Graphene also exhibits self-healing property, when exposed to molecules containing carbon, such as hydrocarbons and organic compounds. Bombarded with pure carbon atoms, the atoms perfectly align into hexagons, completely filling the holes.[8]

Graphene is the only form of carbon and one of the very few materials which has every atom available for chemical reaction from two lateral sides. Atoms at the edges of a graphene sheet also have special chemical reactivity. Graphene can be easily modified with oxygen and other functional groups to from substitute compounds such as Graphene Oxide (GO).

The precise structure of Graphene Oxide has been deliberated over the years. The primary contributors are the complexity of the material due to its amorphous form and the lack of precise analytical techniques for characterization. One of the major advantages of the Graphene oxide is its easy dispensability in water and other organic solvents. This property of GO makes it suitable for imbibing in a polymer or ceramic matrix, drastically altering their electrical and mechanical properties.

On contrary to its oxide, Graphene is hydrophobic in nature and impermeable to all gases and liquids (vacuum-tight). Various methods have been devised to alter this innate property by introducing air-born hydrocarbons, prolonged exposure to UV light.

2. Method of Synthesis

The most promising, inexpensive and readily accessible approach for deposition of reasonably high quality of graphene is Chemical Vapour Deposition (CVD) onto transition metals substrates such as Ni, Pd or Cu. Initially reported Graphene was prepared by using mechanical exfoliation of highly oriented graphite crystal. Although this method is labor intensive and difficult to reproduce, graphene produced by this method has lowest number of defects and highest electron mobility.[10]

However, large quantities of the graphene sheets of desired dimensions, required for most applications, cannot be obtained from this method. Recently, several high-throughput approaches for graphene synthesis such as chemical vapor deposition (CVD) have been developed.

The Low Pressure Chemical Vapour Deposition (LPCVD) involves disintegrating the hydrocarbon gas methane at a specific high temperature to build uniform layers of carbon (as graphene) on a pretreated copper substrate. Copper is preferred because it has almost zero solubility of carbon even at 1000°C. This gives easier control over the deposition of graphene on the copper surface as the cooling rate does not affect the graphene thickness. The growth on copper is simple and straightforward making high quality graphene over large area readily accessible. Furthermore thin Copper foils are inexpensive and can be easily etched with solvent so that the transfer onto desired substrates (SiO_2, Si) can be readily achieved. This gives easier control over the deposition of graphene on the copper surface. Graphene growth is strongly affected by imperfection sites on the copper substrate. By proper treatment of copper surface and precise selection of growth parameters, the quality and uniformity of graphene are significantly improved and the number of graphene layers can be controlled. It is found that micro-topography of the Cu surface strongly affects the uniformity of grown graphene while the purity of Cu film determines the number of synthesized graphene layers at low pressure conditions.[9][10]

Prior to deposition of graphene on the Cu foil, the substrate must be annealed at high temperatures in a hydrogen reducing atmosphere. This annealing stage is important for increasing the copper grain size and rearranging the surface morphology to facilitate the growth of graphene flakes. Wet chemical pre-treatment by dipping in acetic acid has also been demonstrated to partially remove Cu_2O.[11]

Once the Cu has been treated at a uniformly maintained temperature as high as 1000°C, the growth of graphene is carried out by introducing the carrier and source gas. A pre-calculated ratio of low methane and high hydrogen gas (1:20) in introduced into the system for a limited period of time under controlled low pressure conditions. Methane is preferred over the other hydrocarbon substitutes (propane and butane) because of its low carbon to hydrogen ratio, effectively providing a mono layer instead of multilayered of graphene. At high temperatures, methane is pyrolyzes to form carbon and hydrogen. The carbon deposits on the Cu foil in hexagonal lattice to form graphene. While hydrogen combines to form its dihydrogen compounds, which are removed as impurities.[12]

One of the most widely used method to evaluate the quality and uniformity of single layered graphene on Cu substrate is Raman Spectroscopy. [13]

For Biomedical applications, extensive oxidation of aromatic structure of graphene is done followed by their dispersion in solution. Resulting Graphene Oxide has high density, OH and COOH groups.[14][15]

3. Applications in Anti-Cancer Drug Delivery

The biomedical applications of graphene-based materials, including drug delivery, have grown rapidly in the past few years. Graphene and graphene oxide (GO) have been extensively explored as some of the most promising biomaterials due to their two-dimensional planar structure, larges surface area, chemical and mechanical stability, superb conductivity and good biocompatibility. These properties result in promising applications for the design of advanced drug delivery systems and delivery of a broad range of therapeutics. Graphene based materials demonstrate excellent capability to adsorb a variety of aromatic bio-molecules through a π–π stacking interaction and/or electrostatic interaction, which make them ideal materials for constructing biosensors and loading drugs.[17] Utilizing its large surface area and sp2-bonded carbon atoms, graphene has been widely used to selectively enrich and detect aromatic molecules and single-stranded DNA. The scheme of GO and graphene as nano-therapeutic drug delivery platforms to carry different therapeutics from small drug molecules, antibodies, DNA, proteins and genes is

presented in Fig. 2. The modification of graphene and GO to build desired graphene drug carriers is of great significance. The surface modification of graphene and GO by covalent chemical bonding is possible due to the presence of defects and reactive oxygen groups in the graphene lattice function as a site for reactivity. Nano-graphene oxide (NGO) is formed by the graphene oxide by converting micrometric lateral dimensions of the sheets to a nano-metric size. This imparts aqueous stability to the NGO in buffer solutions and other biological media by covalently grafting polyethylene glycol (PEG) star-polymers onto the chemically activated surfaces and edges. Upon grafting PEG stars onto the –COOH groups, we obtained a product (NGO–PEG) with high solubility and stability in salt and cellular solutions, which is desirable for biological applications. In order to use graphene and GO in practical clinical applications, it is essential to confirm their bio-compatibility and toxicity through extensive in-vitro cell study. Though the reports indicate low cell toxicity of graphene, GO and their hybrid structures as drug carrier, the results remain conflicting.

A simpler method to build a GO drug delivery system for anti-cancer therapy is direct immobilization of anti-cancer drug molecules (DOX) on graphene and GO surfaces. DOX, an anthracycline antibiotic, has been widely used as an anti-cancer drug in cancer chemotherapy intravenous administration. The drug distribution to tumour sites by this method is limited due cellular barriers of the tissues, which can be prevented using nano-carriers such as graphene and GO. Loading of DOX on GO is achieved by a simple mixing in an aqueous solution with the aid of sonication, which delivers a very high concentration of drug on the graphene surface. The controlled loading of DOX is achieved via π-π stacking and hydrophobic interaction. One of major disadvantages of chemotherapy and radiotherapy currently used for cancer treatment is their limited specificity to cancer cells, which could lead to undesired side-effects on normal tissues and organs. The advantage of targeted anti-cancer drug delivery compared with conventional cancer therapies is an exceptional selectivity and ability to kill cancer cells specifically on tumor sites without inadvertent side-effects.[16][18]

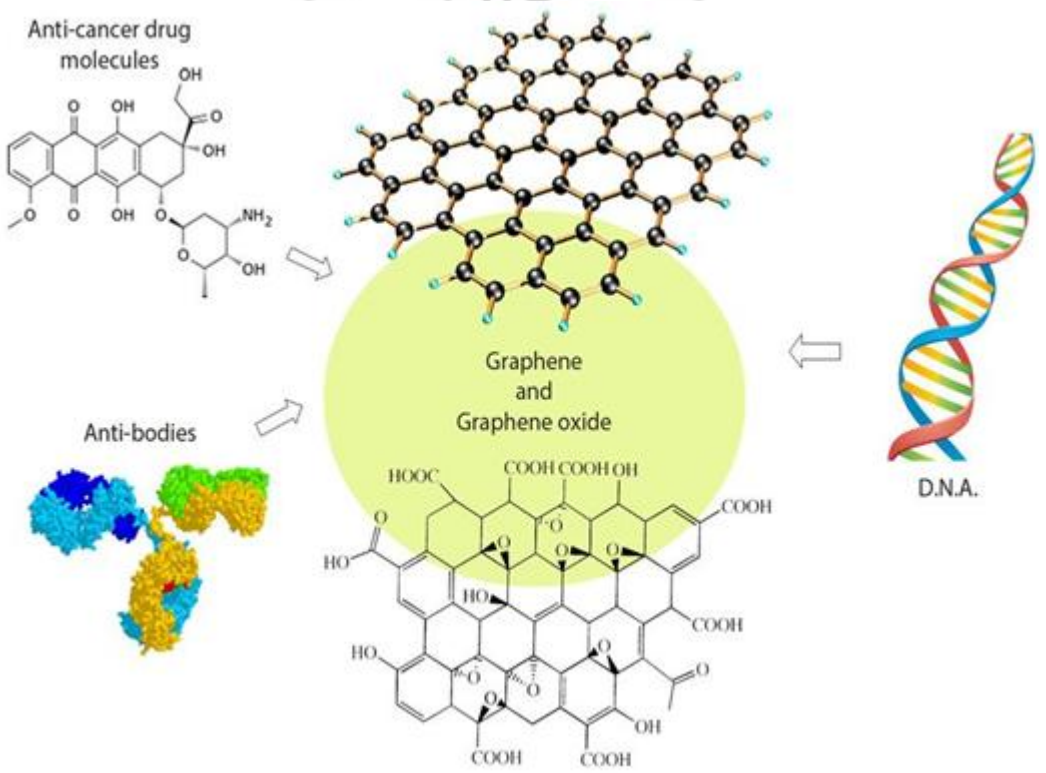

Figure 2: Scheme of GO and graphene as nano-therapeutic drug delivery platforms to carry different therapeutics from small drug molecules, antibodies, DNA.

4. Conclusion and Future Prospects

As a result of their unique properties and fascinating structure, graphene and its derivatives have found extensive application in bio-medical area in the recent years. Although the advances are exciting and encouraging, the use of graphene based material for bio-medical applications is still in infancy with lots of challenges remaining. Synthesis of uniform graphene can help increase the repeatability required for accurate bio-molecule detection and drug delivery. Hence, new methods for preparing inerratic graphene sheets need to be developed. In summary, graphene and its derivatives emerge as a novel nano-material platform for biomedical applications, yet many challenges need to be solved by effective collaborations crossing multiple disciplines including chemistry, physics, biology and medicine.

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