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BIOMEDICAL APPLICATIONS OF THE GRAPHENE-BASED NANOMATERIALS

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ABSTRACT

Among entirely diversified 2D materials, graphene has brought in comprehensive research attention within the bounds of the latest 2-3 decades owing to its captivating properties. The scrutiny of graphene contributed a huge amelioration as well as innovative dimensions to materials, research, and nanotechnology. Graphene-based nanomaterials are swiftly evolving as "two-dimensional wonder materials" payable to their novel framework in addition to surpassing mechanical, optical, and electrical properties which are used in electronics and entirely distinct domains. This article precisely scrutinizes contemporary breakthroughs of graphene-based materials in favor of biomedical implementations. Remarkably, graphene-based biosensors for small biomolecules (glucose, dopamine, etc.), proteins, and DNA identification have been outlined; graphene-based bioimaging, drug delivery, and photothermal therapy applications are delineated thoroughly. Future aspects of graphene-based materials in favor of biomedical implementations and potential hurdles in this quickly creating territory are, likewise, talked about.

Keywords: Graphene, Biomedical Application, Drug Delivery, Biosensing, Bioimaging.

I. INTRODUCTION

Our cosmos is packed with materials, and these are the backbones of our modernistic civilization. Together with these materials, carbon-based materials are well-known and postulate a considerable role in human progression [1]. Among the most influential necessities in conventional technology is the evolvement of innovative and competent drug-delivery systems able of edifying the therapeutic profile in addition to the effectiveness of therapeutic agents. The evolvement of several inventive drug-delivery systems has been facilitated by breakthroughs in innocence and nanotechnology, which have endued the invention of novel nanomaterials [2, 3]. The Holocene innovation of graphene has inspired a thriving curiosity in inquiring into this novel material in favor of drug delivery implementations. Since it was an unanticipated innovation in 2004, there had been a lot of buzz about it [4, 5]. The fundamental building block of other carbon allotropes such as 0D fullerenes, 1D carbon nanotubes, and 3D graphite is graphene, a single-atom-thick layer of sp^2 hybridized carbon atoms ordered in a honeycomb lattice [6]. In the domain of energy technology, newborn graphene-based materials have had a marked impact [7-9], hydrogen storage [10,11], and biosensing [12,13],as a result of its matchless electronic, optical, thermal, as well as mechanical properties [14-17], This comprises the abundant surface area ($2630 m^2/g$) [18],extraordinary electrical conductivity (1738 siemen/m) [19], robust mechanical strength (about 1100 GPa) [20], unsurpassed thermal conductivity (5000 W/m/ K) [16], and ease of functionalization [21,6].Graphene-based materials hold outstanding electrochemical in addition to optical properties, as well as the competency to adsorb a broad variety of aromatic biomolecules via π–π stacking and/or electrostatic interactions, making them ideal materials for biosensors and drug loading. Graphene oxide (GO) (as one of the raw materials) can also be readily altered with targeting ligands to assist targeted imaging and drug delivery, gratitude to plentiful oxygen-containing groups linked to its honeycomb-like six atom carbon rings [22]. However, it wasn't up to the time that Dai et al. announced graphene oxide (GO) as a competent nanocarrier designed for drug administration in 2008 that graphene-based materials were introduced first time into the domain of biomedical science [23]. As a repercussion, it's no wonder that graphene has whipped up a lot of curiosity in nanomedicine and biomedical implementations, were specifically altered graphene can

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be soiled in favor of anti-cancer/gene delivery, biosensing, bioimaging, antibacterial uses, cell culture, and tissue engineering. Graphene has been frequently employed to selectively enrich and refine materials due to its massive surface area and sp2 -bonded carbon atoms, detect single-stranded DNA and aromatic compounds (ssDNA) through interactions among π–π stacking [24,25]. Graphene oxide is readily functionalized thanks to its abundant oxygen-containing groups. Due to its high, intrinsic near-infrared (NIR) absorbance, GO has also been put to use as a photothermal agent for cancer treatment, with promising therapeutic results [26,27]. The application of graphene in bioassay and biomedical fields, such as biomolecule detection, bioimaging medication administration, and phototherapy, will be talked about in this article. Forthcoming possibilities and problems for using graphene-based materials in biomedical programs will also be discussed.

II. PROPERTIES OF GRAPHENE

Graphene has been widely investigated as far as its appealing attributes since its seclusion in 2004. As a two-dimensional material, graphene has a huge surface space of around 2630 m2/g [28]. The solid C–C covalent associations inside the graphene sheet make it perhaps the strongest material, with Young's modulus of 1100 GPa and fracture strength of 130 GPa [29]. The π–π bonds underneath and higher than the nuclear plane give graphene an excellent thermal and electrical physical phenomenon. Single graphene has been distributed to possess a thermal physical phenomenon of 5000 W/m/K [16]. The electrical conductivity of graphene has been accounted for to be 10000 S/cm [30], joined with the super high characteristic nature of 200000 cm2v-1s-1 [31,32]. Many parts of graphene properties might be found somewhere else [18,33]. Here, we fundamentally harp on the properties of graphene-based materials that are intently accepting their biomedical applications. The honeycomb grid development of one atom thick layer of graphene joins two comparable sub-cross sections associated along by σ bonds with each molecule having free π electrons causative towards a delocalized electron organization. For graphene, the free π electrons at a high thickness on its planar surface make it fitting for electrophilic responses with numerous natural atoms, for example, click reactions, cycloadditions, and carbine addition reactions [34].

Meanwhile, the conjugated basal plane allows graphene to act with several drugs or alternative biomolecules containing aromatic structures via π–π stacking to fabricate biosensors [35]. The hydrophobic character of graphene may also be used to absorb a lot of hydrophobic organic molecules or polymers via van der Waals interaction [36]. In terms of GO, rGO, and different graphene derivatives, additionally to the higher than noncovalent π–π stacking and van der Waals interactions, the abundant oxygen functional groups on these derivatives gives additional ways in

which to immobilize molecules or biomolecules through each noncovalent interaction, including hydrogen bonds and ionic interactions, and covalent bonds via chemical reactions. Oxygen-containing groups, primarily ionic carboxylates and hydroxylates, will participate in ionic interactions or hydrogen bonding with the analogous ionic components of biomolecules to facilitate the loading of the latter, which may be used for drug or gene delivery applications [37,38]. Meanwhile, the formed basal plane permits graphene to act with a few medications or option biomolecules containing aromatic structures through π–π stacking to create biosensors [35]. The hydrophobic person of graphene may likewise be utilized to absorb a lot of hydrophobic organic molecules or polymers using the van der Waals association [36]. As far as GO, rGO, and diverse graphene subsidiaries, moreover to the higher than noncovalent π–π stacking and van der Waals connections, the abundant oxygen useful gatherings on these subordinates gives extra manners by which to immobilize particles or biomolecules through each noncovalent association, including hydrogen bonds and ionic collaborations, and covalent bonds using synthetic responses. Oxygen-containing gatherings, essentially ionic carboxylates and hydroxylates will participate in ionic collaborations or hydrogen holding with the undifferentiated from ionic segments of biomolecules to work with the stacking of the last mentioned, which might be utilized for medication or quality conveyance applications [37, 38].

The shocking mechanical properties of graphene have conjointly roused scientists to create graphene-based composites with expanded mechanical strength for fluctuated biomedical applications. Graphene, as a building up filler, will work on the mechanical properties of numerous delicate materials, similar to hydrogels or polymer films [39], breaking strength of single layer imperfection free graphene is around multiple times more

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than steel making it one among the strongest materials tried [40]. Young's modulus, Poisson's quantitative connection, and fracture strength for deformity-free graphene are 1 TPa, 0.149 GPa, and 130 GPa, severally [41]. The mechanical properties of graphene are dictated by an assortment of techniques like numerical simulations (e.g. molecular dynamics) [42–44], force-displacement, force volume, and nano-indentation atomic force research (AFM) [45–47].

Graphene has a high thermal and electrical physical phenomenon due to the - holding underneath and higher than the nuclear arrangement GO, on the opposite hand, has a lot of lower mechanical attributes than unadulterated graphene (Young's modulus in the scope of 0.15–0.35 TPa) [48, 49]. Paper-like layered GO platelets, for instance, have a 32 GPa versatile modulus and a fracture strength of 120 MPa [50]. Individual GO particles were stream-directedly collected to make these platelets. Crosslinking singular particles with divalent particles and polyallylamine can work on the mechanical qualities of GO films [51,52].GO films prepared at fluid/air interface by vanishing the hydrosol or those prepared by the decrease of GO scatterings with hydrazine have shown higher durability and stiffness than those prepared by filtration [53,54]. Due to its high strength, graphene has been investigated for upgrading the mechanical properties of polymeric materials. Graphene support into polymethyl methacrylate (PMMA) and polyvinyl liquor (PVA) extensively expanded the modulus and hardness of those composites for biological applications [55]. These supported composites with expanded modulus and hardness are fitting for clinical inserts, hydrogels, and frameworks used in tissue designing applications. The particular construction of graphene and its solid C-C holding gives brilliant thermal and electrical physical phenomena with a low steady of thermal extension. Single-layer graphene has higher thermal and electrical conductivity due to low defect thickness inside the precious stone cross-section. The thermal conductivity of single-layer, deformity-free graphene is ~4500 to 5200 W/mK that is higher than that of graphene oxide (~ 2000 W/mK) [56], multiwall carbon nanotubes (~ 3000 W/mK), and single-divider carbon nanotubes (~3500 W/mK) [41, 57].

Graphene and rGO have superb electrical physical phenomena that might be utilized to create electrical biomedical gadgets, including field-impact semiconductor biosensors, and to go about as a substrate for semiconducting cell culture gadgets [57–59]. The low electrical physical phenomenon of GO, which results from structure defects, limits the immediate uses of GO in electrically dynamic materials and gadgets, in any case, the oxygenated functional groups of GO will be utilized to immobilize fluctuated electroactive species through covalent or noncovalent bonds to manufacture delicate electrochemical frameworks [60]. In addition, the acceptable dispersibility of GO in a few polar solvents, huge water [61-63], simplifies it to technique GO.

Extraordinary electrical physical phenomenon and thermal properties of graphene can be valuable not just in electronic gadgets anyway furthermore in biomedical gadgets for measure cell potential and as a substrate for conductive cell culture gadgets and biosensors [64–66].

At last, the optical properties of graphene-based materials are useful for biomedical applications. Monolayer graphene has a light conveyance of 97.7% of the absolute occurrence of light over a spread of frequencies [67]. Light absorption and optical image distinction increase with the increase in the number of layers of graphene [68]. When graphene size is decreased to the nanoscale to frame nanoribbons, it will discharge inborn photoluminescence attributable to band holes instigated at this nanoscale. Comparable properties are resolved in GO and GQDs, which empower scientists to utilize these graphene-based materials for biomedical imaging [24, 69]. Also, GO is an effective fluorescent quencher for an assortment of fluorophores through nonradioactive electronic excitation energy move from the fluorophore to GO; this property has been abused for biosensing, especially as a fluorescence reverberation energy move identifier, given its huge sorption cross-sectional [70–72]. Also, graphene and its subordinates include solid optical ingestion inside the close infrared reach, making them amazing specialists for photothermal treatment [27].

III. BIOMEDICAL APPLICATIONS OF GRAPHENE

DRUG / GENE DELIVERY

Straightforward physisorption through - π arrangement can be utilized to focus on some hydrophobic medications, like doxorubicin and docetaxel, with antibodies of the decision to kill harmful cells. The large specific surface, -π arrangement, and electrostatic or hydrophobic bonding of graphene can favor high drug

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accumulation of less soluble drugs of high potency and strength. Liu et al. [23] synthesized a PEG-activated nanoscale graphene oxide (NGO) layer loaded with the SN 38 analog of camptothecin (CPT). This complex (NGO - PEG - SN38) exhibits good solubility in the water while maintaining the high strength and effectiveness of SN38. To specifically target malignant growth cells, the CD20+ antigen (an activated glycosylated phosphoprotein overexpressed in cancer cells) is further immobilized in NGO via binding to polyethylene glycol [24]. It has been shown that the drug delivery system developed is pH-dependent, as the hydrophilicity and solubility of DOX increase in an acidic environment. Zhang et al. [73, 38] contain two anticancer drugs (DOX and CPT) with folic acid and SO3H groups, which are formed in a controlled manner by GO via -π alignment. The combined loading of the two drugs by GO with folic acid ligand showed significantly higher specific targeting and cytotoxicity against MCF-7 cells, human breast cancer cells with folic acid receptors, and, more importantly, significantly higher cytotoxicity than GOs loaded only with folic acid. One active drug ingredient. Functionalization with cationic polymers, such as PEI. It is used as a non-viral gene vector because it can interact strongly with negatively charged phosphate ions in DNA and RNA [74]. This makes transfection easy and effective, increases cell selectivity, and reduces cellular toxicity. The resulting PEI-GO facilitates the loading of siRNAs (small interference RNAs that can inhibit protein expression via cleavage of target messenger RNA) via electrostatic adsorption and aromatic cancer drugs via p-p stacking. PEI-GO/Bcl-2 and PEI-GO/DOX-directed siRNAs were then transferred to Hela cells. As siRNA targets Bcl-2 and cancer drugs, DOX has a synergistic effect and offers higher transfection efficiency with reduced PEI cytotoxicity and increased anti-cancer activity.

BIOSENSING AND BIOIMAGING

The sensing or detection of biomolecules is very important for biomedical, environmental, and protection purposes and can be done with the help of biosensors. Subsidiaries of graphene, including GO, artificially reduce GO (rGO) [75], and doped graphene [76] is being concentrated to provide comprehensive detection and biosensor applications for biomolecules such as thrombin [77], oligonucleotides [78], ATP [79], amino corrosive [97] and dopamine [98].

At present arranged biosensors-based GO have been created, for example, (1) work of fluorescence extinguishing limit of graphene which is successful and hardly any FRET-based biosensors have been coined (2) FRET-based biosensors of graphene have been planned positioned on their electric property [99].

Self-organized and controllable graphene biomolecules allow the construction of ultra-sensitive biosensors to confirm different DNA and atoms [100, 82]. GO-based biosensors were developed using outstanding physicochemical properties such as large surface area, outstanding electrical directivity, and the heavenly capacity for stacking particular biomolecules with synthetic or actual affiliations [101,102].

The complex ultra-thin graphene films created by the layered collection strategy exhibit a synergistic movement as opposed to the reduction of H2O2. Ultrafine graphene films stimulate the production of modern biosensors and electrochemical sensors [103].

IV. PHOTOTHERAPY

Phototherapy, notwithstanding chemotherapy and gene therapy, is a helpful methodology that can be utilized to treat a wide assortment of issues. Phototherapy, including photothermal treatment (PTT) and photodynamic treatment (PDT), can handle the ailment by express light brightening [104]. PTT practices an optical-absorbing specialist to produce heat under light illumination; so biological tissues are presented to a raised temperature to help the specific destruction of unusual cells [27]. Liu et al. at first declared the integrated application of GO joined by PTT in successful tumor suppression [105]. The PTT field has been giving substantial thought to graphene because of its critical optical retention in the close infrared reflectance range. Zhang et al. established DOX-loaded PEGylated nanographene oxide (NGO-PEG (polyethylene glycol)-DOX), which can transport together heat and drug to the tumorigenic zone in one system [106]. Hu et al. set up rGO-marked quantum speck (QD-CRGO) nanocomposite that joins PTT treatment with cell/tumor fluorescence bioimaging. The stage for PTT of brain tumors was rGO functionalized with biocompatible porphyrin. This PGO was shown to be more stable than rGO, and it also resulted in a sizeable number of brain cancer cells being destroyed in vitro [107]. PTT, then again, can't be utilized alone to kill tumor cells since heat is sent unevenly in these cells [108]. PTT is

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used related to different procedures that might incorporate altering GO qualities to upgrade helpful adequacy. A photosensitizer (PS) is bombarded with proper light to produce free radicles or reactive oxygen species (ROS) that irreversibly harm malignant growth cells in PDT [109]. Its dissolvability and biocompatibility, Zhou et al. immobilized hypocrellin-A (HA, a perylenequinonoid hydrophobic non-porphyrin photodynamic antitumor medication) onto GO through the π–π stacking joint exertion, hydrophobic impact, and hydrogen-holding affiliations [110]. Singlet oxygen is created when GO–HA is excited at a particular frequency of light. HeLa cells were utilized to show high cell retention of GO–HA, just as impressive as cell killing brought about by light illumination. Photothermal treatment joined with photodynamic treatment was demonstrated to be helpful by Tian et al. [111]. Chlorine6 (Ce6, a photosensitizer particle) was loaded on PEGylated GO and provided to KB cells as a composite (HeLa subsidiary cells). The transport of Ce6 was found to be supported by a low-power thickness laser (808 nm) and mild local heating caused by the graphene's photothermal effect. Because of the regularly utilized photos, PDT is as yet a test. PDT is as yet a test, as the regularly utilized photosensitizers are hydrophobic.

V. SCAFFOLDS FOR MAMMALIAN CELL CULTURE

The graphene CVD substrate is biologically reasonable intended for human mesenchymal cells (hMSCs) and human osteoblasts. Cell lines refined in the organization of graphene showed a more serious level of expansion, development, and separation [112] when coordinated to those become on SiO [113-115]. The utilization of assorted GO materials for cell cultures of respiratory organ epithelial tissue has been expressed not to impact the imperativeness and biological responsiveness of the cells [116-118]. NIH-3T3 fibroblast's conduct was inspected in the scope of carbon nanomaterial-coated substrates, including GO, carbon nanotubes, and RGO. The carbon nanomaterial-coated substrates had higher grouping transfection effectiveness and biocompatibility [119]. In tissue engineering, graphene/chitosan films have an immoderately encouraging implementation in enhancing and restoring tissue functions [120]. The CVD-created graphene substrate was likewise discovered to be biocompatible for hMSCs and human osteoblasts, considering faster cell multiplication and elevating cell improvement and separation. Multilayered GO nanosheets gathered by layer by layer procedure will improve the mechanical properties of electrolyte multilayer films for higher connection of cells [121].

VI. GO-BASED ANTIBACTERIAL MATERIALS

Silver nanoparticle preparation and antibacterial result on GO sheets are reportable [122]. GO has been set inside the presence of sodium citrate and silver nitrate. Characterization of GO was done physicochemically by abuse thermogravimetric examination (TGA), XRD, TEM, UV–Vis, and Raman's spectroscopic investigation. Fan et al. [123] prepared perceptible separate GO and rGO paper from their suspension by vacuum filtration method and found that these papers show the solid antibacterial impact. Considering the quantifiability and minimal expense of the graphene-based antibacterial paper, this work opens new possibilities for the utilization of GO in ecological and clinical applications.

Interestingly, the Gram-negative Escherichia coli bacterium with an outer membrane was more resistant to the cell membrane damage caused by the nanowalls than the Gram-positive Staphylococcus aureus lacking the outer membrane. Moreover, the rGO nanowalls were more dangerous to the bacteria than the GO nanowalls. The better antibacterial activity of the rGO nanowalls, consistent with the researchers, is because of the better charge transfer between the microorganism and therefore, the additional sharpened edges of the rGO nanowalls, throughout the contact interaction. Later Akhavan et al. [124] investigated the antibacterial impact of graphene nanosheets inside the assortment of nanowalls sat on stainless steel substrates for both Gram-positive and Gram-negative models of the bacterium. Curiously, the Gram-negative Escherichia coli bacterium with an external layer was more impervious to the cell film harm brought about by the nanowalls than the Gram-positive Staphylococcus aureus coming up short on the external film. Besides, the rGO nanowalls were more perilous to the microscopic organisms than the GO nanowalls. The better antibacterial action of the rGO nanowalls, steady with the analysts, is a direct result of the better charge move between the microorganism and in this manner, the extra sharpened edges of the rGO nanowalls, all through the contact association. Liu et al. [125] the instrument of antibacterial effect of four graphene subordinates, graphite (Gt), graphite oxide (GtO),

GO, and rGO, was explored further. They establish that the antibacterial pursuits decline within the order of GO, rGO, Gt, and GtO. GO and rGO shows more noticeable antibacterial action than others [126] by causing layer pressure. The pressure is produced by the pointed uneven corner of graphene, which brings about plasma film harm, the discharge of polymer, and film integrity loss [127].

When the concentration, incubation time, and therefore, the conditions are the same, GO shows the absolute best antibacterial action as rGO, Gt, thus GtO. They relegate the antibacterial impact to every layer and aerophilic pressure, thus proposed a three-step system for the antibacterial impact, actually like that of carbon nanotube, for example, (1) deposition of the cell on graphene-based materials, (2) film pressure when sharp nanosheets straightforwardly contact cells of the body and (3) oxidization, free of superoxide anion, is fit to materials dependent on graphene. The microorganism movement of GtO is a lot stronger in contrast with GO [128]. This work is critical for us to understand the GO-microscopic organism's collaboration and to direct the improvement of better graphene-based antibacterial materials.

VII. CONCLUSION

Graphene and graphene-based composites have extraordinary electronic, natural, mechanical, and optical properties. In this review, we have described the biomedical applications of graphene-based nanomaterials, including drug and/or gene delivery, biosensing and bioimaging, phototherapy. Different types of graphene, its derivatives, and composites are introduced, and their properties associated with biomedical applications have been discussed. The extraordinary features, such as a large specific surface area, superior mechanical strength, and distinctive optical properties, of graphene-based materials, make them ideal candidates for loading various medications or genes for distribution, as well as acting as imaging agents. The development of a novel biosensor based on graphene has significant functionalization under numerous physiological conditions with a loss in few properties. As an emerging field, research on nanomaterial scaffolds of graphene for the application of stem cell culture needs special attention. To build therapeutics based on graphene, researchers might standardize its derivatives as well as check functionalization of this on the biological field to know the response of cells to many graphene derivatives. Graphene may come up as a unique nanoparticle for use in biomedical research by effective association with diverse branches of science.

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