Graphene – a promising material in prosthodontics: A review.

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Abstract
Dental materials are expected to be biocompatible, non-cytotoxic, with the ability to maintain a mutual interaction with the host and performs the proper functions. In 2004 Graphene, where carbon atoms of sp2 hybridisation are organised in a single layer, was invented by "Prof. Andre Geim and Prof. Konstantin Novoselov" in 2004. It possesses excellent physical and mechanical properties. The properties like excellent biocompatibility and antimicrobial nature and ability to function alone or combining with other biomaterials, offer various opportunities to be used in multiple clinical applications. The motto of this review article to put some light on the overall status in the development of graphene and its application, function, and future perspective.

Keywords: Graphene, graphene oxide, tissue engineering, titanium implants.

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Introduction

The dental materials which come in contact with the dynamic oral cavity, it comes into proximity with various fluids and oral structures like saliva, gingival crevicular fluid, oral mucosa, and water. Mechanical failures of those materials can occur as it is exposed to various temperatures, functional force and a variety of abrasion. So, there has always been a quest for unfolding newer materials that are biocompatible, nontoxic, biodegradable, and should be able to withstand various mechanical and physical insult within the oral cavity to ensure adequate performance and long-term durability.

"The promising mechanization of the 21st century", Nanotechnology, is the process of fabricating materials dimensionally less than l00 nm with distinguishable properties and functions.[1] In recent times carbon containing nanomaterials have been taken into a scientific consideration after the formulation of fullerene and carbon nanotubes in 1985 and 1991 respectively. Graphene is unfolding as the "wonder material" of the 21st century. Carbon has multiple applications in the sector of science and technology. Various allotropes of carbon and its nanostructures can be produced by permutation and combination of carbon atom hybridization. Graphene is one such allotropes of carbon. Nobel Prize was awarded to "Andre Geim and Konstantin Novoselov" for isolating Graphene first in the year 2004.

Graphene is a lucrative material for nanotechnology applications as it is extremely thin and lightweight and made up of one layer of carbon atoms arranged hexagonally.

Graphene has multiple implementations in the modern science and technology field because of its acceptable physical and chemical properties like, biocompatibility, electrical conduction, higher mechanical strength, high surface area and transparency. Graphene can improve the physical properties of various dental materials and has a high chance to be applied in different disease diagnosis, bioimaging, malignancy treatment, drugs and gene transporting.

This review article highlights the development of graphene along with its application, function, and future perspective.

1. STRUCTURE OF GRAPHENE AND ITS DERIVATIVES

The 2-dimensional structure of graphene has sp2 hybridized carbon atoms present in the form of a sheet with thickness of 10 nanometers resembling a honey-comb lattice. The plane of sp2 hybridization consists of s, px and py along with pz which is at right angle to the plane and is unbonded. This 2-dimensional plane consists of a sigma bond with an interatomic length of 1.42 Å, making graphene structurally sturdy than the sp3 hybrized diamond. The increased mechanical resistance of the 2-dimensional graphene, in terms of intrinsic tensile strength (130.5 GPa) and young's modulus (1TPa) is attributed to the in-plane C-C-C bond. [2]. The interaction of Vander Waals forces within the layers of graphene due to the presence of weaker π bonds, facilitates their gliding on the subsequent individual layers under shear stress.[3]

GFNs or graphene family nanomaterials consist of ultrathin graphite, reduced graphene oxide (rGO), graphene oxide (GO), few-layer graphene (FLG), and nanosheets of graphene (GNS) and they differ with regard to the properties of the surface, number of layers present, and the individual size of their molecular. Within the graphene family, graphene oxide or GO comes with the utmost importance and is produced by energetic oxidation of graphite and comprises of a variety of chemically reactive functional groups that are present on their surface, that facilitates interaction with proteins, polymers, biomolecules, and DNA.

2. GRAPHENE SYNTHESIS

One of the important criterions in the production process of graphene depends on separating the layers of graphene in order to achieve the desired properties. Graphene is produced majorly by the following techniques:

i. Mechanical Exfoliation/Cleavage

Mechanical exfoliation or cleavage breaks the weaker forces of Van der Waals present in the layers of the graphene sheets [4]. The various techniques of exfoliation include unzipping carbon nanotubes, exfoliation in liquid phase, mechanical exfoliation, and exfoliation of graphite oxide, etc.

ii. Chemical Vapour Deposition or CVD

In this method of graphene production, hydrocarbons present on the surface of a metal are decomposed in the presence of a catalyst. CVD is considered as the finest method for producing graphene as the number of metallic residues are drastically less.

iii. Hummer's method

This chemical-based technique is used to synthesize graphene in substantial amount. In Hummer's method, graphite is oxidized in conc. H2SO4 in presence of an oxidant, e.g., KMnO4. Setting the temperature at a constant level, oxygen peroxide and water are slowly added in order to obtain the graphene oxide sheets, that are washed with HCl in order to separate the remaining Mn. [5]

4. BIOLOGICAL PROPERTIES OF GRAPHENE

A. Biocompatibility

To introduce a novel biomedical material clinically, it should be biocompatible i.e., the material would not create any adverse effect in contact with living tissues. Biocompatibility depends on various factors like morphology, surface charge, shape, number of layers, etc. These factors can influence characteristics of cellular absorption and particular functional groups attached on the surface can change the interchange of biomolecules like protein and micronutrients. [6]

Literature have advocated that 50ug/ml concentration could a critical limiting point for GO toxicity on mammalian cells and increasing the concentration might be hazardous to T lymphocytes and human fibroblast cells. [7,8] Depending on the size of GFN, the accumulation location and toxicity level can differ in various organs. Nanoparticles with sizes less than 100 nm can get into cells, less than 40nm and less than 35nm can get into the nucleus and the blood-brain barrier respectively. [9,10]

Mechanism of Toxicity [11]

- Due to oxidative stress the elevated ROS (reactive oxygen species) level oxidizes DNA, lipids, and proteins molecules which induce programmed cell death or necrosis.

- Graphene directly influences the cell mitochondrial activity by dissipating mitochondrial membrane potential, resulting in an increased level of ROS and cellular apoptosis.

- A lower degree oxidised GO has increase number of free electrons which facilitate more hydroxyl ion production from H2O2. Oxidative and thermal stress is increased due to the genesis of hydroxyl ions and electron exchange system of the cytochrome C/H2O2 which damages the mitochondria and in turn impose a stronger oxidative effect and toxicity on healthy cells [12]

Olteanu et al. studied the cytotoxic consequences of graphene oxide on human dental follicle stem cells, thermally reduced graphene oxide (TRGO), and Nitrogen-doped graphene (N-Gr). The result revealed that GO increased the intracellular ROS generation. Cells viability were decreased and the membrane potential of mitochondria was altered at higher levels (40 ug /mL) At lower concentrations (4 ug/mL), showed a high antioxidant defence. [12]

B. Antibacterial Effect

Dental biofilm associated with teeth and other structures are aetiology of dental diseases. It has been proven that GNFs show the antimicrobial property against microorganisms such as Escherichia coli, Streptococcus aureus, Klebsiella sp., and Pseudomonas aeruginosa, though oral pathogens were included in few studies. Streptococcus mutans, the gram-positive facultative anaerobe is the cause of dental caries formation and Porphyromonas gingivalis along with Fusobacterium nucleatum gram-negative anaerobic bacteria causes inflammation of periodontium and root canal.

The possible mechanism for antimicrobial actions of graphene is: [13]

- Blade-like graphene structures present on its surface pierce the microbial cell membrane which physically damages it and causes an efflux of cellular materials leading to cell expiration.

- Chemically oxidative stress-induced ROS could inactivate intracellular protein, dysfunction of the mitochondria and lipid peroxidation.

• On metal surfaces graphene aggravates transfer of electron from the bacterial membrane, thus produce reactive oxygen species free oxidative tension to the membrane of mitochondria, which in turn interrupts transportation of electrons in the respiratory series and leads to the destruction of microbial wholeness and cell expiration.

He et al. evaluated that the nanosheets made from GO were very efficacious in interrupting the growing of dental microorganism. At 40 ug/mL growth of P. gingivalis , F. nucleatum was hampered, whereas at 80 ug/mL, S. mutans was killed by GO. [14,15]

Graphene showed improved antimicrobial abilities against oral pathogens when combined with other compounds [16,17] Graphene - zinc oxide (GZNC) nanocomposite shows much lower level of toxicity and forms a distinctive nanointerface which interacts with microorganisms as compared to ZnO, which disturbs physical integrity and stability of biofilm and reduces the carcinogenicity of S. mutans significantly. [18,19]

C. Biodegradability

Biodegradability is one of the important variables that determine the fate of graphene and its derivates in vivo.

According to "Rajendra Kurapati et al. and Sourav P. Mukherjee et al." [20.21] that graphene oxide can be successfully biodegraded by Myeloperoxidase. Nonfunctionalized graphene was more degradation resistant. Prof. Bianco along with his team evaluated the effects of myeloperoxidase, on two types of graphene of single- and multiple-layer forms made by two different processes in water.[20] After that they were kept in proximity with MPO within the presence of H2O2. This peroxidase is readily degraded and oxidized. From the results it was their conclusion that readily dispersible graphene could be broken down by neutrophils.

5. PHYSICAL PROPERTIES

The impressive physical properties of graphene and its derivatives like toughness, elasticity, stiffness, etc. make it a unique and superior dental material. The various physical properties are mentioned in table 1.

6. USES OF GRAPHENE IN DENTISTRY

A. Implants

Today titanium or Ti implants are considered a superior treatment modality for the replacement of natural teeth due to their favourable biocompatibility, reliability, and predictability. However, the inherent inertness of titanium make sit susceptible to develop a fibrous layer around the implant. This can lead to implant failure making Ti implants a superior option, but prone to modifications and subsequent improvement. [22]

It has been seen that Ti implants coated with graphene oxide or GO are better than Ti implants alone. The improvements are attributed to the properties like cell osteogenic differentiation and proliferation, as well as biocompatibility [23]. GO-coated Ti implants also demonstrate antibacterial properties that are more efficacious when the GO is functionalized with silver nanoparticles and antibiotics, which acts as an anti-bacterial substance.

Antibacterial property against *P. gingivalis* and *S. mutans* and other facultative anaerobes or aerobes are said to improve when GO-coating are combined with minocycline hydrochloride because of the synergic effect of GO and minocycline. [23]

B. Membranes

Graphene when used in GBR (guided bone regeneration) with other membranes, effectively prevents soft tissues from growing into the developing bone. [24] Additionally, graphene complies with the five design criteria as stated by TV Scantlebury: integration of tissues, cell-occlusivity, clinical manageability, biocompatibility, and space-making.[25] Collagen membranes integrated with GO on Human Gingival Fibroblasts (HGFs), leads to diminished deformability, better stiffness, reduced hydration and improved surface roughness in comparison to non-coated ones. [25]

C. Addition to PMMA –

Polymethylmethacrylate resin (PMMA) when used with graphene results in superior mechanical properties, lesser polymerization shrinkage, and overall improved antimicrobial properties. [26]. Graphene being a heat conductive material causes complete polymerization of PMMA. Graphene reinforced polymethylmethacrylate resin has a higher modulus and improved resistance to abrasion due to the equal distribution of tension within structures. [27]

D. Resins and Cements

Since resins, cements, and adhesives are porous and are prone to dissolution and failure, the addition of graphene nanoplates (GNPs), which are commercially available as dental adhesives act as nanofiller. This leads to inhibition of *S. mutans*. The 'graphene-gold' nanocomposites are also effective fillers as large number of nanoparticles effectively reinforce the commonly used dental composites. Fluorinated graphene when used with conventional GICs (glass-ionomer cements) are seen to be more effective against bacterial inhibition with superior mechanical properties.

E. Teeth Whitening

A nanocomposite composed of reduced GO and Cobalt Tetraphenylporphyrin (CoTPP) was created to be a catalyst for teeth whitening. Standard photoactivation process of hydrogen peroxide which is used in bleaching of teeth has been seen to be more effective when used in combination with CoTPP. [28]

F. Dental Bacteria Detection

Carbon nanotubes, nanowires, and graphene can be used to develop electronic sensors. Graphene has impressive optical characteristics which facilitates various flexible electronic applications and biosensing. [29] [30]. Elastic modulus of l TPa [5], intrinsic strength (42 Nm-1), and high interfacial adhesion, favours adhesion of graphene onto tough surfaces like silk that can be used as a substrate for transferring the passive electrodes to the tissue surface. These electrodes act as transistors that can detect a particular type of organism. [30]

G. Biofilm Inhibition

Bacterial biofilms are capable to endure several antibacterial agents and thus contribute to oral hard and soft tissue pathogenic mechanisms. Therefore, it becomes quintessential to find techniques that will arrest the formation of bacterial biofilms. Zisheng Tan along with his colleagues in their study concluded that graphene oxide when added to a developing biofilm effectively curbs the bacterial activity during the initial stage of formation of biofilm.[31]

H. Tissue Engineering

Scaffolds are crucial in tissue engineering and they should be to furnish a biocompatible three-dimensional environment in order to ‘support’ and ‘guide’ the bone regeneration process, and at the same time should be capable of stimulating the multipotent cells to proliferate and differentiate. [32] A few studies have delineated that graphene can increase the rate with the human mesenchymal stem cells (hMSCs) proliferates and differentiates into bone forming cells without signs of toxicity. [33] The addition of graphene oxide to the chitosan sulfate scaffold accelerates ontogenetic potential.” [34]

Dental pulp stem cells or DPSC are multipotent stem cells of mesenchymal origin that can be easily procured from an extracted tooth.[35] These cells are capable of undergoing both osteoblastic and odontoblastic differentiation, which makes them a promising candidate for tissue synthesis and regeneration. Rosa et al. established the potential of graphene oxide to allow dental pulp stem cell adhesion and proliferation.” [36]

Periodontal ligament stem cells (PDLSCs) which can be extracted from pulpal and periodontal tissues, when used with GO scaffold, can also undergo differentiation and immunomodulation, into cementoblasts and fibroblasts. [37] [38]

7. SHORTCOMINGS OF GRAPHENE AND ITS DERIVATES

Bio-applications of graphene are much studied, still there are certain shortcomings which needs to be addressed before commercializing graphene and its products.

- Increased mechanical failures in dental implants have been witnessed and this has a direct correlation with the manufacturing procedure as the dimensions of the defects in graphene and its derivatives are directly dependent on their production mechanisms. [39].
- The possible mechanisms of graphene toxicity in biological systems are still under research. [40] However it was found that graphene-based biomaterials may produce oxidative debris, leading to cytotoxicity. Therefore, purity of graphene and its derivatives should be stressed during the various manufacturing procedures. [41] It has also been seen that the physicochemical properties like presence of functional groups, coatings, charges, structural defects, etc., leads to invitro and invivo toxicity. [42,43,44]

8. CONCLUSION AND FUTURE PERSPECTIVE

The functionalization with various biomaterials makes graphene a favourable candidate besides its other properties, like physical strength, thermal stability and electrical conduction. It is the goal of the future that graphene and its derivatives can be used for the biomedical application, as an antimicrobial and/or anti-cancer drugs, and understanding their toxicity. Outer surface of graphene should be investigated for treatment of genetically involved disorders or in vivo gene transportation.

The evolving science of nanomaterials based on graphene as nanomedicines and materials to be applied in dentistry are budding day by day. Besides its excellent mechanical characteristics, graphene along with its derivatives can be operationalised with various biologically active molecules which improve the properties of different scaffolds that helps in regeneration of lost tissue in dentistry.

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