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REVIEW

A review of carbon-based materials and their coating techniques for biomedical implants applications

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Abstract

Carbon-based materials have emerged as an excellent class of biomedical materials due to their exceptional mechanical properties, lower surface friction, and resistance to wear, tear, and corrosion. Experimental studies have shown the promising results of carbon-based coatings in the field of biomedical implants. The reasons for their successful applications are their ability to suppress thrombo-inflammatory reactions which are evoked as an immune response due to foreign body object implantation. Different types of carbon coatings such as diamond-like carbon, pyrolytic carbon, silicon carbide, and graphene have been extensively studied and utilized in various fields of life including the biomedical industry. Their atomic arrangement and structural properties give rise to unique features which make them suitable for multiple applications. Due to the specificity and hardness of carbon-based precursors, only a specific type of coating technique may be utilized for nanostructure development and fabrication. In this paper, different coating techniques are discussed which were selected based on the substrate material, the type of implant, and the thickness of coating layer. Chemical vapor deposition-based techniques, thermal spray coating, pulsed laser deposition, and biomimetic coatings are some of the most common techniques that are used in the field of biomaterials to deposit a coating layer on the implant. Literature gathered in this review has significance in the field of biomedical implant industry to reduce its failure rate by making surfaces inert, decreasing corrosion related issues and enhancing biocompatibility.

Keywords Biomedical implants · Implant coating · Substrate · Precursor gases · Coating material · Coating techniques

1 Introduction

Medical devices have become one of the rapidly growing industries globally due to the ever-increasing rate of accidental injuries, vehicle crashes, diseases, and many other fatalities which have helped the medical device industry to become a fundamental part of healthcare systems. According to WHO, there are more than 2 million different types of medical devices being used throughout the world including apparatus, machines, implants, software, and materials. Implantable medical device is a major category of medical devices majorly comprising cardiac, brain, bone, and dental implants whose primary responsibility is to restore injured human body part or function [1]. The market for medical implants was worth 88 billion USD in 2019 and by 2023, it is expected to reach 147.46 billion USD with a growth rate of 19% which was only 7.1% during 2012–2017 [2]. In 2001, about 26 million people in the United States had an implant inside their body [3]. By the virtue of countless efforts of researchers and industrialists, numerous materials, drugs, and polymers have been introduced in medical implants which save millions of lives and extend life expectancy.

Despite many efforts of researchers, medical implants continue to fail due to corrosion [4], material leaching [5],

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loss of mechanical strength [6], tissue rejection [7], or loss of function [8]. Both short- and long-term implant failure are concerning because it requires the efforts of clinicians and capital for reimplantation. To avoid extra burdens, many strategies and modifications were introduced in biomedical implants to improve the biocompatibility, strength, and topographical properties which may help the implant to perform its function for a longer period. Surface topography plays a crucial role in deciding the fate of foreign body objects inside a human body. The surface characteristics like roughness, nanopores, texture, and wettability are some of the deciding factors for cell adhesion [9], immune response activation [10], degree of biofouling [11], thrombo-inflammatory cascade activation [12, 13], and fibrotic capsule formation [14]. Typically, surfaces of the implants are improved by passive and active coatings. The passive coatings are inert and minimize the excessive attachment of platelets and cells due to their inherent wettability and surface texture. These coatings act as a barrier to protect implants from ionic attacks of body fluids which have the ability to slowly disintegrate the foreign body objects and ultimately cause tissue rejection. In addition, these coatings provide corrosion resistance, reduce material leaching, and strengthen mechanical properties of the implants to increase their endurance and life span. Different materials including calcium, bioactive glass, carbon-based materials, and hydroxyapatite are reported to be used as passive coatings for biomedical implants [15, 16]. In contrast, bioactive coatings are composed of drug loaded polymers which accelerate lesion healing [17], reduce cell proliferation [18], occlude thrombo-inflammatory cascades [19], and stagnate activation of the immune system [20]. Currently, biomedical implants have hybrid coatings consisting of both passive and active layers which help in wound healing and also extends the life span of implants.

Carbon based materials have a myriad of applications due to their excellent chemical, mechanical, thermal, and biological properties. The empty outer shell of carbon makes it suitable for bonding with other materials at an atomic level and produces millions of different compounds by forming four covalent bonds. Carbon based coatings have excellent mechanical and physical properties over a wide temperature range, have chemical inertness, are biocompatible, hemocompatible, and wear, corrosion and erosion resistant which makes them suitable for multiple industries including aerospace, automobile, heavy machinery, textiles, plastics, energy, and food preservatives. All the allotropes of carbon (graphene, diamond, amorphous, fullerenes) have multiple applications in the biomedical industry and many studies have reported their suitability and effectiveness as an inert coating material [21–24].

Due to hardness of carbon-based materials and requirement of high-temperature conditions, specific coating techniques are utilized including vapor deposition-based techniques, thermal sprays, and laser deposition. There are some other suitable techniques like 3D printing [25, 26], laser cutting [27], electrospinning [28], and dip coating [29] which have been utilized for biomedical applications for decades; however, this article focuses on the various vapor deposition and laser deposition type coating techniques. Previously, many studies in literature solely focused on either carbon-based materials or coating techniques. This paper will be providing insights on both materials and techniques by principally focusing on biomedical implants which could be beneficial for the selection of carbon allotrope and its coating technique for biomedical applications.

2 Carbon-based coatings

Carbon is one of the most important elements of the periodic table which provides the foundations of life, as it is a constituent of 95% of compounds on the earth [30, 31]. It has the ability to not only bind with other elements but also with other carbon atoms as well and also tailor the number of bonds and energies; thus, multiple allotropes of carbon are generated. These allotropes act as excellent coating material and their atomic variations give them specific structures and shapes which are suitable for different medical applications. These allotropic carbon coatings and their applications are explained in the coming sections.

2.1 Diamond like carbon coating

Diamond like carbon (DLC) has been used in multiple fields of life because of its stability, inertness, and excellent tribological, and mechanical properties. DLC is hard and wear-resistant; hence, making it a suitable material to coat industrial tools, batteries, knives, compaction devices, and wear-resistant surfaces [32]. It also has excellent biocompatibility which allows it to be utilized in the biological realm for multiple applications [33]. The structural analysis of DLC demonstrated that it is amorphous in nature and has differing ratios of sp^2, sp^3 bonded carbon, and hydrogen. The amorphous matrix usually has sp^3 nodules in an sp^2 bonded matrix. In contrast, graphite has sp^2 bonding with a planer configuration in which a single carbon molecule makes a double bond and two single bonds with two different atoms (mostly carbon atoms). The carbon having sp^3 bonding possesses a tetrahedral arrangement by making three single bonds [34]. The different combinations of these three elements impart varying properties to DLC coatings and the application depends upon their concentration and arrangement [35].

The properties of DLC betwixt and between diamond and graphite include higher hardness, lower friction coefficient, excellent tribological properties, and lower wear rate [32]. It has many applications in the field of biomedicine due to its hemocompatibility, anticancer, antithrombogenic, and antibacterial properties [36]. DLC is mainly coated on cardiovascular stents to reduce thrombogenicity and to improve the mechanical properties of the stents. The arrangement of carbon atoms in DLC coating makes them inert and hydrophobic which avoids the attachment of blood clots to the surface coating. In addition, the diamond like morphology promotes endothelial healing and tissue repair at the target site. Hasebe et al. administered the adsorption of proteins on DLC coated surfaces since it was the first event of coagulation cascade and thrombus formation. This study also demonstrated the repression of cell proliferation and blood coagulation due to DLC coating [37]. Similar results can be found in many other studies [38–41]. Coronary stent MOMO® is the commercially available DLC stent that has demonstrated non-inferiority results when compared to MULTI-LINK VISION stent and proved its efficiency and effectiveness in 99 patients from 19 different centers in Japan [42]. In another study, Gorzelanny et al. fabricated a hybrid surface of a bone implant by combining DLC coating with silver nanoparticles to improve the anti-proliferation and anti-bacterial properties. The inert and antiproliferative properties of DLC when complemented by the strong antibacterial properties of sliver material resulted in an excellent mammalian cell compatible surface [43]. Some other studies also demonstrated an improvement in the properties of cardiovascular stents and other medical implants [44, 45]. Overall, DLC coatings are excellent candidates to diminish thrombus and inflammation-related issues of biomedical implants.

2.2 Pyrolytic carbon coating

Pyrolytic carbon is a synthetic material that is made by the thermal deposition (400–2500 °C [46]) of hydrocarbons under a vacuum. It was introduced in the 1960s and it was first used for the coating of nuclear materials. Nevertheless, since then, it has been used for multiple other applications, especially in the field of biomedical devices [47]. Pyrolytic carbon has a turbostratic structure [48] in which carbon atoms are covalently bonded with each other and make a loose hexagonal structure. The crystallites of pyrolytic carbon are randomly oriented and are spaced at 0.348 nm. There are also fine crystalline regions in the pyrolytic carbon in the order of 2.50–4 nm [49]. The good mechanical strength, roughness, durability, physical strength, and biocompatibility of pyrolytic carbon make it a suitable candidate for the coating of biomedical implants and other devices. It has been found compatible with soft and hard tissues due to its inability to evoke thrombo-inflammatory cascades [50].

The major application of pyrolytic carbon was in the field of heart valves in which either the whole artificial heart was made of pyrolytic carbon [51] or only the surface was coated with pyrolytic carbon [52]. In addition, it has also been used for the coating of cardiovascular stents i.e., Cre8 stents. In this stent, the coated surface is called a bio-inducer surface which expedites the stent endothelialization and decreases the risk of thrombosis [53]. The results of Cre8 stent demonstrated better performance than control group and improved clinical results in NEXT and other trials [54, 55]. Other isotopes including low-temperature isotropic pyrolytic carbon (LTIC) have also been extensively investigated and studied and have been used for the coating of medical implants. It is a highly energized and hydrophobic material that is suitable for biomedical applications [56].

2.3 Silicon carbide coating

Silicon carbide is from a diamond like carbon category and is commonly obtained from silica sand and petroleum coke. It possesses excellent stability, hardness, and resistance to chemical attacks. Its common application is to be used as an abrasive material and protective coating for different machines.

SiC has a crystalline structure composed of Si and C atoms. The atoms are covalently bonded by making tetrahedral structures. These structures have electrons in sp^3 hybrid orbitals and generally hold 4.5 eV energy. Ogwu et al. found that Si-doped a-C:H coatings (Si-DLC), which lowered the electrical resistivity, effective work function, and surface energy, leading to reduced platelet aggregation and enhanced hemocompatibility. Apart from electrical properties, surface wettability is also a crucial determinant affecting hemocompatibility [57]. Many other studies demonstrated the reduction in platelet aggregation and corrosion by SiC coated surfaces [58, 59]. Furthermore, there are many commercially available cardiovascular stents (i.e., Orsiro drug eluting stent) that are coated with SiC to improve the mechanical strength, reduce thrombo-inflammatory reactions, and improve hemocompatibility [60]. BIOFLOW clinical trials series and BIONYX trial have proven the superior results of Orsiro as compared to other stents i.e., Xience, Biofreedom, and Onyx stents [61, 62].

2.4 Graphene coating

Graphene is a nanomaterial that is synthesized by the isolation of a single layer of graphite. Due to the tunable surface chemistry of graphene, it also exists in the form of graphene oxide and reduced graphene oxide. Both fundamental and applied research attaches great importance to graphene due to its excellent properties i.e., high surface area, high electrical and thermal conductivity, and excellent chemical and mechanical properties. It also has applications in the biomedical industry due to biocompatibility and hemocompatibility. The noteworthy applications of graphene are in the food industry and sensor fabrication.

The structural analysis of graphene showed that carbon is arranged in the form of hexagons by making honeycomb lattices. It has π-electron clouds with sp^2 hybridized carbon atoms. Ideally, graphene has 0.14 nm and 0.35 nm C–C bond length and thickness, respectively. A single carbon atom of graphene forms three strong σ bonds with its neighboring atoms making a lattice that may exist in two chiral forms: A and B [63].

Graphene is a miraculous material which is existed in multiple forms i.e., graphene sheets, graphene quantum dots, graphene oxide or pure graphene. Each type of graphene brings different advantages and applications. For instance, graphene quantum dots have smaller size and have functional groups like hydrogen and oxygen molecules incorporated into it; therefore, they are used for scavenging free radicals, biomedical imaging, drug delivery and photoelectric related applications [64]. Graphene oxide is widely used in semiconductors, fuel cells, and energy storage devices. In biomedical sensors, it is used in field-effect transistors (FETs) which helps in chemical and biological sensing. Graphene oxide has also found suitable for gene therapy and gene delivery because it provides the protection to vectors and DNA during delivery [65]. For biomedical implants, graphene coating is used to enhance the surface properties, durability and biocompatibility [66].

The hydrophobic character of graphene sheets makes it an excellent candidate to be utilized in a fluidic environment; therefore, it has been used to coat biomedical implants to reduce the attachment of blood cells and other cellular entities [67]. Many studies have proven the improved lesion healing and reduced thrombosis due to graphene coatings on cardiovascular stents [68, 69]. In conclusion, graphene and its different forms have applications in drug delivery, gene delivery, cancer therapy, bioimaging, and biosensing [70].

2.5 Pure graphite coating

Graphite is an anisotropic compound that is different from diamond on the basis of atomic bonding and hybridization. In contrast to diamond which has both sp^2, sp^3 bonded carbon, graphite only has sp^2 hybridization. This bonding allows the carbon atoms to stack upon each other and form a hexagonal configuration as shown in Fig. 1E. The crystalline structure of graphite is electrically and thermally conductive which makes it suitable to be used in batteries, lubricants, high temperature refractories, and electric vehicles [71].

Graphite has a slight hydrophobic behavior which can be tweaked as per requirements through structural and configurational modifications. For example, Kozbial et al. reported the absorption of airborne hydrocarbons can decrease the hydrophilic character of graphite [72]. In the biomedical

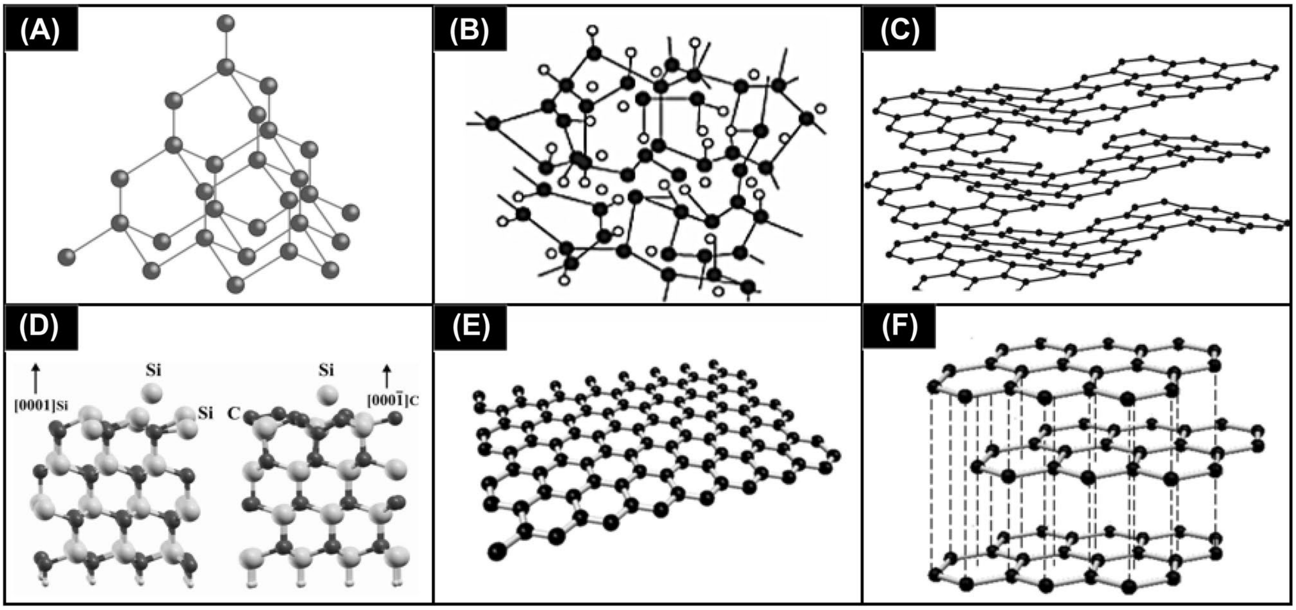

Fig. 1 The atomic arrangement of different allotropes of carbon **A** Tetrahedral arrangement of carbon atoms in pure diamond showing the presence of c–c-c and having 1.544×10^{-10} bond length **B** Amorphous coating of DLC showing a combination of sp^2 and sp^3 hybridization **C** Hexagonal array of pyrolytic carbon having weak interlayer of bonding **D** Tetrahedral bonding of Si–C–Si and C–C–Si bonds in SiC having up to ~ 1.85 Å bond length **E** monolayer, planar, and hexagonal lattice structure of graphene having 0.142 nm bond length **E** sandwich-like structure of graphite having 1.421 Å bond length

industry, graphite has demonstrated a myriad of applications. In a study, Shahriarinour et al. developed a pencil type graphite sensor for the assessment of cholesterol levels which had sensitivity up to 4.98 nmolL^{-1} [73]. Similarly, graphite based sensors for heart and glucose monitoring were described by Tang et al. and Lima et al. [74, 75]. In addition, graphite has been reported to be used as a bone cement [76], antimicrobial agent [77], and coating agent for heart valves [78].

3 Nanostructures of carbon

The nanostructures of carbon have opened new avenues of research in the field of biomedical sciences, tissue engineering, automobile, and fuel industry. Carbon itself has a myriad of properties and characteristics which makes it a lifeline of many industries; however, the nanostructures enhance these properties by manifolds and make carbon more desirable and beneficial for industrial applications. The combination of nanotechnology and carbon materials accelerated the natural inclination of forces including covalent bonding, hydrogen bonding, and van der Waals forces which made the material extremely lightweight, ultra-strong, durable, and highly thermally and electrically conductive. The careful investigation of carbon nanostructures demonstrated that each one of the nanostructures had its unique characteristics, properties, and applications. The details of different nanostructures of carbon are explained in the coming sections.

3.1 Carbon nanotubes

Carbon nanotubes (CNTs) are an exquisite type of carbon-based materials that has numerous and divergent applications. It has been widely explored in the biomedical field for its applications in biosensing, drug delivery, tissue engineering, imaging, diagnosis, and cancer therapy. CNTs are formed by the coordination of three carbons which are pyramided from sp^3 hybridization towards sp^3 hybridization.

These are available in the form of a single cylinder or multiwall tubes. The diameter of single and multi CNTs are ≈ 0.4 nm and > 30 nm, respectively. Both types of CNTs have different applications. The single walled CNTs are ultra-light weight; therefore, these are suitable for electrochemical energy storage, photovoltaics, nanoelectronics and thermoelectric power generation [79]. In biomedical field, there are different applications of single welled CNTs i.e., Yang et al., reported the use of single CNTs as drug carriers in Alzheimer's disease [80] and Chen et al., described the use of single CNTs for drug delivery to prevent the tumor progression [81]. In comparison, multi walled CNTs are popular for the applications of solar cells, flat panel displays and transistors. Yola & Atar reported the use of multi walled CNTs in immunosensors for tumor detection [82]. In another study, use of multi walled CNTs was reported for detection and analysis of cancer progression and metastatic potential [83]. In addition, different studies have reported the site specific drug delivery through multi walled CNTs [84, 85]. These have also shown potential in the field of biomedical implants as studies have reported applications of multi walled CNTs for corrosion resistance and uncontrolled cell growth suppression through targeted drug delivery [86, 87].

To synthesize CNTs, chemical vapor deposition is used. The commercial uses of CNTs are explained in Table 1. CNTs possess snacking effects which helps them in penetration in membranes and increase their biocompatibility [88] and makes them suitable candidates for the diagnosis of diseases [89], biosensor development [90], drug delivery [91], anticancer therapy [92] and targeted therapy [93].

Table 1 Details of applications of carbon nanostructures and their manufacturers

Sr #	Material	Overall applications	Biomedical applications	Carbon manufacturers
1	Carbon nanoparticles	Delivery of therapeutics, food packaging, light control, nanoceramics	Drug delivery, biosensing, anticancer therapy, tissue engineering, personalized medication, and biomedical imaging	American Elements [USA] CHASM Advanced Materials, Inc [USA]
2	Carbon nanotubes	Batteries, automobile parts, sports goods, electromagnetic shields, electronics, device modelling, boat hulls, sporting goods, and water filters	Gene therapy, drug delivery, tissue engineering, biosensing	Arkema [USA] Nanocyl [USA] Klean Commodities [USA] Hyperion Catalysis International [USA]
3	Carbon fibers	Sports goods, tennis racquets, archery bows, aircraft parts, sailboat masts, automobile springs, and spacecraft parts	Wound dressing, biosensing, face masks, and tissue engineering	Hexcel [USA] Mitsubishi Rayon Co. Ltd. [USA]
4	Carbon dots	Photocatalysis, chemical sensing biosensing, photovoltaic devices	Bioimaging, drug delivery, medical diagnosis	Nanoshell [USA]

In the biomedical field. Pahlevanzadeh et al. increased the strength of load bearing bone implants made of PMMA-based cement [94] and Francis et al. reported the suitability of coating of CNT-reinforced chitosan-based ceramic composite on magnesium based biomedical implants to increase the anticorrosion and antibacterial properties [95]. Mondal et al. used the thin films of CNTs as an alternative to induce pluripotent stem cells which proved to be better than stem cells as it maintained pluripotency, and induced the differentiation of ciPSC in regenerative medicine applications [96].

3.2 Fullerenes

Fullerene is a soccer ball shaped allotrope of carbon which is composed of sixty carbon atoms. It has π-electron systems, and the long curvature and hollow spheres of these systems make them suitable for multiple applications. The large surface area of fullerenes makes it appropriate for exo-functionalization which facilitates the attachment of amino acids and peptides for medical applications [97]. Fullerenes have found to be an excellent nanoplatform for cancer detection and management. In a study, the autophagy and anticancer potential of fullerenes was investigated and application of fullerenes in chemotherapy was reported [98]. These have also been found suitable for bioengineering based solution and promotion of osseointegration in bone implantation [99].

3.3 Carbon nanoparticles

Carbon nanoparticles are a widely explored class of materials that have numerous applications in the field of biomedicine, biomedical implants, sensors, automotive mobiles, and many other. fields Carbon black is the most famous example of nanoparticles which is widely used in pigments, cosmetics, inks, coatings, and automobile tyers. Carbon nanoparticles have a diameter of 3–10 nm and are synthesized through carbonization, heating, activation, and grinding. The structural analysis showed that they have an electronic configuration of [He] $2s^2 2p^2$. Currently, carbon nanoparticles are dominating over metal nanoparticles and are considered an excellent material to be used in various fields due to their stability and performance.

3.4 Carbon nanofibers

Carbon fibers have been extensively used in aircrafts, sports cars, and their equipment due to their hardness, durability, and corrosion resistance properties. Carbon nanofiber is a quasi-one-dimensional carbon material that has a diameter up to 100 nm. According to its structural analysis, it lies in between carbon fiber and carbon nanotube. It is a strong material and has strength up to 8.7 GPa which is the reason for its multiple applications. It is usually synthesized by catalytic decomposition reactions, chemical vapor deposition, and electrospinning. In the field of biomedical engineering, carbon nanofibers are used to increase the strength of biomaterials in tissue engineering, cell regeneration, and cancer treatments. In the field of biomedical implants, Buschbeck et al. described carbon nano fibers as neural implants in insects to assess their activity and reported them as a suitable candidate to replace metal electrodes [100].

3.5 Nanoribbons

Nanoribbons are one of the most fascinating classes of carbon. These are one dimensional, finite and planner structures of graphene which have different types of structural arrangements i.e., zigzag, armchair or intermediate character. The applications of these structures also vary when their structure changes i.e., electronic properties are achieved by using edge structure [101]. In biomedical applications, graphene nanoribbons are used in biosensing and drug delivery [102]. These are also used as therapeutic agents to increases the efficiency and efficacy of treatment regimens [103].

3.6 Carbon nanoflowers

Carbon nanoflowers are a recent class of three-dimensional carbon nanostructures which has similarities to the plant flowers. These nanoflowers have structural and morphological similarities to natural flowers and their petals are excellent sites for the storage. In biomedical industry, nanoflowers have been used for diagnosis and treatment purposes because of their ability to interact with human body at cellular level. The most interesting application of nanoflowers is in cardiovascular disease because of their ability to trigger the regrowth of blood vessels [104, 105]. Nanoflowers have also been found to effective for cancer therapy as in a study, microbial transglutaminase nanoflowers demonstrated effectiveness in treating breast cancer [106]. In a recent study, nanoflowers were used in microneedles to monitor glucose levels in body [107]. Due to lesser toxicity effects of nanoflowers, these are being investigated in the field of biomedical implants; however, a lack of data exists in literature regarding applications of nanoflowers for biomedical implants (Fig. 2).

3.7 Carbon quantum dots

Carbon quantum dots are an emerging class of carbon materials that have polymer-like and fluorescent properties. These are a type of carbon nanoparticle having a discrete and quasi-spherical carbon structure that can be obtained during the purification of single-walled carbon nanotubes. The carbon atoms are arranged as sp^2-graphitic carbon which

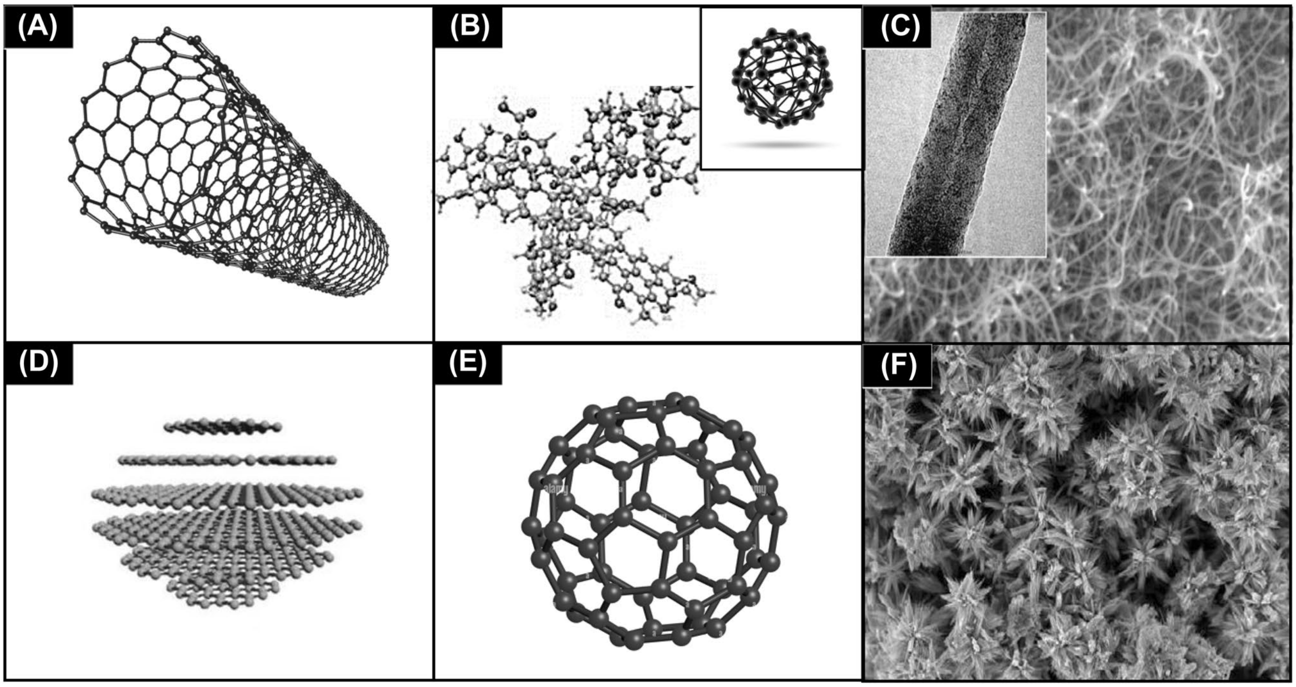

Fig. 2 Nanostructures of carbon **A** Honeycomb mesh like structure of carbon nanotube which is made by the wrapping of individual layers of carbon around each other **B** carbon nanoparticles having [He] $2s^2$ $2p^2$ configuration **C** Electrospun nanofiber having carbon layers stacked in the form of cones **D** Quasispherical carbon quantum dots possessing amorphous to crystalline carbon base Quantum dot **E** Bucky ball structure of fullerenes **F** Nanoflowers under electron microscope depicting similarities with natural flowers of plants

combines with sp^3 hybridization resulting in imparting florescence to the quantum dots. Their size is usually less than 10 nm. This class of material is playing a significant role in the field of biomedicine as it has applications in diagnosis, bioimaging, material fabrication, drug delivery, synthetic chemistry, biosensing, and materials science.

4 Toxicity related issues

The traces of carbon could be found in every aspect of life and its nanostructures have made human lives easier. The development of nanostructures of carbon requires different types of processing that modifies the physicochemical and structural properties and increases the toxicity of the material which is a major concern for carbon-based materials [108]. The researchers have worked on optimization of these material and modifying them in such a way that their toxic levels were lessened and fall under the acceptable range [109]. Toxicity of carbon-based nanostructures is witnessed when high concentration of material is used i.e., Delorme et al. reported a persistent inflammation in rats after 90 days' exposure to carbon nanofibers at 25 mg/m^3 concentration [110]. Similarly, another study mentioned the inflammation at 1.5 mg/m^3 concentration of multi-welled carbon nanotubes [111]. Despite debatable toxicity, carbon-based materials have been used in bioimaging, diagnostics or different treatment regimens and preclinical studies suggested insignificant or non-toxic effects [112]. There are many factors which help in the reduction of toxicity i.e., type of solvent, size of carbon material, synthesis process and byproducts [113]. Due to advancement in biomedical field, the toxicity levels of these materials have been controlled and reduced; therefore, clinicians can now use these materials without any hesitation.

5 Carbon-coating techniques

Apart from nanostructures of carbon, the coating of carbon materials has garnered much attention due to their excellent properties. Studies have shown that carbon is difficult to coat on target sites through traditional coating techniques like dip coating and spin coating; however, high temperature-based techniques were found to be the most suitable for coating purposes. Therefore, the details of different coating techniques for carbon materials and their applications in the biomedical industry are discussed here.

5.1 Vapor deposition based techniques

The coating techniques are selected on the basis of coating material and the type of substrate because the type of material of target site influences the coating process and adhesion properties. For carbon-based materials, multiple types of coating techniques are used which are selected on the basis of substrate material, intended applications, and thickness of the coating layer. Multiple coating techniques and their process and requirements are explained in the following sections.

5.1.1 Chemical vapor deposition

Chemical vapor deposition (CVD) is a sophisticated technology for materials processing and is utilized to deposit thin films with the help of chemical reaction of gas-phase precursors. It uses chemical reactions from a thermally induced substrate surface to provide a solid coating of reaction product by supplying reagents in gaseous form. Vapor-phased substances are condensed to produce solid phase material [114]. CVD is a lucrative technique because it can accommodate a large number of precursors and coat various types of thin films. Only a few elements from the periodic table, such as noble gases, halogens, and a few actinides and alkali metals cannot be deposited using this method. The chamber of CVD harbors a vapor–solid reaction in which precursor gases move and react with each other in a heated vacuum and deposit multidirectional and assorted coatings.

For decades, CVD has been used to coat the surfaces of different medical devices with various types of materials. Carbon-based materials are the obvious choice of material to be coated through CVD and many studies have reported the improvement in the medical devices after these coatings. Recently, Kheradmandfard et al. reported the exceptional improvement in the corrosion and wear resistance of Ti alloy after coating Si/DLC nanocomposite through CVD [115]. Moreover, Ti and TiN based materials are popularly coated through CVD [116]. In literature, different types of carbon coatings including graphene [117, 118] and pyrolytic carbon [119–121] have been successfully applied in the biomedical industry for multiple applications. The CVD based coatings may improve the tribological and performance based properties as well as biocompatibility of biomedical implants.

In addition to innumerable benefits, there are multiple drawbacks of CVD including utilization of high temperature, reactive precursor gasses and requirement of safety gears for operators which results in higher cost and material constraints. To avoid the temperature related issues of CVD, plasma enhanced chemical vapor deposition was introduced which has advantages of low toxicity and substratum constraints such as inorganic materials, in particular, low temperature and chemical stability, solvent and corrosion resistance, and substrate limits due to complicated geometries and composition.

5.1.2 Physical vapor deposition (PVD)

PVD has been used for the coatings of different industrial machines and parts to improve their mechanical surface properties. Initially, it was associated with poor adhesion and uniformity related issues which were resolved by process and machine optimization. Currently, operators have full control over deposition rate, structure, and temperature for substrate coating on the target. It also has computer numeric control which makes it suitable for industrial processes and coating of materials at a larger scale.

PVD uses atomization or vaporization processes that do not involve chemical reactions for material coatings to grow coatings on a surface from the atomic level. These atomic coatings are deposited in the presence of vacuum and plasma or an electrical environment and PVD deposits a line-of-site impingement type of coatings. Chowdhury et al. coated Ti6Al4V alloy with AlTiN and CrN through PVD for aerospace applications and reported the improvement of mechanical properties and wear resistance of the specimens [122]. Similarly, Vega et al. demonstrated the improvement in wear and corrosion resistance by introducing the interlayers of Ti through PVD in TiN coatings [123]. Krella investigated the influence of the deposition process of PVD coatings through cathodic arc evaporation based PVD and reactive magnetron sputtering based PVD on the degradation rate under cavitation erosion. The results exhibited the phase transformation Fe-γ → Fe-α′ of substrate regardless of coating conditions and techniques; however, coatings through reactive magnetron sputtering underwent intense transformation showing that lower density coatings are not suitable for erosion related applications [124].

The coatings of magnesium based implants through PVD had been popular in the field of biomedical industry. Vignesh et al. coated the surface of magnesium with iron and hydroxyapatite to improve the mechanical, biological, and corrosion related properties as well as ameliorate the degradation rate of magnesium [125]. Bahi et al. coated Ti with $(Ti/TiN)_9$ and $(Ti/TiN)_9/TiO_2$ through PVD to improve their performance in the biological environment and demonstrated the improvement in biocompatibility, tribological, and corrosion resistance related properties [126]. Generally, PVD based coatings are notorious for their lesser adhesion to the substrate, and an optimization process is needed for better adhesion. Nißen et al. optimized the process of a-C:H:Cu coating on Ti6Al4V alloy using a hybrid of PVD/PECVD coatings and reported that controlling Cu mole fraction and bias voltage of substrate is crucial to achieving better adhesion of film to substrate [127]. Many other studies have also reported the applications of PVD in the biomedical industry.

The PVD has an advantage over CVD in terms of temperature related challenges because it requires a lower temperature as compared to the CVD chamber. In addition, it uses a solid precursor which makes it suitable for many organic and inorganic compounds and elements. However, PVD based processes and coatings face some challenges like limited adhesion, lack of uniformity in the coating's thickness, and inability to coat inside the implant or tool surface [116]. Scientists are improving PVD processes and machines to increase the favorability of the coating.

5.1.3 Plasma enhanced chemical vapor deposition (PECVD)

PECVD is an advanced version of CVD and was introduced to solve the problem of high coating temperatures because numerous materials could be degraded at higher temperatures making them unable to coat through CVD. Therefore, the thin-film deposition at considerably lower temperatures on organic or inorganic materials was started to be done by using electrical energy to form a plasma that ionizes natural gas and produces free radicals, which are then polymerized to form a deposition layer.

PECVD is a hybrid coating process that combines technologies of CVD and high energy plasma to avoid the high temperature requirements of conventional CVD. In this process, the organic molecules are subjected to electron beams to produce free radicals which ultimately polymerize and stick to the target surface generating a deposition layer. To make the process efficient, later low-intensity electron beams were introduced to create layers on target surfaces and avoid material decomposition related issues [128, 129]. In addition, radio frequency based PECVD became popular for organosilicon based coatings [130, 131].

PECVD has been used in the field of biomedical implants for coating purposes. There were multiple studies in literature that demonstrated the benefits of these techniques which are described here. Eurídicea et al. used PECVD to coat amorphous C:H films on the surface of Ti6Al4V alloy to improve the chemical and biological responses of body against the alloy [132]. The analysis of human peripheral blood mononuclear cells (PBMCs) demonstrated the reduction in inflammatory reaction and immune response activation. In another study, the mechanical properties and hardness of titanium bone implants were improved after SiC deposition through PECVD [133]. J Huran et al. characterized the SiC coating through IR, AES, and RBS. The existence of Si–C, Si–H, and C-H bonds was confirmed through the IR spectra of specimens [134]. Another study demonstrated the analysis of PECVD coated amorphous silicon carbide on vascular stents to improve biocompatibility and mechanical strength. Precursor gases such as Silane (SiH_4), methane (CH_4), and phosphine (PH_3) are employed to deposit n-doped a-SiC:H [135]. Many other studies proved the non-cytotoxicity and biocompatibility of the PECVD based coatings [136, 137]. In summary, PECVD is an effective technique to coat biomedical devices and implants to improve their mechanical and biocompatibility properties (Fig. 3).

5.2 Plasma spraying

Plasma spraying was an amazing technology that emerged after World War II to improve the function of machines and their parts with a thin layer of coating which was done with the help of plasma that could melt ceramics or metal powders. These molten materials were then sprayed over the target surface to deposit a protective coating. Plasma spraying has many advantages including low cost, rapid deposition rate, low probability of thermal damage of material, chemically inertness, and the ability to coat at a relatively low temperature.

Plasma spraying has enormous uses in the field of biotechnology and biomedical devices. It is used to improve the mechanical, material, and corrosion properties of biomedical implants and other devices. The adhesion strength of coatings deposited through plasma spray coating techniques depends on two factors: the nature of the coating material and the nature of the target material. Plasma-sprayed HA or CaP coatings have been reported to have poor adherence with the target in several investigations and scientists are trying to optimize the process conditions to achieve maximum adhesion.

Many studies reported the coating of Ti–6Al–4 V alloy through plasma spraying. The coatings were composed of HA/Titanium or HA/yttrium stabilized zirconia (YSZ)/Ti–6Al–4 V. These coating showed better adhesion to the target due to the inclusion of Ti in HA coating which also reduced the residual stress created during the spraying process. [140, 141] Yang et al. coated Ti and CoCrMo implant materials with ZrO_2 coatings and discovered that ZrO_2 (4 percent CeO_2) had high adhesion. ZrO_2 (4 percent CeO_2) coatings have average adhesion strengths greater than 68 to titanium and greater than 67.7 MPa to CoCrMo, with failure occurring within the ZrO_2 coating [142].

5.3 Thermal spraying

Thermal spraying is a rapidly growing technique that has multiple applications in heavy industry, agriculture industry, and other fields. Many advanced and sophisticated thermal spray machines are used in the automobile industry for the coating of vehicle parts [143]. Thermal spray coatings are formed by the successive impact of a stream of spray droplets in fully molten or partially melted states, followed by flattening, rapid cooling, and solidification. The heating and accelerating of the spray materials are necessary to create

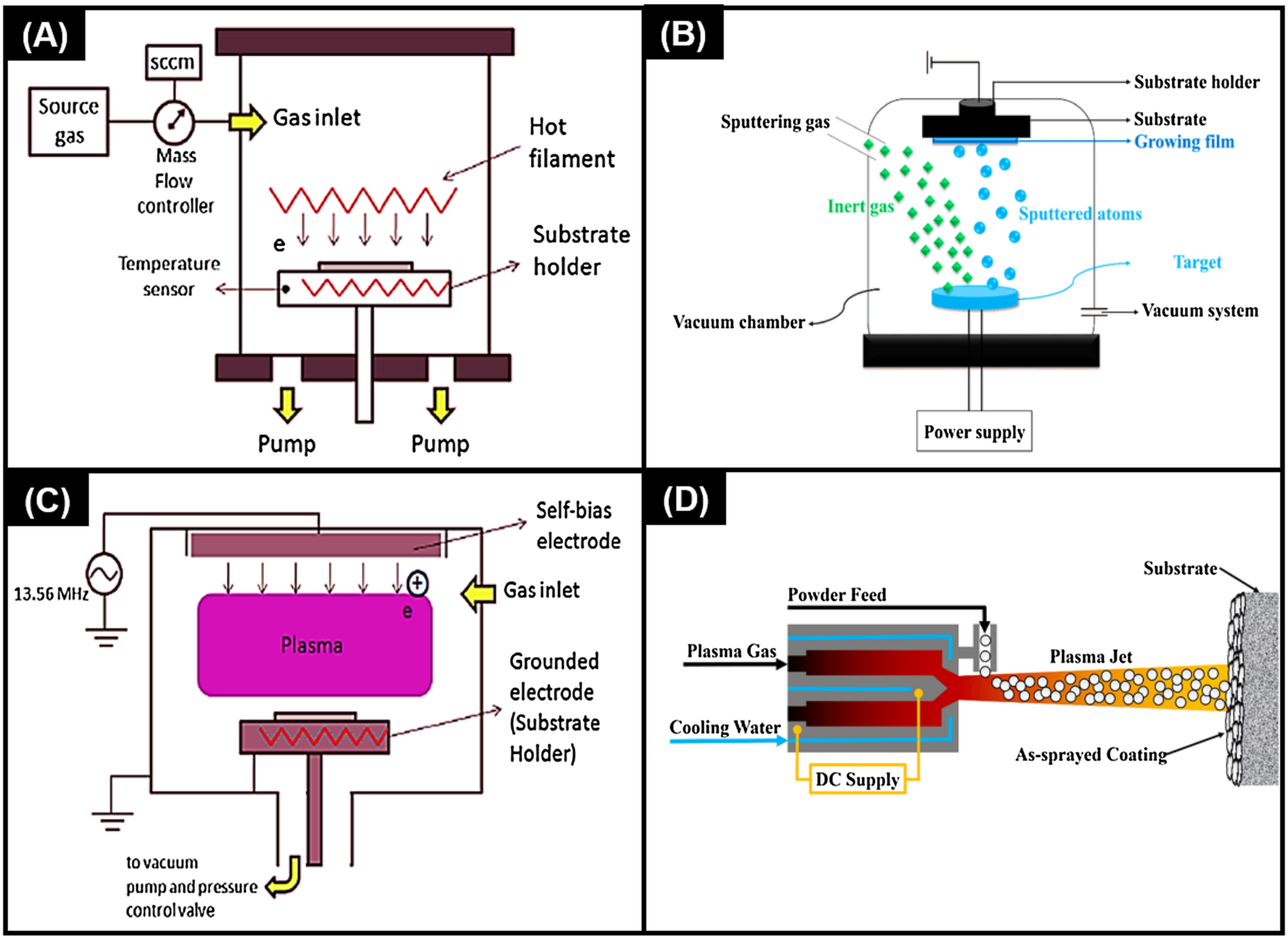

Fig. 3 Schematic of vapor disposition-based systems **A** Thermal reactor of CVD having gasses as precursor materials for coating **B** line-of-sight coating process of PVD which utilizes solid material as a source of material vapors **C** PECVD chamber having ability to generate plasma and operate at lower temperature and deposit dielectric thin films [138] **D** Plasma spray having 30 mbar–900 mbar pressure which is used to the formation of plasma jet by a transferring arc between the cathode and wire [139]

fine spray droplets. Chemical reactions such as metal alloy oxidation during heating may occur which may change the chemical compositions and phases of the spray materials and add additional functional properties to the coatings. The parameters of the droplets, including temperature, velocity, and size, which are determined by spraying processes and conditions, influence the interaction of the spray particles with the spray flame, and coating deposition processes [144, 145].

The thermal spray approach is getting a lot of attraction and is being embraced as a new way of coating that improves the biocompatibility and mechanical properties of biomedical implants. Precursors in the form of solution or suspension are used to coat the target substrate and impart desirable qualities in thermal spray. There are three types of plasma sprays: flame, plasma arc, and electrical arc sprays. In addition, a few other techniques use plasma spray to coat their targets including atmospheric plasma spraying (APS), vacuum plasma spraying (VPS), liquid plasma spraying (LPS), suspension plasma spraying (SPS), high-velocity oxy-fuel (HVOF), high-velocity suspension flame spraying (HVSFS), detonation gun spraying, and gas tunnel type plasma spraying (GTPS).

Plasma spray has been used in the biomedical industry to coat the targets for the applications of improved biocompatibility, body response, and mechanical properties. Gadow et al. and Prashar & Vasudev have reviewed many studies and provided strong evidence from literature that plasma spraying is a suitable technique to increase the osteoconductive and biocompatibility of bone implants [146, 147]. In another study, Vilardell et al. studied the effects of three different sprays (thermal, cold, and high velocity oxy fuel spray) and observed their effects on cell adhesion and proliferation. The results indicated the response of cell and grain size hydroxyapatite differs by varying the spray type [148]. Liao et al. reviewed the biocompatibility, anti-infective and anti-corrosive properties, and wear-resistance of cold spray coatings and found them to be suitable for biomedical applications and biological atmospheres. Overall, it may be concluded that thermal spraying is a potentially suitable technique for biomedical applications to improve their microstructure, as well as mechanical, and biological properties [149, 150].

5.4 Laser deposition

Laser deposition is another popular method for coating biomedical implants which uses high power density laser with low frequency bandwidth. In this process, laser beam evaporates the material and deposits a layer of vaporized material on the implant's surface. The ablated material generates a plasma plume of highly excited atoms, ions, electrons, and molecules because the focused pulse layer has a high energy density. By modifying the deposition rate, thickness of the coating is optimized. Arias et al. experimented with the adhesive characteristics of amorphous and crystalline hydroxyapatite as a coating material, and optimized the coating process and thickness of coating layers. This study concluded that the combination of amorphous and crystalline hydroxyapatite increases the adhesion and strength of coatings [151]. In another study, Blind et al. deposited the hydroxyapatite on titanium alloys to optimize the roughness and adhesion related parameters [152]. These hydroxyapatite based coatings have many applications in the field of biomedical implants which were reported by Hidalgo-Robatto et al. [153], Pradhaban et al. [154], Chen et al. [155] and others [156–158] (Fig. 4).

6 Discussion

Diseases are a part of nature and despite huge technological advancements in diagnostic and therapeutic strategies, the elimination of diseases could not be done. Although there had been huge improvements, the complete annihilation of diseases has yet to be achieved. One of the most important parts of the medical industry is biomedical implants which have been used to cure heart clogged/blocked arteries for decades and no one can deny their importance. Apart from their cardiovascular applications, these are widely used in the treatment of bone and dental issues. When an implant is placed inside the human body, it is expected to perform its desired functions without initiating thrombo-inflammatory cascades, immune response, and other undesired reactions which can cause multiple allergic reactions and implant-induced coagulation cascades resulting in implant failure leading towards reimplantation and in the worst case scenario, body part failure. To avoid such drastic consequences, researchers are required to introduce modifications or coatings which have ability to combat corrosion, fracture, toxicity, and poor mechanical strength of the implant. To overcome all these issues, the most suitable way is the deposition of the coating layer on a biomedical implant surface with a suitable material. For successful implant fabrication, there are two main factors that one must keep in mind: one is the material that needs to be coated on the implant and the second technique is to coat material on the implant.

Carbon is an excellent material that is also part of the foundations of life on the earth. It has been popular in the industries like fuel, heavy machinery, automobile, paints, plastics, and even the food industry. In addition, it has excellent hemocompatibility and biocompatibility which makes

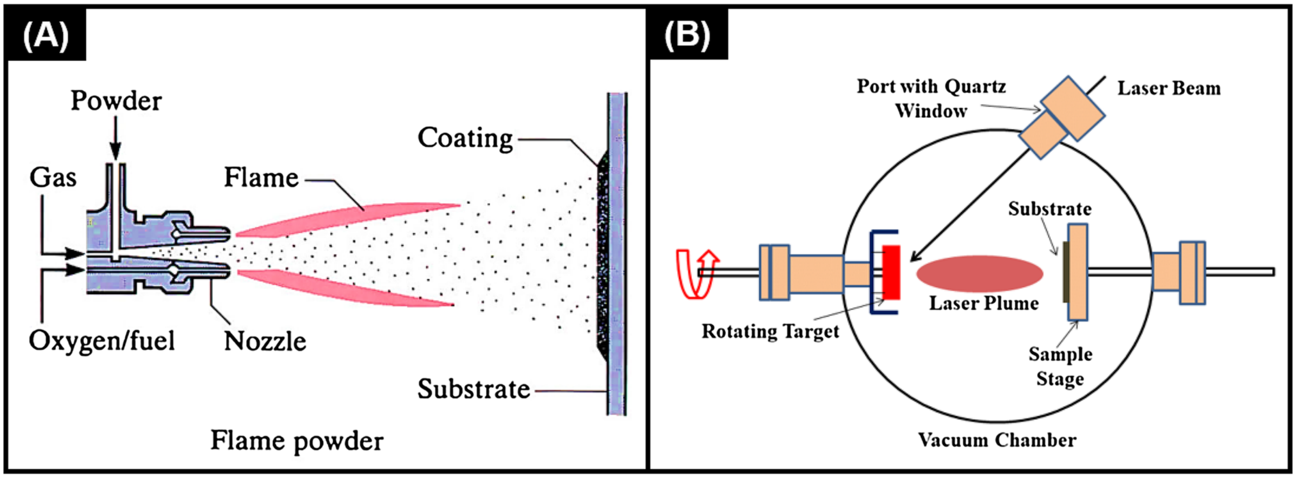

Fig. 4 Schematics of thermal spray and laser deposition **A** melting of source material and formation of thermal spray for coating purpose **B** Utilization of laser beam to evaporate the source and deposition of material through laser deposition technique [159]

it a suitable candidate for biomedical applications. Carbon based surgical tools and heart valves have been reported to perform better than other materials. Carbon fiber is found to be an excellent wound healing gauze that has the ability to endure harsh environmental conditions. Carbon has also been used in stem cell technology and tissue regeneration and has shown promising results. The thin films and coatings of carbon may mimic the human body functions favorably and provide a suitable environment for the ibroblasts, osteoblasts, and macrophages at the lesion site without evoking any inflammatory or immune reaction. Because of its durability and hardness, it has been observed to improve the performance and load bearing properties of hip and knee joints which minimizes the rate of corrosion and material leaching, resulting in lesser debris formation. It also acts as a barrier to lock the metal components inside the implant and blocks the release of ions from metallic implants into body fluids. Due to wettability properties, carbon films have a tendency to prevent thrombogenicity by appropriately minimizing the platelet activation and adhesion. Additionally, the hemocompatibility and biocompatibility of carbon films can be improved by the incorporation of materials like silicon, titanium, nitrides, or oxides.

The use of modified carbon-based materials has gained popularity due to the enhancement of properties i.e., structural, electrical, thermal, mechanical, and optical. In addition, the introduction of nanotechnology augmented unique features which sparked the interest of researchers for biological applications. Due to the freedom of manufacturing any type, shape, or nanostructure of carbon, multiple types of functions were obtained; however, a particular focus was on drug delivery systems. The primary function of these systems targeted drug delivery and mimicked protein channels which helped to improve lesion healing. In medical implants, it helped to reduce the failure rate of implants. The adaptability and characteristics of carbon-based nanomaterials and coatings provide the solutions to issues like infections, delayed wound healing, and osseointegration. Furthermore, due to the enhancement of mechanical properties, the life span of implants is also increased.

Selection of technique for the surface modification and coating is an important factor which is selected based on the working environment, type of problem, and materials involved. There are many techniques that can be utilized to coat the material for example sol–gel, electrostatic deposition, thermal spraying, plasma spraying, dip coating, laser coating, physical and chemical vapor deposition, etc. In the current era, the widely used techniques for coating biomedical implants are physical vapor deposition, chemical vapor deposition, and plasma-enhanced chemical vapor deposition. Every technique carries some disadvantages along with many advantages. For example, chemical vapor deposition requires high temperatures to deposit a coating layer on the substrate; however, it can accommodate a large number of precursors and is widely used in coating different materials including TiN, carbon, and silicon. Despite many advantages, it may affect the physical and chemical nature of the substrate due to the utilization of high temperatures. To avoid this issue of high temperature, the new technique was introduced as plasma-enhanced chemical vapor deposition in which the deposition of thin film on organic or inorganic material at a relatively lower temperature than CVD by using electrical energy to produce plasma which ionizes the gas and free radicals are produced which undergo radical polymerization. Table 2 lists all the coating processes commonly utilized in biomedical implant coating. It summarizes all the benefits and drawbacks of employing various ways to deposit layers on biomedical implants. Based on the benefits and drawbacks, it is simple to determine which technique is most appropriate.

Although, carbon has been extensively studied and utilized in various fields of life, its applications are still limited in the field of biomedical devices and implants. Currently, only a handful of products are available in the market which are using carbon based technologies and coatings to improve the results and functions of devices. There is a need to develop cost effective and efficient methods for the production of nanostructures at the industrial level with controlled morphology. CNTs and carbon quantum dots are gaining popularity due to their efficiency and better results. In the future, these may be replacing traditional carbon fiber and drug delivery devices, particularly in vaccine delivery and gene therapy. These are also expected to be used as reinforcing materials to increase the mechanical strength and hardness of materials. In conclusion, carbon-based nanostructures and coatings would be utilized in a myriad of materials to improve the functions of materials and structures.

7 Conclusion

The excellent structural and functional properties of carbon allotropes make them suitable candidates for the passive coatings of biomedical devices and potentially provide a solution to existing problems of medical implants like thrombosis, uncontrolled proliferation, delayed wound healing, and inflammation at the lesion site. Due to its exceptional structural properties, carbon enhances the mechanical strength of materials and makes them able to withstand harsher conditions, both inside and outside the body. In addition, it has the ability to increase the material inertness and corrosion resistance of medical implants which reduces the material ion leaching and prevents the initiation of foreign body object reactions to the body; thus, reducing the chances of implant failure. Despite the availability of suitable material and other conditions, implants fail due to the selection of

Table 2 Advantages and disadvantages of different coating techniques

Deposition method	Advantages	Disadvantages
Sol–gel method	Coats 3D complex porous substrates, low processing temperatures, relatively cheap, very thin coatings (< 1 μm)	Should be processed in a controlled atmosphere
Electrostatic deposition	Uniform coating thickness on flat substrates, relatively cheap	Only coats exposed area and coatings are fragile
Electrophoretic Deposition	High deposition rates, uniform thickness of coating, coats complex 3D porous substrates	Cracks in coating and high sintering temperatures
Thermal spraying	High deposition rates	Only coats exposed area, coating decomposition due to high temperature, rapid cooling may result in amorphous coating
Plasma spraying	Low-cost process, fast coating, smooth coating layer, interconnected pores for multilayer coatings	HAp film density fluctuates that effects uniformity, expensive equipment, higher processing temperatures initiates, grains formation, and poor bonding of HAp film and metal surface
Dip coating	Inexpensive, coatings applied quickly, coat complex 3D porous substrates	High sintering temperatures, film thickness can vary from top to bottom (wedge effect), and fragile coating due to high thickness (in mm range)
Bio-mimetic coating	Lower reaction temperature, easily processed, complex shapes	Time taking process, needs a constant pH system and requires solution makeup
Pulsed laser deposition	Versatile method and uniform coating	Costly process, pre-treatment of sample required, and line of sight technique
Sputter coating	Thick HAp coating layer, best for flat substrates, good bonding of HAp film and metal surface	Lengthy coating process, expensive method, unable to process difficult shapes and an amorphous coating layer
Physical vapor deposition	Does not require the usage of special precursors and is safer because of the absence of toxic precursors and by-products	Low deposition rate, production of thin coating layer, requirement of annealing time
Chemical vapor deposition	Avoid the line of sight, high deposition rate, production of thick coating layer, Co deposition of material at same time	Requirement of high temperature, possibility of toxicity of precursors, mostly inorganic material can be used
Plasma enhanced chemical vapor deposition	High deposition rate, low temperature, and both organic and inorganic material can be used as precursors	High-cost equipment, existence of toxic and explosive gases, and existence of compressive and residual stress in the films

inappropriate coating techniques; therefore, the selection of a suitable coating process is important for the development of a successful implant. Physical and chemical vapor deposition techniques are considered appropriate for the coating of carbon materials due to their ease, cost-effectiveness, and efficiency. There are many other techniques that are suitable for coating medical implants like laser deposition and thermal sprays; however, each technique is associated with some limitations and drawbacks which effect the performance of medical devices. In a nutshell, the selection of appropriate carbon allotrope, carbon nanostructure, and coating technique are important factors that ultimately improve the hemocompatibility, biocompatibility, mechanical strength, and corrosion resistance of biomedical implants.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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