ISSN 2515-8260 Volume 09, Issue 01, 2022

ANALYSIS ON CARBON NANOCARRIERS BASED DRUG DELIVERY SYSTEM FOR IMPROVED ANTICANCER DRUGS

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ABSTRACT

Cancer is the leading cause of death worldwide, according to the most recent WHO data report. Cancer was responsible for almost 9.6 million deaths last year. Oncologists have found the most cases of cancer from colorectal to skin to hepatic to prostate to stomach and from breasts. Surgery, chemotherapy, and radiation therapy are the three main cancer treatment options now available. Chemical compounds are typically employed in chemotherapy, a type of cancer treatment, to destroy cancer cells. A crucial aspect of cancer treatment, chemotherapy is done either alone or in conjunction with other methods such as surgery and radiation. It is critical. Epidermal growth factor inhibitors, anthracene derivatives, and platinum compounds are all common anticancer drugs. Traditional chemotherapeutic treatments are highly powerful and may kill cancer cells at very low doses, but non-specificity is still a serious problem in clinical applications for these drugs. Various anticancer drugs delivery systems have been developed to fix or overcome these difficulties. These limitations have been eliminated and the therapeutic efficacy of anticancer treatments has increased with the development of nanotechnology-based drug delivery systems (nanomedicines) in recent decades. Drug molecules in nanomedicine are either adsorbed to or encapsulated in a nanocarrier in order to make it more effective. A nanocarrier is made up of biodegradable and biocompatible materials and has at least one dimension smaller than 100 nm. Carbon-based nanomaterial Graphene oxide nanosheets (GONS) were employed in this study to develop an anticancer molecular drug delivery system.

1. INTRODUCTION

1.1 Tumor

Apoptosis is a process that all healthy cells in the human body go through. Apoptosis is a process in which cells divide, develop, and eventually die according to a predetermined cell pathway. To put it another way: "falling off" is the Greek word for apoptosis, which was coined in 1972 by scientists Kerr, Wyllie, and Currie. Even though it rapidly degrades, grows continuously, and eventually ceases to exist if any cell does not follow this preprogrammed pathway, tumour growth begins. In the body, this increases the number of cells, which results in new lumps or masses of tissue. Tumors that are benign (non-cancerous/non-malignant) are not harmful to the body as a whole, but can invade or spread to neighbouring tissues or organs. Tumors can develop and interact with our numerous systemic systems, such as the digestive and neural systems, as well as the circulatory system, and can release hormones that can affect body processes, as well.

According to WHO's latest data sheet, cancer is the world's second-leading cause of death, with an estimated 96 lakh people dying from it in 2019 and an additional >17 lakh people being diagnosed with it.

There are currently over 200 different varieties of cancer that can harm a person's health. Most cancers are called for the organ in which they begin to originate, such as hepatic, breast, and brain tumours, and so on. Any portion or organ of the human body might be affected by cancer. Men's common organs include the rectum, lung, colon, stomach, and liver, whereas women's common organs include the stomach, colon, rectum, breast, lung, and cervix.

1.2 Specific characteristics of cancer cells

There are numerous differences between cancer cells and normal cells. Normal cells, on the other hand, follow apoptotic signals, which normally tell cells to divide, develop, and eventually die after a certain period. Cancer cells, on the other hand, are unspecialized and do not respond to apoptotic signals, so they continue to divide and spread throughout the body. The amount of reductive cysteine or glutathione in cancer cells is also larger, both in the cytoplasm and in the endosomes. Cancer cells can potentially infect nearby healthy cells and the natural environment around them. A huge number of fresh and healthy cells are stimulated by infected cancerous ones so that more blood with oxygen and nutrients is supplied to a tumour environment, which is necessary for the development and growth of a higher number of cancerous cells and tissues.

1.3 Drawbacks associated with traditional treatment with chemotherapy

The prevention and treatment of several dangerous malignancies are currently possible thanks to powerful medications. Current chemotherapeutic medications, on the other hand, are not very effective in the clinic due to a variety of restrictions or downsides. This class of anticancer drugs is doomed to failure due to a variety of factors, including poor absorption (reduced bioavailability), poor metabolism (poor efficacy), and rapid elimination from the body. Since patients needed prolonged treatment, high daily doses, and frequent dosing, the growth of multidrug-resistant bacteria was facilitated by this. To circumvent these problems, the most effective drug delivery system is required to increase drug concentration in cancer tissues and organs while also reducing toxicity and eliminating unwanted side effects, improving bioavailability, and decreasing the emergence of drug resistance.

1.4 Delivering of therapeutic agents using nanotechnology

A drug delivery system based on nanotechnology (nanomedicine), will be possible to improve the therapeutic efficiency of chemotherapeutic medications by increasing their bioavailability while minimising adverse effects, and by releasing them at a therapeutically optimal pace and concentration. Compared to standard therapy, nanomedicines have the potential to give a more effective treatment with fewer side effects for patients. Biocompatible, non-toxic, non-immunogenic, non-toxic nanometer-sized (10-9 m) carriers (particles/materials) are used in nanomedicine to entrap and load chemotherapy medications, as the name implies. Among the advantages of nanocarrier technology are increased blood retention time, increased stability and cell penetration capability, and targeted administration (to infected cells/tissues and organs). Other advantages include avoiding intracellular endosomal absorption and long-term drug release. When it comes to cancer therapy and prevention, 'Cancer Nanomedicine' stands out as the most useful medical application of nanotechnology.

2. REVIEW OF LITERATURE

The use of folic acid-conjugated GONS by Sousa, M. et al. (2018) demonstrated site-specific delivery of hydrophobic anticancer agent camptothecin (CPT). In two different cancer cell lines, including J774 a mouse macrophage tumour cell line and HepG2 human hepatocellular carcinoma with overexpressed folate receptor, the effectiveness of CPT-loaded FA-GONS was examined. In this study, folic acid was used to deliver CPT to the GO-targeted cells only. Folic acid was used in this study. The powerful anticancer effect of CPT was first obtained by coupling folic acid (FA) to PEG.

Nanographene oxide (NGO) nanoformulations loaded with dopamine (DA) (targeted molecule) were developed by Masoudipour et al. in 2017 to improve treatment efficacy while also limiting the negative impact on healthy cells via site-specific delivery to DA receptor-positive cancer cell lines.. Amide bonding was used to link the DA ligand molecules to the NGO. MCF-7, a cancer cell line with DA receptors, and HEK-293, a cell line without DA receptors were used in this work (human embryonic kidney). Against both cancer cell lines, MTX-loaded and DA-coupled NGO with loaded MTX were compared to see which was the most risky.

Dorniani, D. et al. (2016) used an enhanced Hummers' process to make graphene oxide (GO). An active anticancer drug, GA, was loaded and delivered directly onto a cancer cell line using the nanocarrier that had been created. It was found that GA loaded most efficiently at a constant pH of 4.71. PXRD, FTIR, HRTEM, Raman, and UV-vis spectroscopy were among the microscopic and spectroscopic methods used to examine the GA-loaded GO nanocomposite. When placed in PBS pH-7.4, the GA-GO NCs released continuously. Different formulations of blank GO (normal fibroblast), GA-GO NCs (liver cancer cells), and pure GA were tested for in vitro cytotoxicity in two different cell lines over a 72-hour period on two different cell lines.

In 2016, Hou, G. et al. synthesised green reduced rGO using natural GA and assessed its various properties utilising PXRD, FTIR AFM, TEM, and so on. After GA was added, the rGO bionanocomposite's Tg (glass transition temperature) and degradation temperature were both raised. The mechanical properties of rGO were also affected by the amount of GA mixed in. The tensile strength and impact strength were also improved when GA was added, from 0.5 to 1.0 percent.

Mehdizadeh, M. et al. used the generic formula (RN=C=NR) to make a biotin-coupled poly (ethylene glycol) bis(amine) (NH2-PEG-NH2) (BPBA) conjugate using carbodiimide chemistry (2016) There were attached the biotin-PEG conjugate to SN-38-loaded polymeric NPs. Biotin molecule site specificity was investigated using the 4T1 breast cancer cell line. These cell lines have a lot of biotin receptor overexpression. Biotin-attached NPs were found to be substantially more harmful than non-targeted drugloaded NPs or unbound drugs, according to cytotoxicity experiments.

3. MATERIALS AND METHODOLOGY

To conduct this research, scientists used Sigma-Aldrich graphite powder (20 mm mesh size), L-fucose, and PBS pH-7.4 tablet along with poly(ethylene glycol) bis(amine) (PBA), gallic acid, biotin, and anhydrous dimethyl sulfoxide (DMSO), as well as anhydrous dimethyl acetate (SAA) (Saint Louis, MO, USA). In addition to sodium nitrate, potassium permanganate and concentrated sulfuric acid, hydrogen

peroxide and N-(3-Dimethylaminopropyl)-N'-ethyl carbodiimide hydrochloride, it was provided by Hi-Media Lab Pvt. Ltd. (Mumbai, India).

DMEM–F12, 3-(2-Benzothiazolyl)-7-(diethylamino)coumarin, gemcitabine hydrochloride, anhydrous triethylamine (TEA), acetic acid, and sodium acetate were used, as well as an antibiotic-antimycotic solution from TCI Chemicals (India) Pvt. Ltd. (Chennai, India). When it came to media, Gibco provided RPMI-1640 (Roswell Park Memorial Institute Medium) and DMEM (Dulbecco's Modified Eagle's Medium) (California, USA). As well as serum from foetal bovine, this study utilised Invitrogen's 3-(4,5-dimethyl-thiazolyl-2 thiazolyl)-2,5-tetrazolium bromide (California, USA). Sisco Research Laboratories Pvt. Ltd. was our first stop when looking for ammonium bicarbonate (Mumbai, India). NCCS in Pune sold us A549 (cancerous lung cells) and MDA-MB-231, which we purchased (breast cancer cells).

3.1 Methodology

3.1.1 Synthesis of graphene oxide nanosheets from bulk graphite

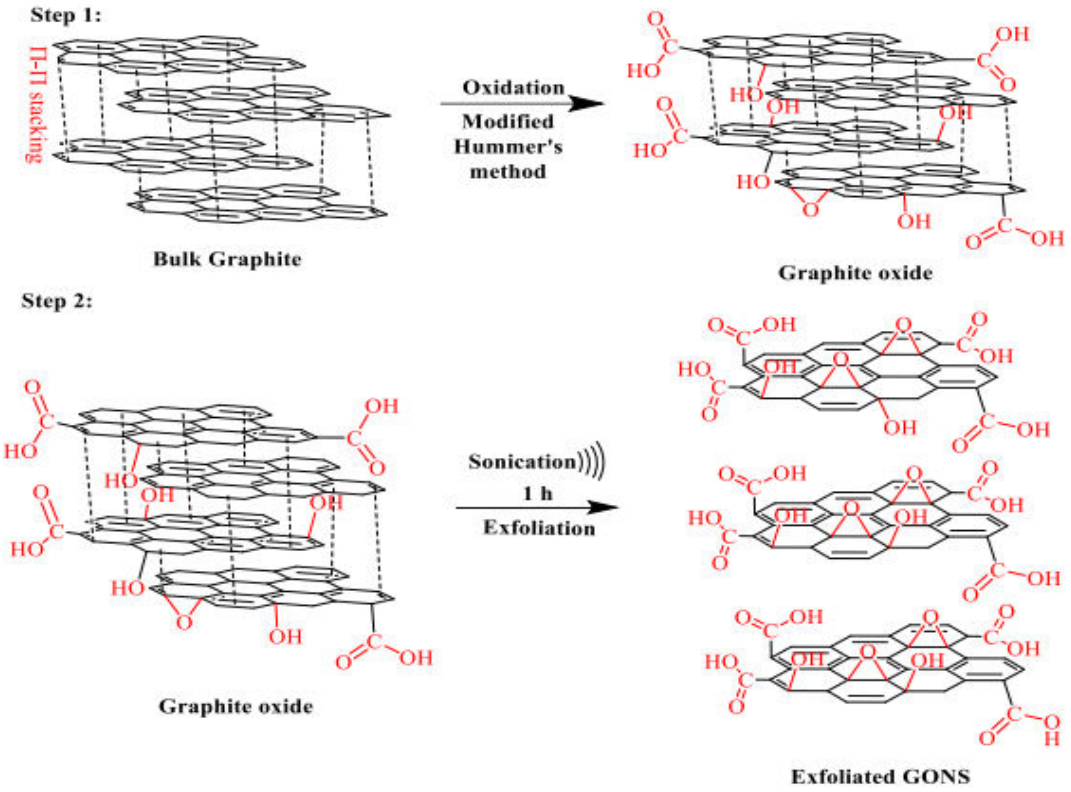

Figure 3.1: Schematic representation of the preparation of graphite oxide from bulk graphite (step-1), preparation of two-dimensional graphene oxide nanosheets (GONS) through exfoliation of graphite oxide (step-2).

3.2 Microscopic analysis

TEM analysis

Transmission electron microscopy was used to examine the surface morphology of graphite bulk and GONS. For an hour, a water bath sonicator from Leela Electronics in Mumbai, India, was used to redistribute the dried graphite bulk and GONS samples in Milli-Q water. Dropping a dispersed sample of the sample onto a carbon-coated copper grid and using a 100 kV Jeol 1010 microscope to capture images were key steps in the research. The samples were air-dried before being imaged with the TEM instrument.

3.3 Spectroscopic analysis

Raman Analysis

The structural identification of graphite bulk and crystal defects on exfoliated GONS was achieved by analysing Raman spectra using a modified Hummers' method and bulk graphite. We used the Horiba LabRAM HR Evolution Raman spectrometer and a 532-nm laser with 1–100% laser power to obtain Raman spectra on pure Si or Si/SiO2 substrates (300 nm of thermally grown oxide).

3.3.1 Gemcitabine hydrochloride-loaded fucosylated graphene oxide nanosheets for site-specific delivery on human lung and breast cancers.

When taken as directed, Gemcitabine hydrochloride (GEM) inhibits the production and replication of genetic material in cells (DNA and RNA). As a result, cell growth is inhibited, which leads to cell death. For pure GEM to have a therapeutic effect, high and frequent doses must be given to patients, resulting in several side/adverse effects like hepatotoxicity and myelosuppression. Human non-small cell lung cancer A549 and human breast cancer MDA-MB-231 cells, which overexpress fucose receptors, can both be treated with GEM delivered via FGONS.

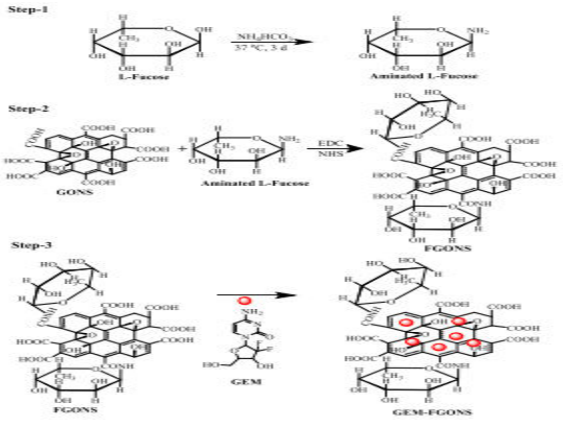

Figure 3.2: Schematic representation of the synthesis of aminated L-fucose from Lfucose (step-1), the preparation of fucosylated graphene oxide nanosheets (FGONS) by conjugating aminated L-fucose to GONS via covalent functionalization (step-2) and the loading of gemcitabine hydrochloride (GEM) on the FGONS (GEM-FGONS) (step-3).

Graphene oxide nanosheet (FGONS) was fucosylated with previously synthesised GONS to give a smart drug delivery system. After that, non-covalent interactions loaded large amounts of GEM onto the FGONS surfaces, resulting in a prepared GEM-FGONS nanoformulation. When used with buffer release media, the GEM-FGONS provides a stable release of GEM for an extended period of time (PBS, SAB). Stability is improved in different biological and cell media by FGONS. The anticancer activity of GEM-FGONS was higher than that of GEM-GONS or pure GEM. For the preparation of GEM-FGONS nanoformulation, a schematic is shown in Figure 3.2.

4. RESULTS AND DISCUSSION

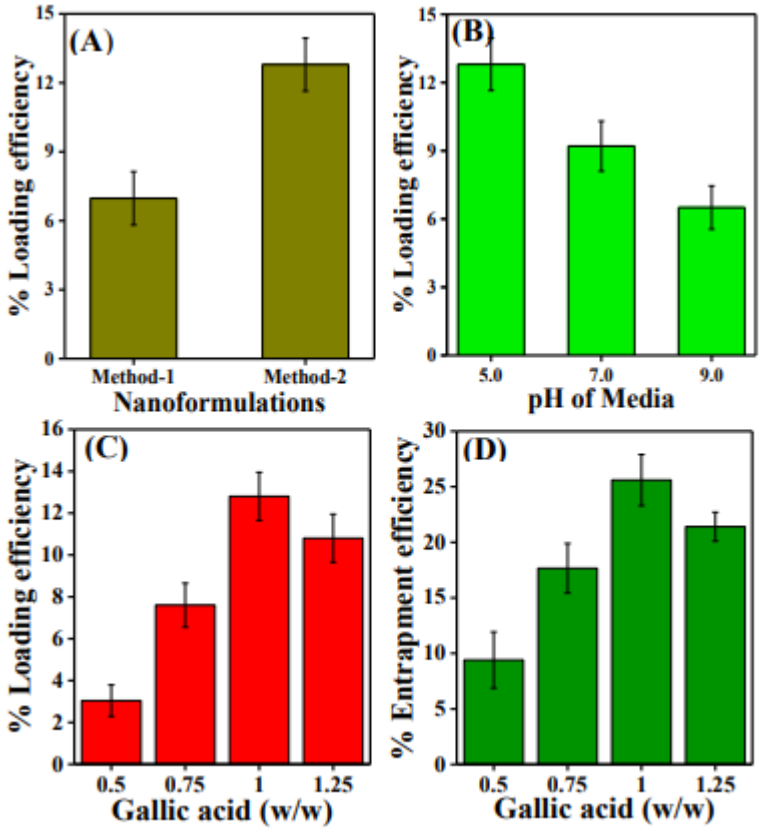

Figure 4.1 : Optimization of gallic acid (GA) percentage loading efficiency (A) methodbased (B) pH of the aqueous medium on graphene oxide nanocarrier (GONC). Optimization of percentage (C) loading- and (D) entrapment-efficiency of GA to GONC. Data shown in the line graph denotes the mean ± standard deviation of three replicates.

Drug molecules are loaded on GONC using a variety of non-covalent forces, including stacking, hydrogen bonding, electrostatic interaction, and van der Waals interactions. A maximum LE of 6.981.16% was obtained at neutral pH when GA was loaded onto the BPBA@GONC in method 1. (figure

4.1A). The functional groups of GONC may have been protected from the BPBA, which was in charge of GA loading on GONC, because of the poor drug efficacy of the BPBA@GONC.

The reverse method (method-2) was therefore tried, in which GA was loaded onto the GONC before being coated with BPBA. This method was also successful. In line with expectations, the formulation's percent LE (13.8% 1.15%) and percent EE (25.6 2.3%) improved. After increasing the GA/GONC weight ratio to 1:1 (GO: GA), the percent LE and percent EE both decreased in proportion to their respective increases in GA/GONC weight ratio.

According to the findings, non-covalent interactions like stacking between GA's benzene ring and GONC's benzene ring are critical for GA's ability to attach to GONC and be loaded. Others, such as GA's three hydroxyl (OH) groups and one carboxyl group (COOH), may not be responsible for this interaction. Many of the carboxyl (COOH) and hydroxyl (OH) groups found in GONC, as well as Vander Waals attractions and other non-covalent attractions, can form strong intermolecular H-bonds with these groups.

Acidic conditions yielded the highest percentages of LE and EE, while neutral and basic conditions came in second and third, respectively (figure 4.1B). 105 The high GA loading in an acidic medium may be due to the protonation of the GA and GONC O and COO groups in acidic medium (pH-5.0).

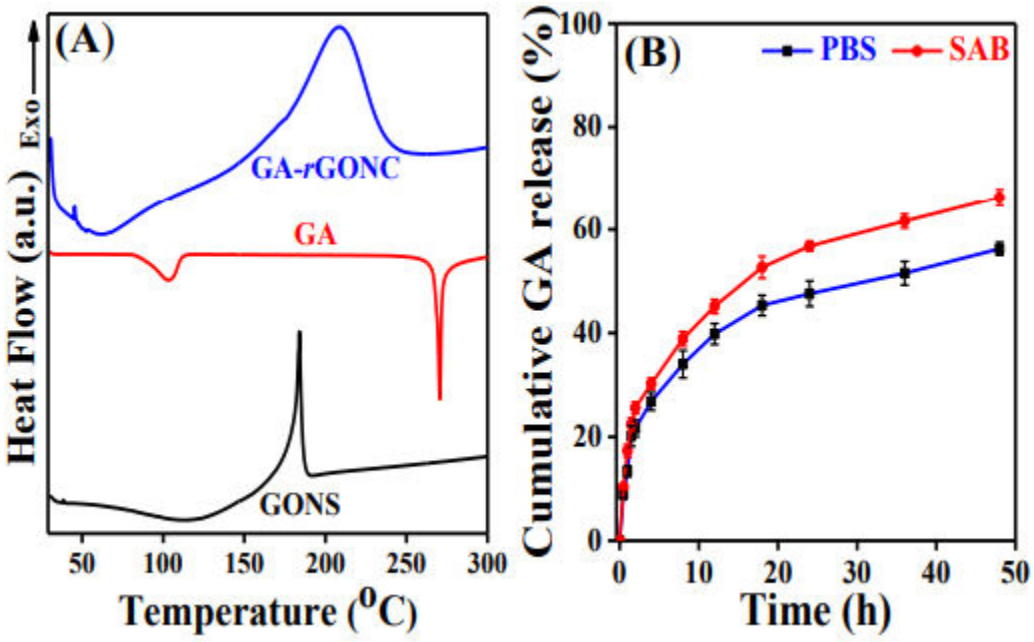

Figure 4.2: (A) Differential scanning calorimetry spectra of graphene oxide nanosheets, pure gallic acid (GA), GA-loaded reduced graphene oxide nanocarrier (GA-rGONC). (B) The in-vitro release pattern of GA from biotin-coupled poly-(ethylene glycol) bis-(amine) coated GA-loaded (BPBA@GA-rGONC) obtained from method-2. Data represented in the line graph are mean ± SD (n=3).

GONS, pure GA, and GA-rGONC DSC thermograms are shown in Fig. 4.2A. A DSC analysis was performed to ensure that GA had been properly loaded and to determine the effects of crystallinity loading and entrapment on GONS. During a 48-hour period, Ga was released in vitro from the BPBA@GA-rGONC nanoformulation in two different buffer media: SAB (pH-5.0) and PBS (pH-7.4) (Figure 4.2B).

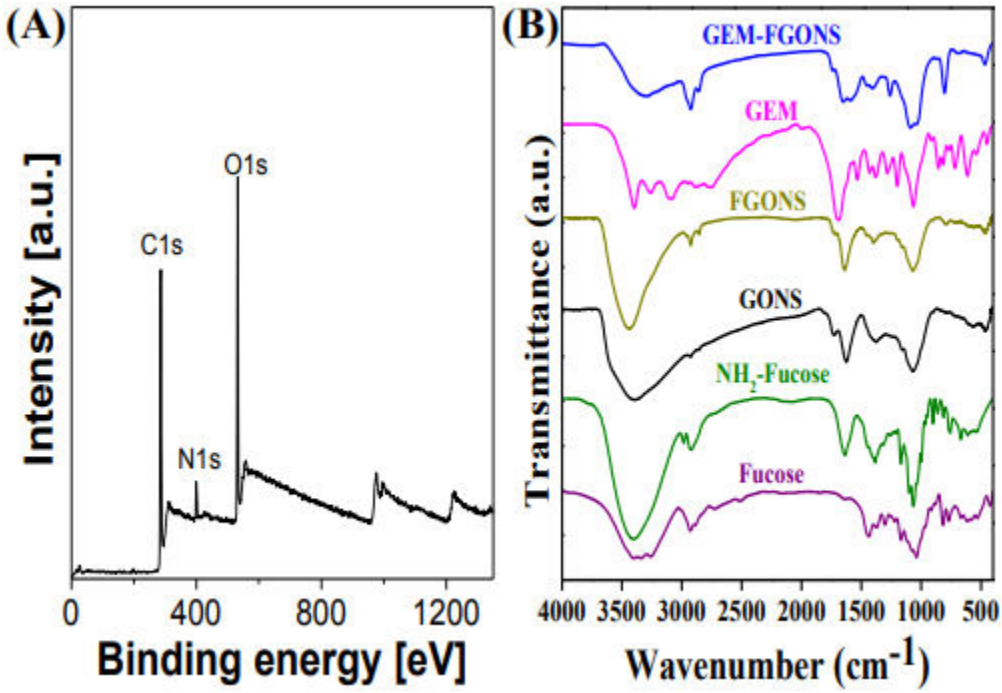

Figure 4.3: (A) XPS spectra of fucosylated graphene oxide nanosheets (FGONS). (B) FTIR spectra of fucose, aminated L-fucose (H2N-fucose), graphene oxide nanosheets (GONS), FGONS, gemcitabine (GEM), and GEM-FGONS.

The XPS spectra of FGONS are shown in Figure 4.3A. To determine whether or not two different species of organisms have developed a bond, XPS is an excellent analytical technique. Researchers have found evidence of an amide bond being formed between aminated L-fucose and GONS in the form of an XPS spectra with a peak in the binding energy between 399 and 401 eV Carbonyl (C=O) groups at 1726 cm-1 of carboxylic acids were moved down in frequency, confirming that linkage (CONH)187 had formed, and the peak sharpness at 3443 cm-1 was also increased by NH stretching, showing that aminated L- fucose had been successfully attached to GONS by means of an amide bond in figure 4.3B.

CONCLUSION

Finally, the few-layered GONS (a two-dimensional carbon-based nanocarrier) was used to deliver anticancer drugs among all nanocarriers studied. A modified Hummers' method from the graphite bulk

was used to create the few-layered GONS. GONS's successful development was confirmed by a variety of advanced characterization techniques (microscopic and spectroscopic). For higher drug loading and sustained (long-term) release of anticancer drugs, large surface area-to-volume ratios confirmed the success of GONS synthesis, which included high dispersibility and stability in aqueous. Oxygenated functional groups found on the surfaces of Gons were easily modified due to the FTIR spectroscopy that revealed this information. New key for increasing bioavailability with sustained release of chemotherapeutic drugs to help reduce toxic concentrations in the human body system is the prepared GONS, which opens new avenues for enhancing therapeutic efficacy by increasing bioavailability and sustained release of drugs.

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