer of graphene	Several layers of graphene	[89]
The catalyst is not optional for synthesis	For the synthesis catalyst not required	[79]
Appropriate control over growth as well as on atmospheric condition is compulsory for bulk synthesis	Bulk synthesis is convenient	[90]
Lack of purity	Negligible impurity	[79,90]
Chance of defect is higher at the time of functionalization	Chance of defect is limited but if occurred, it is a challenging task to improve	[90]
Convenient for characterization and evaluation	Holds a very complex structure	[79, 90]
Comparatively flexible and easy to twist	Difficult to be twisted	[90]

5.2 *Synthesis of Carbon Nanotubes*

Carbon nanotubes can be manufactured by a range of methods but well-known include laser ablation, arc discharge, and chemical vapour deposition. Processes like laser ablation, arc discharge and chemical vapour discharge are fallen under the category of physical and chemical processes, respectively [52]. In the process of laser ablation, high power laser is used which helps to vaporize graphite source combined with a metal catalyst. Since graphite contains carbon that transforms large numbers of single-walled carbon nanotubes (SWNTs) on the metal catalyst [53]. And in arc discharge method, high quality but limited quantities of SWNTs and MWNTs are manufactured by introducing electric discharge from the electrode (carbon-based). However, in chemical vapour deposition (CVD), carbon nanotubes are produced in a chamber by reacting hydrocarbons (for example CH_4) with an appropriate metal catalyst [48]. All of these methods come with advantages and limitations. Some of them listed in Table 5 and Fig. 2.

6 Functionalization of Carbon Nanomaterials

Carbon nanomaterials, fullerenes, graphene and carbon nanotubes (SWNTs, MWNTs & DWNTs), in organic (especially in an aqueous solvent) are poorly soluble. Like, carbon nanotubes stick together and from as bundles due to strong

Table 5 Carbon nanotubes (CNTs) synthesis method

Synthesis methods	Advantages	Disadvantages	References
Chemical-vapor deposition (CVD)	Cost-efficient; scalability; continuous operation process; low operating temperature around 500–800 °C; diameter can be adjusted	Lack of quality i.e. Wall structure contains significant defects and deposits of carbonaceous contamination; a combination of SWNTs and MWNTs	[79, 91]
Arc-discharge (AR)	Simplicity and versatility on the basis of carbon-based material and catalyst; better quality nanotubes produce; minor defects; economical process	Significant consumption of energy; lack of capability for industrial up-scaling; high temperature required (>1700 °C); shorter length of CNTs produced	[10, 73]
Laser ablation (LA)	Synthesis at room temperature; generate high purity and yield of tubes	Purification of the crude product is must; method restricts till laboratory scale; expensive process	[79, 73]

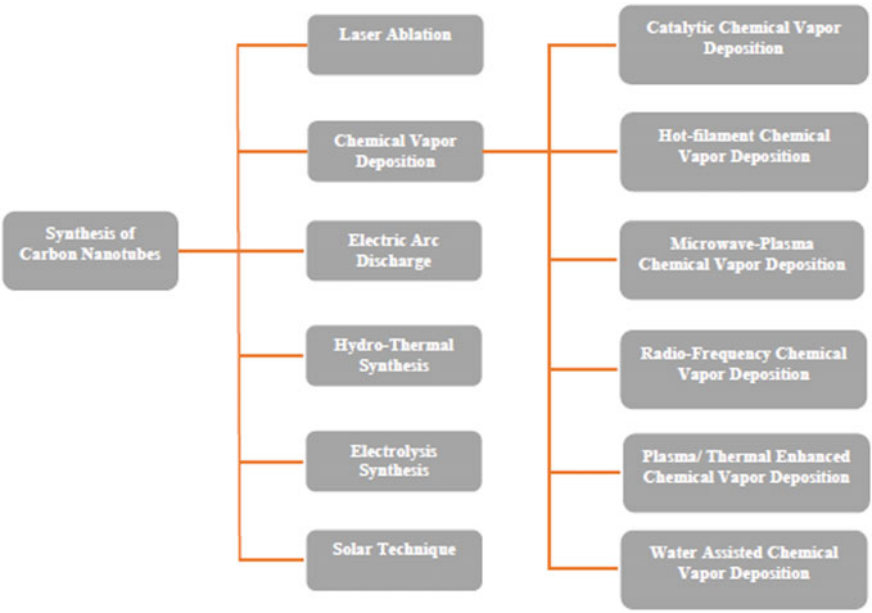

Fig. 2 Synthesis approaches of carbon nanotubes

hydrophobic interactions which later make it difficult to apart. The formation of bundles trend makes the processability of carbon nanomaterials complex and challenging their integration into aqueous based biological media, which considered essential for the applications related to bio-medical [17]. Therefore, functionalization of carbon nanomaterials is important in order to attain their remarkable strengths. As a result, a significant part of the current journals on carbon nanomaterials has an emphasis on improving their solubilization and dispersion using functionalization methods. In fact, massive range of applications in many fields has opened through functionalized carbon nanomaterials, particularly carbon nanotubes and graphene because of their extraordinary properties like lightweight, significant aspect ratio, and electrical conductivity, as well as mechanical, thermal strength. Furthermore, carbon nanomaterials uses have become applicable in many fields because of the modification of its surfaces. The exceptional physiochemical properties of functionalized carbon nanomaterials have been used for anti-viral drug development, energy, treatment for cancer, applications for biotechnological, and aerospace. Moreover, theoretical work has also been done to understand as well as optimize functionalization. On the other hand, non-functionalized carbon nanomaterials carry limitations like the capability to generate stable bundles/aggregates due to highly significant interactions, e.g. van der Waals force, strong π–π stacking. Consequences of the aggregation bring undesirable changes, like affect the aspect ratio plus declines the nanocomposites properties. Therefore, stable dispersion and functionalized role are vital in order to attain better nanomaterial support system.

The functionalization of nanomaterials with the mandatory moieties relies on the base material chemistry. And the functionalization mode on nano's surface mainly relies on the problem and proposed use of the material.

In the past, many procedures had discovered; among them, the well-known that still applies today include covalent and non-covalent functionalization. All these approaches are with organic and inorganic compounds help to attain improved solubility and dispersibility. For example, the use of pristine carbon nanotubes, particularly in living organism and cells bring toxic effects, therefore functionalization is essential to be concerned [17]. Furthermore, due to the availability of carboxylic, epoxy and hydroxyl groups, covalent functionalization is more preferable. In addition, covalent functionalization suited as better moieties for functional group conversion. Besides this, the existence of an sp^2 hybridized π network gives the chance for non-covalent interaction among host species and carbon nanomaterials [54]. Thus, modifying the surface of carbon nanomaterial in order to retain the remarkable properties is a challenging task. At present, different functionalization techniques for both covalent and non-covalent have developed for carbon nanomaterials.

6.1 Covalent Approach for CNTs

Lately, carbon nanotubes have received significant interest because of its astonishing unique electronic, optical, mechanical, thermal, and structural properties [55], especially for medical and material science fields. But the insolubility of carbon nanotubes is a chief barrier for its use in real world. The insolubility of carbon nanotubes is generally due to its hydrophobic structure, surface area, forces like Van der Waals, etc. There is only one solution for the carbon nanotubes issues (insolubility and poor dispersion) which scientist discovered, and that is a modification of the carbon nanotubes [56]. Furthermore, there are numerous approaches for covalent functionalization of carbon nanotubes among other oxidation reactions, oxidized carbon nanotubes with esterification and amidation reactions, halogenation, ozonolysis, plasma activation, electrophilic/nucleophilic additions, mechanic/electrochemical functionalization, polymer grafting, nucleophilic/radical additions, treatment with ionic liquid and oxidized carbon nanotubes with complexation reactions [57]. However, for biomedical applications, strategies developed particularly for covalent functionalization include surface oxidation of carbon nanotubes, radical additions, cycloaddition reactions and its followed functionalization with biologically related molecules [58].

6.1.1 Oxidation Treatment

Covalent modification approach with various oxidizing acids/oxidants is most common because of their capability of attaching the preferred function groups,

hydroxyl or carboxyl, on the surface of carbon nanotubes as well as tailoring the surface composition. Carbon nanotubes with the functional groups attached not only provide a positive effect for their dispersibility in different solvents but also the contact with varies compounds, for example, polymers. Some of the well-known oxidizing agents for the oxidation of carbon nanotubes are sulphuric acid (H_2SO_4), nitric acid (HNO_3), tri-oxygen (O_3), hydrogen peroxide (H_2O_2) and potassium permanganate ($KMnO_4$). Oxidizing agents like H_2SO_4, HNO_3 and $KMnO_4$ generate carboxyl groups while H_2O_2 and O_3 produce hydroxyl groups into the nanotubes [59]. However, hydrogen peroxide and tri-oxygen are categorized under mild oxidant. As an example covalent amide connection established when a mixture of single-walled carbon nanotubes (oxidized) and PEG-NH_2 sonicated for the duration of 30 min plus centrifugation to generate NH_2-PEG-modified carbon nanotubes. Moreover, oxidation of single-walled carbon nanotubes with addition covalent conjugation with amino acids shows sp^3 carbon atoms [14]. However, the outcome of two oxidizing agents generates two functional groups connect con-currently on the nanotubes. Further functionalization makes these groups to be used as anchor sites either for esterification or amidation reactions which can be applicable widely for the conjugation of water-soluble organic molecules, hydrophilic polymers such as nucleic acids, peptides or polyethylene glycol, as a result, multifunctional carbon nanotubes manufactured [60]. Multifunctional carbon nanotubes possess greater chemical reactivity as well as selectivity, therefore considered better and preferable compared to other functionalized carbon nanotubes [61]. Another method for the oxidation of graphene also allowed as an alternative for the carbon nanotubes oxidation. As graphene and MWNTs both have sp^2-hybridized carbons, therefore it makes them easier to oxidize. The most well-known approach for the oxidation of graphene is Hummers. As a matter of fact, various improved Hummers method has been used for unzipping carbon nanotubes with well-developed oxidation mechanisms. Consequence of mechanical mixing surely enhances the dispersion but also cause damage and length shorten of carbon nanotubes. Since, scanning electron microscope (SEM) is used for the morphology of MWNTs before and after oxidation treatment. With an outer diameter range from 10 to 20, 30 to 50, and >50 nm clearly showed varies in tube diameter as well as roughness along the walls of the tube after gone through acids treatment. In addition, MWNTs diameter slowly narrowed due the oxidation process (cited from [62]). However, treatment like ultraviolet [63], plasma [64] and microwave irradiation have been used either for incorporation of surface oxygen/for the attachment of various functional groups to the carbon nanotubes. In terms of mechanical mixing, for example, conventional reflux method is usually used at the time of oxidation. In comparison with reflux, functionalization of carbon nanotubes with ultra-sonication use may help to generate carboxyl, carbonyl and hydroxyl content greater on the MWNTs. It is because sonication method develops the greater surface area as well as defects sites for the functional group [65]. Experimental results showed that the ultra-sonication help to decrease the stacking of carbon nanotubes in bundles, and destroyed the tubes structure integrity [59].

Some of the drawbacks of oxidation treatment are that it grows defects on nanotubes surface, CNTs oxidization leading Hole doping, and introduce impurity states at the Fermi level. On the other hand, oxidation treatment helps to remove the raw materials impurities, cut/shorten the length and expand the CNTs. However, minimizing the CNTs length through oxidation treatment comprehensively based on the rate and extent of the reaction which let the rise of new length distribution. Carbon nanotubes with open and oxygenated ends are the consequences of cutting mechanism [66]. However, the oxidative stability particularly depends on diameter and production process of the carbon nanotubes.

6.1.2 Cycloaddition Reaction

Cycloaddition reaction is another well-known process that includes direct additional reaction, for example, 1, 3-Dipolar, carbene, nitrene etc. In cyclo-addition reactions, sidewalls are the primary objective where reaction occurred. The outcome of this covalent approach upgrades carbon nanotubes strength as it the helps to enhance the solubility of water, different organic solvents etc. [58]. However, analogues of carbenes are nitrenes, compounds of electrophile reagents which add-up C=C bond. Thermolysis of alkyl azidoformates required for the functionalization of carbon nanotubes on the side walls through nitrenes. Development of pyrrolidine rings on the surface of carbon nanotubes with the use of 1, 3-Dipolar cycloaddition of azomethine ylides [67]. For many biomedical applications, these pyrrolidine rings can be substituted with various functional groups, for example, peptides, therapeutic agents, fluorescent molecules, etc. [58]. Like nitrenes, functionalization of carbon nanotubes using carbenes followed the same path. At first, deprotonation of imidazolinium cation produced nucleophilic carbenes, and then each −ve charge/moiety is replaced to the tubes, and at last carbon nanotubes functionalized [67]. Moreover, this approach sub-categorized with varies direct additional reaction, like amidation, esterification, thiolation, halogenation, and hydrogenation [68]. Like in the process of thiolation, CNTs involved with the thiol group through subsequent carboxylation sonication, reduction with the supports of $NaBH_4$, and chlorination with $SOCl_2$, led by thiolation with Na_2S and NaOH mixture to the CNT open end. The aftermath of cycloaddition reaction, enhance the strength of nanotubes and improve the solubility in aqueous solution, many organic solvents etc. [58].

6.1.3 Radical-Additions

Radical addition reaction falls under the category of covalent functionalization approach. A chemical agent such as aryl diazonium, sodium nitrite etc. is involved in radical addition reaction. Among these chemical agents, aryl diazonium coupling is more preferable due to its easiness and higher yield. In aryl diazonium coupling, first prepared aryl diazonium salts [58]. In 1858, Peter Griess discovered aryl diazonium compound while he was manufacturing a product. The word ‘diazo’

Table 6 Surface modification approaches for carbon nanotubes using aryl diazonium salts

Approaches	Materials	Mechanism	References
Chemical	SWNTs and MWNTs	Under iso-amyl nitrite, in-situ produced aryl-diazonium salts, reaction temperature 60 °C	[70]
	Carbon nanotubes	Aryl-diazonium reduction through H_3PO_2 (hypo phosphorus)	[70]
	Carbon black	In-situ produced aryl-diazonium salts in water under $NaNO_2$ and excess HCl	[70, 92]
Microwave	SWNTs and MWNTs	Arene radical reaction	[70]
Thermal	SWNTs	The mechanism was not notified in the manuscript	[70, 93]

originated from French and means di-nitrogen [69]. Furthermore, Jean Pinson, the modern surface chemistry father, could be accredited for aryl diazonium salts. Since its discovering, this salt has significantly considerable for organic synthesis of a number of vital compounds, for example long known azo dyes. This salt has become an ideal diazonium salt for the illustration of proof of new concepts, for example, modification of the surface, bio-sensor, clay related nano-fillers etc. At present, commercially available aryl diazonium include 4-nitrobenzenediazonium tetra-fluoroborate, 4-bromobenzenediazonium tetra-fluoroborate, 4-formyl benzene diazonium hexafluorophosphate and 4-aminodiphenylamine diazonium sulfate. However, aryl diazonium can be prepared by the introduction of $NaNO_2$ aqueous solution to aromatic amine solution under additional hydrochloric acid which later cooled down below 5 °C in a water bath [70]. In addition, CNTs can be envisaged through modification with isolated aryl diazonium and in situ prepared aryl diazonium from aromatic amines under $NaNO_2$ (medium acidic). On the other hand, in situ prepared aryl diazonium which guarantees significant grafting density of aryl groups on CNTs through pure iso-amyl-nitrite. This alternative route generates functionalized CNTs of higher solubility and processability in organic solvents (functionalization degree of one out of twenty atoms of carbon) and polymeric blends, respectively. This approach proved to be effective due to less time for the reaction as well as less consumption of solvent. Scalable is an option under this approach therefore paving the way for its use in more application, for example, growth of structural materials. Therefore, this approach seldom considered for application related to biological [58]. Table 6; listed the approaches and reaction mechanism for the modification of carbon nanotubes using aryl diazonium salts.

6.2 Non-covalent Approach for CNTs

Some other advantages of using non-covalent approach include biocompatibility, stability in very biological solutions and a functional group that required additional bio-conjugation. Lately, long-range single layers graphene has been prepared using non-covalent approach (π–π stacking) for a wide range of application. Since carbon nanotubes hold significant specific area which benefits them with high loading capacity along the following molecules. Through the route of non-covalent functionalization, carbon nanotubes have been positively covered/absorbed by amphiphilic molecules such as pyrene, derivatives of naphthalene, proteins, RNA, DNA, polymers, peptides, and surfactants [71]. Carbon nanotubes dispersion generally relies on chemical characteristics, amphiphilic molecules and solvent category and concentration as well as dispersing conditions [58]. Lightweight surfactant, few organic molecules as well as amphiphilic polymers are used as agents for non-covalent approach functionalization. Molecules of surfactants for the carbon nanotubes modification react with carbon nanotubes hydrophobic side and results in replacing to hydrophilic. This interaction of surfactants with carbon nanotubes makes them soluble not only in water but also in the wide range of solvents [72]. Synthetic peptides use also another route to disperse carbon nanotubes, as they capable to cover and solubilize the tubes. Some other surfactants capable to disperse carbon nanotubes include Odium dodecyl sulfate, cetyl-trimethyl ammonium bromide, non-ionic Tween-20 [73], Gum Arabic, salmon sperm DNA, chitosan [74]. Among all carbon nanotubes types, particularly for functionalization multi-walled carbon nanotubes are considered suitable for this approach as the damage is slightly low [75].

Moreover, functionalization of carbon nanotubes through non-covalent approach using meso-porphine and 5, 15-bis-porphyrin enhance the properties of tubes like biocompatibility, solubility in aqueous solution, luminescence etc. [73]. Among all poly-ethylene-mine (a hydrophilic character with polar head) use for carbon nanotubes functionalization and improve nanotubes water solubility significantly [76].

Furthermore, aromatic molecules are more strongly absorbed on the surface of graphite compared to aliphatic because of the π–π interaction among graphite surface and amphiphilic molecules of aromatic components as well as electrostatic and van der Waals interaction involvement [77]. This effect noticed in pyrene-containing molecules which is a non-covalent modification agent. In addition, to attaining successful dispersion of carbon nanotubes, surfactants (cationic, anionic/non-ionic) have been widely used. However, hydrophobic regions length and hydrophilic structure of the surfactants are the factors on which guaranteed carbon nanotubes dispersion based. Moreover, higher critical mi-cellar concentration, minor stability and partial interaction with cellular proteins are few limitations surfactants face in a biological environment. Several of these limitations can be avoided through the PEG-modified phospholipids [58] use which holds different functional groups that required additional functionalization with targeting and therapeutic molecules.

7 Conclusion and Perspectives

The discovery of carbon nanomaterial, particularly CNTs has aroused the attention of many researchers to study in-depth the capability of this remarkable material. In addition, functionalization approaches open completely new chapter for considering CNTs in many application where initially restricted to use. However, massive successful researches have carried out, and the outcome of these researches categorized CNTs as distinct biomaterials that hold potential to medical applications in bone engineering and orthopaedics techniques due to their outstanding capability of accelerating bone repair/restoration. Additionally, experimental results reflect that f-CNTs are capable to transmit cells without apparent cytotoxicity that eligible f-CNTs to use as a delivery vehicle for a range of biologically energetic molecules such as drugs, deoxyribonucleic/ribonucleic acid, and protein. Moreover, functionalization techniques assist in removing metallic containments and enhance the biocompatibility of CNTS, and allow them to be considered as a promising material for application related to bone tissue engineering.

In the past, CNTs were used with polymers but due to the issues like toxicity, aggregation restricted its use with polymers. Some of the experiments conducted in the past based on CNTs-polymers were MWCNT-Polycaprolactone, Polypropylene-MWCNT-nHA, Sodium hyaluronate-SWCNTs etc. However, functionalization of CNTs will certainly solve such issues and will allow its use as filler material with different polymers, and consider them appropriate for bone defects, replacement or loss.

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