



Graphene - A Multifaceted Panacea

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1 | INTRODUCTION

Advances in technology have greatly influenced the field of dentistry in recent times. The advent of nanotechnology is one such advance that has helped improve the properties of dental materials when incorporated into them. Since dental materials are placed within the oral cavity and are constantly in contact with saliva and water, exposed to temperature changes, masticatory forces and acidic substances consumed by the patient, wearing away of the material has always been a concern. There has thus, always been an interest in developing dental materials with improved lifespan in the oral cavity. Nanotechnology has helped greatly in moving towards achieving this. Various nano-materials have been incorporated into dental materials to enhance their properties. Graphene is one such nanomaterial and its derivatives have attracted great attention, owing to their excellent physicochemical

Abstract

Graphene-based materials have high mechanical, physiochemical, antibacterial, and stem cell differentiating properties and thus been shown to have advantageous properties in biomedical and dental applications due to their versatility. Although graphene-based materials have displayed great advantages in augmenting the functioning of many dental materials, little research has been performed to specifically test the biocompatibility of graphene for dental applications. As compared to the body, the oral environment varies greatly and must be considered when evaluating biocompatibility requirements for dental applications. This review will discuss in-vitro and in-vivo studies that assess graphene's cytotoxicity, antibacterial properties, and the various applications of graphene in the field of dentistry to evaluate the overall biocompatibility and use of graphene-based materials for dental applications.

KEYWORDS

Graphene Oxide, Anti-bacterial property, Bioactivity, Tissue Engineering, Implant coating

property, morphology, biocompatibility, multi-differentiation activity, and antimicrobial activity.¹ It is a carbon-based nanomaterial consisting of two-dimensional sheets that are made up of sp² hybridized carbon atoms bonded together in hexagonal structures.²

2 | BACKGROUND

Graphene was first isolated in 2004 by Novoselov et al.³, and it consists of two-dimensional sheets that are made up of sp² hybridized carbon atoms bonded together in hexagonal structures. It has unique structural, chemical and thermal properties which has led to its utilization in various fields like biomedical, electronics, energy production, bimolecular sensors etc. Graphene nanomaterial is available as ultrathin graphite, few layer graphene, graphene oxide [Go], reduced graphene oxide[rGo] and graphene nanosheets.⁴ Graphene derivatives are widely

applied in the dental fields of restorative materials, adhesives, cements, primers and many more because of properties such as biocompatibility, anti-microbial efficiency and excellent physico-mechanical properties. Pristine graphene - that is graphene in its original, pure, unoxidized form - enjoys superior properties to its oxidized counterpart, but pristine graphene isn't easy to come by and its lack of abundance has held back the development of graphene-based functional devices.⁵ As per literature, there are more than 2,942 studies related to graphene-based materials for dental applications.¹ This emerging research in regard to graphene seems promising and hence has prompted this review of literature with an intent towards evidence based application of graphene in dentistry.

3 | METHOD OF COLLECTING DATA

Review is facilitated by literature search through online and offline modes, that provided us with 26 relevant publications in regard to graphene and its applications.

4 | PROPERTIES OF GRAPHENE

4.1 | BIOCOMPATIBILITY

When used in dental materials, graphene is in constant contact with the oral tissues and saliva. It is thus essential for the material to be bio-compatible. Researchers have studied its biocompatibility in various studies. They have found various factors to be involved in determining its biocompatibility. Up to date, the affected factors involved concentrations, surface functionalization, and so on. Some researchers showed that the toxicity of Graphene oxide to fibroblast cells was minimal when the concentration of Graphene oxide was lower than 20 µg/ml. whereas, the cytotoxicity of graphene oxide increased when the concentration was up to 50 µg/ml.⁶ Wang et al. investigated the cytotoxicity of graphene oxide in mice and the results demonstrated a dose-dependent toxic behaviour in vivo. The cytotoxicity of graphene oxide increased when the concentration was increased.⁷ When the concentrations of Graphene Oxide were 0.1 and 0.2 mg, there was no toxicity detected. With the increase concentration to 0.4 mg, chronic toxicity was observed in mice.⁷ Diana et al. investigated the cytotoxicity of GO, nitrogen-doped graphene (N-Gr), and thermally reduced Graphene Oxide (TRGO) on human dental follicle stem cells and analysed the involved specific mechanism. The result showed the lowest cytotoxicity of GO and the highest cytotoxicity of TRGO.⁸

4.2 | ANTI-BACTERIAL PROPERTY

The anti-bacterial property of graphene has gained interest as it can lead to help achieve infection control when added into dental materials. The antibacterial effect of graphene-based materials was first

discovered by Huet al.⁹ A complete understanding of the anti-bacterial property of graphene is yet to be completely understood. Many researchers have proposed different theories. Physical damage is induced by blade like graphene materials piercing through the microbial cellular membrane causing leakage of intracellular substance leading to cell death.¹⁰ Wrapping and photo thermal ablation mechanism could also provoke bacterial cell damage by enclosing the bacterial cells, providing an unique flexible barrier to isolate bacteria growth medium, inhibiting bacteria proliferation, and decreasing microbial metabolic activity and cell viability.² Chemical effect is primary oxidative stress mediated with production of ROS [reactive oxygen species] as excessive intracellular ROS accumulation could cause intracellular protein inactivation, lipid peroxidation, and dysfunction of the mitochondria, which lead to gradual disintegration of cell membrane and eventual cell death.¹¹

4.3 | APPLICATIONS IN DENTISTRY

4.3.1 | Graphene added to PMMA

Polymethyl methacrylate resin has been used in dentistry from many decades for fabricating denture bases due to advantages, such as easy manufacturing process, low cost, low modulus of elasticity, easy repair, and good aesthetics. However, the limitations of PMMA [polymethyl methacrylate] such as low mechanical properties, large polymerization shrinkage, and the poor inhibition of biofilm formation reduce the lifespan of the material.¹² In recent studies, researchers have tried the addition of graphene oxide into polymethyl methacrylate for improving the mechanical and antibacterial properties of PMMA. Because of the mechanical effect of graphene on PMMA, Azevedo et al. has achieved the definitive maxillary full-arch rehabilitation by incorporating Graphene oxide into the PMMA resin. Review after 8 months revealed satisfactory mechanical and aesthetic outcome, indicating that the addition of GO [graphene oxide] to PMMA resin would be a good choice for prosthetic rehabilitation.¹³ Bacali et al. reported on PMMA with graphene-silver nanoparticles (Gr-Ag), and the mechanical properties, hydrophilic abilities, and the morphology of the composites were further evaluated. The results showed that the compression parameters, bending, and tensile strength of the Gr-Ag fillers were significantly higher than the pure PMMA group, indicating that the addition of Gr-Ag improved the mechanical properties of PMMA resin. Moreover, Bacali and his co-workers also assessed the antibacterial properties of Gr-Ag-modified PMMA, and the results confirmed that Gr-Ag-modified groups showed higher inhibition effect in all Gram-negative strain, *Staphylococcus aureus*, *E. coli*, and *Streptococcus mutans*.¹⁴

4.3.2 | Use of graphene in restorative dentistry

It is always desirable for restorative materials to have a prolonged life in the oral cavity. The added advantage of anti-bacterial property of graphene can help in infection control. Graphene when added to GIC has shown to cause a significant improvement in its mechanical and biologic properties. Fluoride graphene [FG] when prepared by hydrothermal reaction of graphene oxide and mechanically blend

with glass ionomer could produce a GICs/FG composites matrix, which could significantly enhance the mechanical, tribological, and antibacterial properties of glass ionomer.¹⁵ Graphene has been used in various types of dental resins to strengthen bonding and adhesive strength in restorative dentistry. However, if the site is not properly sealed, bacteria can easily access the cured dental tissues through cavities at the tooth restoration interface.² In addition, adhering materials onto dentin is challenging since dentin has higher water content compared to enamel and is less mineralized. Graphene nanoplatelets have been studied for antimicrobial and antibiofilm properties and combined with polymer materials to act as better dental adhesive. From the study, the graphene nanoplates inhibited the growth of *S. mutans* bacteria in vitro and demonstrated good mechanical performance without decreasing adhesive strength.¹⁶

4.3.3 | Application of graphene in implants

Titanium implants have in recent times become a popular choice of prosthesis to replace missing teeth. Titanium has been shown to have good osseointegration property. At the hard tissue interface, osteogenic properties of implant material are essential for osseointegration while at the soft tissue interface, to ensure a tight epithelial seal preventing bacterial invasion is obligatory. Failure of implants can happen due to poor osseointegration and peri-implantitis of titanium and its alloys.¹⁷ Therefore, many surface modifications by graphene-based materials have been used to improve the bioactivities of titanium and its alloys.¹⁸ Gu et al. successfully constructed single-layer graphene sheets on the titanium substrates by PMMA-mediated method.¹⁹ The studies conducted showed that graphene sheets exhibited superior adhesion and proliferation properties of human gingival fibroblasts (hGFs), human adipose-derived stem cells (hASCs), and human BMSCs (Bone Marrow Mesenchymal Stem Cells) compared with the control.²⁰ When graphene is coated on titanium substrate, the hydrophobic character of graphene film exerted self-cleaning effect on its surfaces decreasing the adhesion of microorganism including *S. sanguinis* and *S. mutans*.²¹ Additionally, compared to titanium alone, graphene possesses osteogenic property enhancing the expression of osteogenic related genes RUNX2 [Runt-Related Transcription Factor 2, COL-1 [CONSTANS-like 1], and ALP [aluerin like protease], boosting osteocalcin gene and protein expression, and consequently increasing the deposition of mineralized matrix.²²

4.3.4 | Tissue Engineering

Tissue engineering is being widely used in repairing and regenerating the defects caused by tumours, traumas, infections etc. Scaffolds provide a platform for the attachment, proliferation, and differentiation of different stem cells in the tissue engineering. Many researchers proved that graphene-based materials were suitable for fabricating or coating for scaffolds in the tissue engineering. A pioneering study demonstrated that graphene and Graphene Oxide can accelerate MSC [mesenchymal stem cell] osteogenic differentiation to different degrees due to π - π stacking, hydrogen bonding, and electrostatic interactions with proteins, which may be the underlying mechanism supporting the coating application.²²

4.3.5 | Teeth whitening

Hydrogen peroxide is a commonly used material for in-office teeth whitening procedures. Though it has proven to be an effective bleaching agent, use of excessive amounts of hydrogen peroxide is associated with side effects such as teeth sensitivity and gingival irritation. Su et al have therefore resorted to combining graphene oxide with hydrogen peroxide to improve the efficiency of the process and reduce the potential side effects.²³ The CoTPP [Cobalt-TetraPhenylPorPhyrin]-rGO [reduced Graphene Oxide] nanocomposite can be used as a catalyst to produce more reactions between the staining molecules and H₂O₂, which accelerate the bleaching process.²³ In summary, graphene-based materials are a promising catalyst for tooth whitening application with proper types and concentrations.

4.3.6 | Drug Delivery

Localised drug delivery systems have garnered the interest of many practitioners as they provide the opportunity to deliver the desired quantity of drug to the site of interest. They also allow the controlled re-release of the drug. This has led few researchers to look into graphene as an avenue to function as a drug delivery system. Graphene Nanosheet structure with high surface area and good water dispersibility is a promising candidate for drug carriers toward specific organs.²⁴ La et al. reported that GO is an efficient carrier for the delivery of therapeutic proteins.²⁵ They applied GO-Ti [graphene oxide-titanium] implants as carriers to deliver BMP-2 [bone morphogenetic protein 2] for bone re-generation and successfully demonstrated that ionized GO can deliver proteins by binding through electrostatic interactions. Furthermore, they used a GO-Ti substrate for BMP-2 delivery as an osteoinductive and SP as a stem cell recruitment agent for in situ bone regeneration and reported that GO has the potential to sustain the release of BMP-2.²⁵ Trusek et al. found that GO had the potential in acting as a drug carrier especially in the therapy of dental inflammation.²⁶

5 | CONCLUSION

Graphene-based nanoparticles are considered a topic of great interest in the field of dentistry. They have shown to be of great benefit in improving upon the performance of various dental materials. Additionally, graphene nanoparticles have been found to have adequate initial biocompatibility in the mouth when it comes to bone and tissue engineering. Addition of graphene has been considered in case of dental cements, adhesives, resins and as bio coatings to implants. Although graphene has been shown to display relatively good biocompatible qualities in various dental applications from in vitro tests, there is still a lack of long-term cytotoxicity studies of graphene nanoparticles in the body, as well as a lack of understanding as to how easily they can be excreted from the body. Various factors such as particle size and concentration have shown to influence the cytotoxicity of graphene. There is thus a need for standardization of biocompatibility requirements for dental applications is also needed with long-term in vitro and in vivo studies to see the long term health effects.

CONFLICT OF INTEREST

There is no conflict of Interest

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