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# Graphene- An emerging star in the field of nanotechnology

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**Abstract**
Graphene, whose discovery won the 2010 Nobel Prize in physics, has been a shining star in the material science in the past few years. Graphene is a nanomaterial comprising of single atomic layer of $sp^2$-bonded carbon atoms tightly packed in a two dimensional (2D) honeycomb lattice. Owing to its interesting electrical, optical, mechanical and chemical properties, graphene has found potential applications in a wide range including biomedicine. In this review, I aim to address graphene as an emerging material in biomedicine, its opportunities and challenges in this emerging field as it has wide range of applications including drug delivery, cancer therapies and biosensing.

**Keywords:** Graphene, material, cancer, emerging.

## 1. Introduction
Graphene is a nanomaterial comprising of single atomic layer of $sp^2$-bonded carbon atoms tightly packed in a two dimensional (2D) honeycomb lattice. Exciting advances in preparation of nanosystem with applications in the medical field have lead to new challenges in the design of smart materials capable of meeting the clinical demands. Therefore, the application of nanotechnology for treatment, diagnosis, monitoring and control of biological systems (recently dominated as nanomedicine) has been declared as one of the most promising fields of research over the last decade [1]. Sp2 carbon nanomaterials notably zero dimensional fullerenes, 1D carbon nanotubes and 2D graphene have gained significant interest from various fields and generated huge impact in the materials, research community since their discovery in 1985, 1991 & 2004 respectively [2].

## 2. Method
A web-based search for all types of articles published on graphene was initiated using medscape, Elsevier and ASEE. The search was subsequently refined. The information taken from sites of specialized scientific journals in the area of nanomedicine and nanotechnology. Some internet sites as nanowerk.com has also been used. The search was restricted to articles published in English, with no publication date restriction.

## 3. Discussion
### 3.1 Discovery
In 1947, Canadian physicist Philip Wallace wrote a pioneering paper about the electronic behaviour of graphite that sparked considerable interest in the field. Nobel Prize winning chemist Linus Pauling in 1960 speculated about behaviour of flat, single layers of carbon atoms. German chemist Hanns Peter Boehm, had spotted them under his electron microscope and named them as “Graphene” in 1962.
Theoretical research into graphene continued for the next four decades, boosted in the 1980s and 1990s by the discoveries of fullerenes (effectively, graphene curled up into balls) and carbon nanotubes (graphene folded into a pipe). Even so, no one could ever actually make the stuff in practice; Graphene was only produced in a laboratory in 2004, by Russian born scientists Andre Geim and Konstantin Novoselov working at the UK's University of Manchester [3].

### 3.2 Origin

Carbon comes in many different forms, from the graphite found in pencils to the world's most expensive diamonds. In 1980, we knew of only three basic forms of carbon, namely diamond, graphite and amorphous carbon. Then, fullerenes and carbon nanotubes were discovered and in 2004, graphene joined the club. Graphene is an atomic-scale honeycomb lattice made of carbon atoms [4].

Graphene is a single-or few-layered sheet of Sp2- bonded carbon atoms that are densely packed in a honeycomb crystal lattice [5, 6].

Graphene is undoubtedly emerging as one of the most promising nanomaterials because of its unique combination of superb properties, which opens a way for its exploitation in a wide spectrum of applications ranging from electronics to optics, sensors and biodevices [4].

### 3.3 Properties of grapheme [5]

#### 3.3.1 Physical properties

1. Large surface to volume ratio.
2. Unique optical properties
3. Excellent electrical conductivity
4. Remarkably high carrier mobility
5. High carrier density
6. High thermal conductivity
7. Room temperature Hall effect
8. Ambipolar field-effect characteristics
9. High signal-to-noise ratio
10. Extremely high mechanical strength

**3.3.2 Chemical properties:** (Chemistry of graphene)

Basically the chemistry of grapheme has also been widely investigated. For biomedical applications of grapheme in physiological environments, proper surface functionalization on grapheme is demanded to render high water solubility and biocompatibility. Hummers oxidization to generate grapheme oxide is oldest and most common method of graphene. Further conjugation of hydrophilic polymers could further improve stability.

For covalent chemistry 1, 3-dipolar cycloaddition is used for functionalization strategy whereas for non-covalent chemistry various molecules and polymers can be used via hydrophobic bindings or omega-omega interactions. This is most commonly used for drug delivery as many aromatic drug molecules can be physically adsorbed on the polyaromatic graphene surface by w̅-w̅ stacking [5].

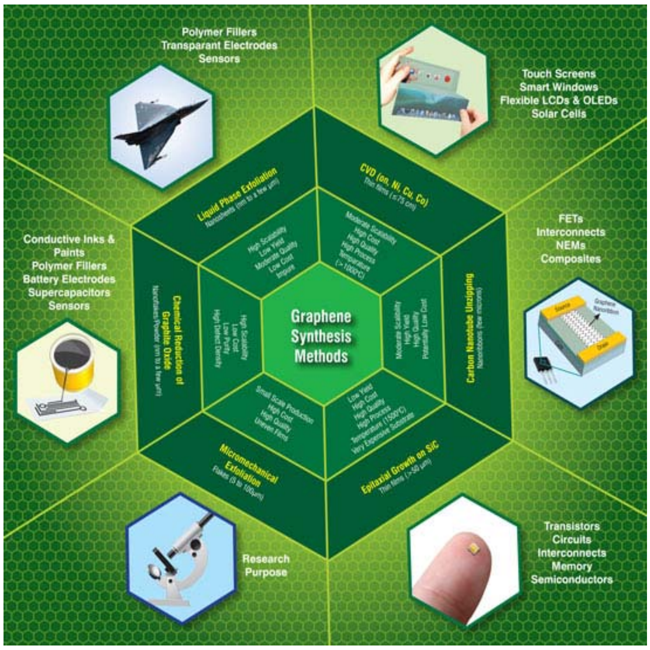
A latest work reported it displays lower NIR-absorbing capability, its photothermal responsiveness and *in vitro* photothermal cancer cell killing efficiency [5].

### 3.4 Interaction with substances

Carbon materials such as carbon nanotubes explored the possible entry into cells. These substances enter via energy dependent endocytosis pathway or passive diffusion owing to needle like structure of nanotubes. But interaction does not reported with graphene till now [2].

### 3.5 Graphene production [4, 5]

Earlier graphene produced by either top-down (the mechanical scotch tape method and chemical exfoliation from graphite) or bottom-up (chemical vapour deposition) methods but these conventional methods involve the use of toxic chemicals and result in generation hazardous waste and poisonous gases. Therefore, these are the green methods developed to produce graphene by following environmentally friendly approaches.




### 3.6 Applications of graphene

The conglomeration of biology and nanotechnology becomes a valuable route and further improves the performance of the devices built on this device. Due to these properties, graphene had a wide range of applications in various fields. Graphene being an emerging concept in biomedicine along with biotechnology had impact on patient treatment and welfare. Hereby, enlisting the uses of graphene highlighting on drug & gene delivery, tissue engineering and cancer therapy.

| **Graphene based biosensors (5)** | |
|---|---|
| 1. Optical sensing | Oligonucleotides (ssDNA, aptamers) Proteins (Thrombin) Heavy metal ions (Antigen) Pathogen (rotavirus) |
| 2. Electrochemical sensing | Biomacromolecules (DNA, hemoglobin) Enzymes (glucose oxidase) Small molecules (hydrogen peroxide, dopamine, glucose, NAD) |
| 3. Electronic devices | Proteins, DNA, bacterium and pH values |
| 4. Matrix for mass spectra | Small molecules (cocaine & adenosine) |
| **Graphene for potential cancer therapy (5)** | |
| 1. Drug delivery | Loading of chemotherapy drugs (doxorubicin & SN38) *In vitro* cancer cell targeting (using antibodies, peptide and folate acid) |
| 2. Photothermal therapy | *In vitro* cancer cell killing under near-infrared light, better than carbon nanotubes. Ultra-high *in vivo* tumor uptake and efficient photothermal ablation of cancer in mice |

Graphene as a single layer alone is not effective therefore, it has been modified in various form for increasing efficiency.

a. **Gene delivery:** Gene therapy is required for treatment of many diseases but the issue which is lacking in this area was development of nonviral gene delivery vectors or carriers with high efficiency of gene transfection. Later, authors going on searching and found that polyethylenimine (PEI) modified with graphene oxide provide a better & efficient result for gene transfection rather than PEI alone which was used earlier for this process. Apart, from this, Bao *et al.* found one more product for application in gene delivery i.e. chitosan based functionalized graphene oxide sheets [10].

b. **Drug delivery:** The use of graphene in drug delivery and biomedicine was first initiated by the Hongjie Dai group at Stanford university in 2008 [5]. It comes into interest because of interaction between hydrophobic drugs and aromatic regions of graphene sheets [10]. The unique structure of graphene of ultra-high surface allows loading drug and aromatic molecules therefore, aromatic anti-cancer drugs like DOX & Camptothecin were effectively loaded on graphene surface via ω-ω stacking and hydrophobic for intracellular drug delivery [1, 5].

   Carbon nanotubes & graphene are surface functionalized with specific biomolecule based on drug delivery for minimizing drug degradation & increasing drug availability. This results by modulation of pharmacokinetics, pharmacodynamics and biorecognition [10].

c. **Tissue engineering:** Ultrastrong graphene oxide paper was prepared from GO sheets which when dispersed in water assembled into well ordered structure under a directional flow and this GO paper was found successful in adhesion and proliferation of L929 cells when mouse fibroblast cell line was cultured [10]. Many other workers have exploited properties of graphene for its use in field of tissue engineering such as graphene hydrogel and its suitability and high biocompatibility of nanomaterials as surface coating materials [10]. 3 D graphene foam because of topographical, chemical and electrical properties has also been used for novel neural stem cell scaffold and helps in neural tissue regeneration [11].

d. **Cancer therapy:** Due to its unique conjugated structure, large surface area and relatively low costs, graphene has open a new horizon in the field of pharmacological applications in-vitro and in-vivo [10]. It has been used in animal models and found its use effective in treating various cancers of body such as:

a. Prostate cancer – detect by prostate specific antigen binding behaviour [8].
b. Pancreatic & GIT cancers – identified by binding behaviour of monoclonal antibody 19-9 [8].
c. Lung cancer- By lung cancer antigen binding [8].
d. Breast cancer- Diagnosis by binding of HER-2 [8].
e. PEGylated nano-graphene with high in-vivo tumor passive uptake and strong near-infrared light absorption used for effective photothermal treatment of cancer and for several xenograft [10].
f. For photodynamic therapy to treat cancer- application of folic acid and sulfonic acid conjugated GO loaded with porphyrin photosensitizers reported [11].

Graphene is also used as a biosensor to detect cancer biomarkers and cancer utility antigen concentration in saliva [7, 8]. Graphene onto a silicon carbide substrate under extremely high temperature and low pressure to form the basis of the biosensor [7]. When biomarker such as 8 hydroxydeoxyguanosine detected in elevated levels indicates increased risk of developing several cancers and this sensor can detect target molecules faster than ELISA [7]. Mannoor stated as with graphene as a conductor and cancer antigen as a resistor they create a sensing platform that can detect & quantify concentration of cancer antigens in saliva and diagnose cancer. Saliva is placed onto the printed circuit board, cancer antigen if present will be attracted to immobilized antibodies. This device has potential of high sensitivity, high selectibility and significantly decreased response time in detecting cancer antigen in the body [8].

Graphene can convert non-ionizing radio-waves into heat energy at microscopic levels and this heat is sufficient to completely destroy proteins and DNA inside individual cancer cells. Since the heating process takes place only within cancer cells, damage to normal cells can be kept minimum [9].

This indicate new approach for destroying even the most resistant cancer cells non-invasively using bio-conjugated graphene nanoparticles and simple radio-waves that is otherwise used in our mobile phones.

### 3.7 Adverse effects/ Toxicity of graphene

There is *in vivo* and *in vitro* toxicity of this material.

1. *In vitro* : a. As we discussed there is toxicity due to production of graphene by chemical vapour deposition technique increased the activation of caspase 3, release of lactate dehydrogenase & generation of reactive oxygen species, in neural pheochromocytoma-derived PC12 cells.

   b. Cytotoxicity of human fibroblast cells at a graphene oxide concentration above 50 mg/l.

2. *In vivo*: Dose-dependent pulmonary toxicity [5].

### 3.8 Challenges & limitations

The potential short and long term toxicity concern of graphene in nanomedicine and cancer therapy [2].

To overcome this biocompatible coating done after PEGylation shows significantly improved biocompatibility and excellent stability and appears to have reduced toxicity [5].

## 4. Conclusions and Future Perspectives

Biomedical applications of graphene are currently being intensively explored by many research groups around the world, producing a lot of promising although mostly preliminary results. For applications towards cancer therapies, graphene-based drug delivery may be combined with other novel therapies such as photothermal therapy and potentially gene therapy, for further improved therapeutic efficacy. Despite the factor that there are still many unresolved issues and challenges in graphene-based nanomedicine, the unique physical and chemical properties as well as interesting shapes and sizes of graphene, are attractive for various novel applications in biological sensing, cancer therapies and potentially biomedical imaging. And also a range of biomarkers associated with different diseases and conditions as well as detecting a number of different biomarkers on the same chip.

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