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Study of adsorption and release of 5-fluorouracil on Graphene oxide as anticancer drug delivery system

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ABSTRACT: One of the most common treatments for cancer is chemotherapy. The most important disadvantage of most drugs used in chemotherapy is the inability to effectively penetrate the tumor tissue, not reaching the effective concentration, and their unwanted side effects on healthy tissues. In recent years, Graphene Oxide has been utilized in various pharmaceutical applications since of its capacity to target particular sites. Within the present work, a modern type of Graphene Oxide was arranged and loaded with 5-fluorouracil for controlled drug conveyance applications. A novel drug conveyance framework was arranged from 5-fluorouracil and Graphene oxide [GO-5-FU], containing Graphene oxide (GO) and 5-fluorouracil (5-FU) anticancer drug for controlled release of drug. This system was synthesized by connecting GO to 5-FU through solid π–π stacking interaction. The 5-FU discharge and stacking were emphatically pH-dependent and suggest an H-bonding interaction between GO and 5-FU. The resultant GO-5-FU was characterized by Fourier transforms infrared spectroscopy (FTIR), X-ray diffraction (XRD) analysis, and, filtering electron microscopy (SEM). Other than that, swelling and in vitro drug discharge considers were also carried out at pH 1.2, 5, 7.4 and 10 at 37°C. Furthermore, the equilibrium adsorption data were analyzed by Freundlich and Langmuir models. The anticancer action of the GO-5-FU was surveyed utilizing an MTT test against MCF-7 and HepG2 cells. The come about findings that the created GO-5-FU are likely to be viable drug carriers for medicate conveyance applications.

Keywords: *Adsorption, Anticancer, Drug delivery, 5-Fluorouracil, Graphene oxide, In vitro, MTT assay, Release*

INTRODUCTION

All over the world, cancer is known as the second cause of mortality, which causes the death of more than 8 million people every year [1]. One of the most common treatments for cancer is chemotherapy. The most important disadvantage of most drugs used in chemotherapy is the inability to effectively penetrate the tumor tissue, not reaching the effective concentration, and their unwanted side effects on healthy tissues [2, 3]. These problems led scientists to think of developing a delivery system to release a controlled amount of drug into the tumor tissue to ensure effective drug delivery and therapy. Drug delivery by nanocomposites is used as an alternative for effective drug delivery and targeting cancer cells, especially in cases where the

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drugs are hydrophobic. liposomes, micelles, nanoconjugates, core shell nanoparticle [4] vehicles and polymer-coated drug-loaded nanocomposites constitute different types of nanoparticle systems. Nowadays, these nanoparticles have been studied a lot due to their effect on the effectiveness of anti-cancer drugs. Therefore, nanotherapy and drug targeting are proposed as major alternatives to chemotherapy [4]. In recent years, GO has been widely used for disease diagnosis, cancer cell imaging, tissue engineering, photothermal cancer therapy, drug delivery, and as a carrier for anti-cancer drugs. Despite these advantages and applications, some reports shows that GO have cytotoxic effects in high concentrations. GO can cause toxic conditions in the body through oxidative stress, production of intracellular active oxygen, inflammation, and apoptosis, so to use this substance, the problem of its toxicity must be solved first [5-11]. 5-Fluorouracil is widely used to treat cancers of the digestive system, colorectal, breast, head and neck. This substance was first identified in 1957 and since then it has been used as a neoplastic drug in chemotherapy. This drug is reported in the list of WHO essential drugs, which shows the importance of this drug in the treatment of cancer. Despite all these uses, 5-fluorouracil usually causes systemic toxicity due to its short half-life in blood plasma and its non-specificity, which causes the need for high doses. The mentioned disadvantages limit the use of this drug. To improve the effectiveness of this drug and to ensure the safety of the patient, the connection of 5-fluorouracil with a delivery system is needed [12-15]. So far, several molecules or polymers have been used to increase the performance of GO, and promising results have been obtained. However, there is still a need to develop GO-based drug carriers. As constituted to our work in synthesis of new compounds [16-18], in this study, a new type of Graphene Oxide was prepared and loaded with 5-fluorouracil for controlled drug delivery applications.

MATERIAL AND METHODS

Instruments

IR spectra were recorded on a Bruker (EQUINOX55) FR-IR. The SEM micrographs were obtained on SEM-S4700, Hitachi (XL30). UV-spectroscopy was carried out on UV-Vis-NIR, Perkin Elmer (RXI).

Solutions and Reagents

Graphite and 5-fluorouracil were acquired from Sigma–Aldrich, Germany (99% immaculateness). Other chemicals were items of Merck and Sigma–Aldrich (Germany) or obtained from nearby providers and utilized as received. Phosphate buffer or acetate buffer were utilized for pH alteration.

Graphene oxide preparation by using modified Hummer's method

Graphene oxide (GO) was arranged from graphite flakes by utilizing adjusted Hummer's method [19]. The step-by-step amalgamation is as takes after: step (1) .10 gr of Graphite flakes and 110cc of H3PO4 and 1 liter of H_2SO_4 (98%) were blended in a 1000 ml volumetric flask kept beneath an ice shower (0-6°C) with stirring ceaselessly. step (2). The test blend was mixed for 2hr at the same temperature and 50 g of potassium permanganate ($KMnO_4$) was included in the suspension exceptionally gradually. The expansion rate is carefully controlled so that the response temperature is less than 14°C, step (3). At that point, the ice shower was evacuated, and the test blend was blended at 30°C tile it got to be pale brownish and kept beneath blending for 2 hrs. For each half hour, increment the temperature to 50°C, step (4). At that point, it was debilitated with the moderate expansion of 100 ml of water. The response temperature was expanded rapidly to 96°C with effervescence, and the color changes to a brown sort of color, step (5). Advance, this solute.

Preparation of Graphene oxide supported 5-fluorouracil

An ordinary method for preparing the GO-5-FU is as follows [20]. 10 mg/mL GO was sonicated with a certain concentration of 5-fluorouracil (5-FU) at pH= 7 for 30 min and after that mixed in the dark at room temperature overnight. All tests were balanced to regarded pH and after that ultra-centrifuged at 12000 rpm for 1h. The resultant blend was separated and decontaminated with rehashing ultracentrifugation (12000 rpm for 10min)/decantation/resuspension in water 3 times. The decontaminated GO-5-FU was

dried beneath a vacuum overnight at 50°C.

Adsorption determination

The impact of test parameters, e.g., pH (1.2, 5, 7.4, and 10), beginning concentration, and temperature on the adsorption of distinctive 5-fluorouracils was examined in a batch mode of operation for a contact time of 0-400min. Tests were executed with distinctive amounts of 5-FU (adsorbent). The run of the beginning concentration was between 10 and 300 mg/L keeping the test condition indistinguishable. For contact time considers, a sedate arrangement of certain pH and known starting concentration was taken with a steady adsorbent amount. The adsorption rate is calculated as follows:

$$\text{Adsorptivity}(\%) = \frac{C_i - C_f}{C_i} \times 100$$

Where, C_f and are C_i the final and initial 5-FU concentrations, respectively. The 5-FU quantity adsorbed at equilibrium (q_e) was calculated using the following equation:

$$q_e = \frac{(C_i - C_e)V}{W}$$

Where, C_i and C_e are initial and equilibrium 5-FU concentrations, V and W are the solution volume, and the mass of the adsorbents, respectively. In this study, all adsorption experiments were done in triplicates and the mean cumulative values were represented.

In-vitro drug release response

The drug release of the GO-5-FU was assessed at 25, 37, 40, 45, and 50°C and pH of 1.2,5, 10, and 7.4. Regularly, 10 mg GO-5-FU was exchanged into dialysis packs with 4 buffer arrangements (pH= 1.2, 5, 7.4, and 10) and delicately shaken at encompassing temperature. The sedate discharge was begun when the dialysis sacks were put within the buffer. At foreordained periods, the 5-FU quantities (W-free 5-FU) within the buffer arrangement were evaluated by UV-Vis at 266 nm. The cruel of 3 estimations was detailed for all 5-FU medicate discharges. The discharge of 5-Fluorouracil from the GO influenced the morphology of the nanohybrid medicates carrier, in this manner, to evaluate any morphological modifications the GO–5-FU nanohybrid sedate carrier tests were examined through Hitachi XL30 SEM-S4700, filtering electron microscopy.

MTT assay for evaluation of in vitro cytotoxicity

MTT measurements were used to assess the cytotoxicity of 5-FU, GO and 5-FU-GO. Briefly, human hepatoma HepG2 and MCF-7 cells were purified in DEME medium supplemented with 10% FBS and 1% antibacterial agent (penicillin-streptomycin array) in a humidified environment at 37°C and 5% CO_2. Cells were seeded in 96-well plates at a thickness of 5×10 3 cells per well containing 100 µl of DEME medium supplemented with FBS and antimicrobials. Plates were placed in a humidified chamber at 37°C, 5% CO_2 for 24 h. The development medium was then emptied and filled with 100 µL of fresh medium containing different concentrations (5, 10, 20, 40, 60, 80, and 100 µg/ml) of 5-FU, GO, and 5-FU-GO. After a 24h incubation period, cells were treated with 20 µL of MTT array and pre-incubated for 4 h. The medium was then aspirated and the formazan gems were split open with 150 µL DMSO. Finally, the well plate was subjected to constant temperature shaking at 37°C for 15 minutes. Percent cell restraint was calculated from the come about utilizing the taking after formula:

Percent cell inhibition = OD control - OD treated OD control × 100%

Where OD Control is the absorbance gotten from untreated control cells and Treated OD is the absorbance gotten from treated cells.

RESULTS AND DISCUSSION

FTIR chemical evaluation was used to ensure the correctness of the Graphene oxide synthesis from graphite powder. In Fig. 1 you can see groups containing oxygen such as epoxy, hydroxyl, and carboxylic functional groups. The FTIR spectrum shows the peaks at 3422 cm^{-1} (-OH stretching vibration), 1744 cm^{-1} (C=O stretching vibration), 1642 cm^{-1} (C=C carboxyl stretching vibration), 1384 cm^{-1} (C- O stretching vibration), 1550 cm^{-1} (C-OH stretching vibration).

The observed peaks and their equality with the char-

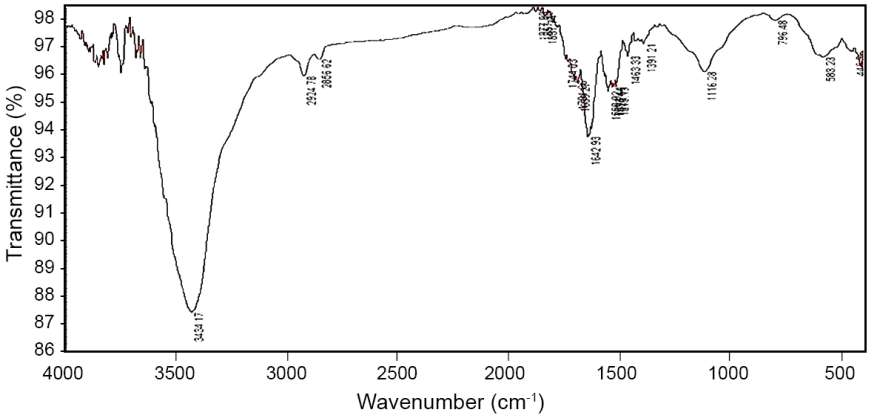

Fig. 1. FTIR diagram of synthesized Graphene oxide

acteristic peaks of Graphene oxide structure indicate the successful synthesis of this nanoparticle from graphite [21, 22]. The 5-FU spectrum shows a peak at 3376 cm^{-1} (N-H stretching vibration), 1715 cm^{-1} (ketoamide stretching vibration), 1645 cm^{-1} (C=O stretching vibration), and 1411 cm^{-1} (C- N stretching vibration) (Fig. 2).

The results related to the binding of 5-Fluorouracil to Graphene oxide are shown in Fig. 3. By comparing the diagram of FTIR, GO and GO-5-FU, we find that the peak at 1744 cm^{-1} has disappeared and a new peak in 812 cm^{-1} was seen, which indicates that a reaction happened between the C=O group of GO and a the-NH group of 5-FU, and GO is successfully connected

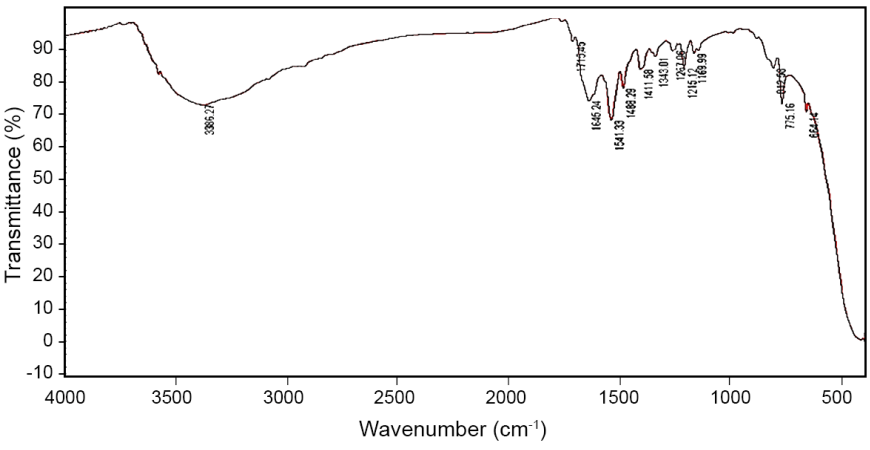

Fig. 2. FTIR diagram of 5-fleurouracil

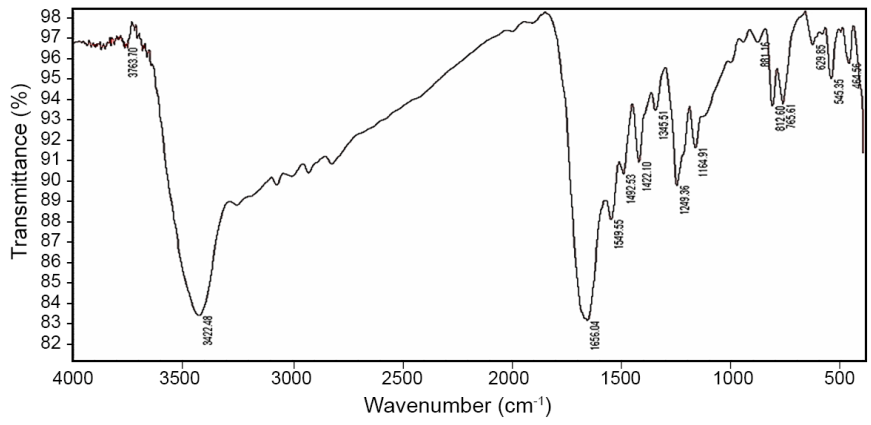

Fig. 3. FTIR diagram of 5-Fleurouracil- Graphene oxide

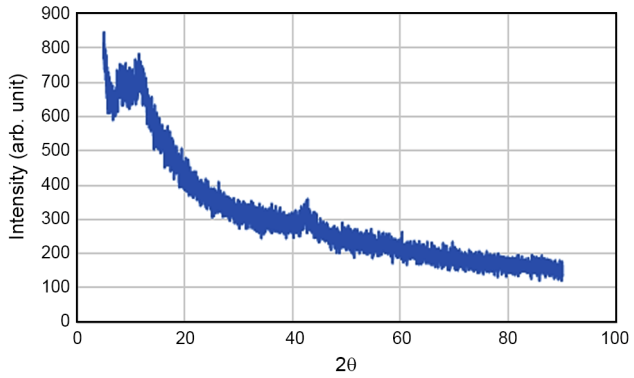

Fig. 4. XRD diagram of synthesized Graphene oxide

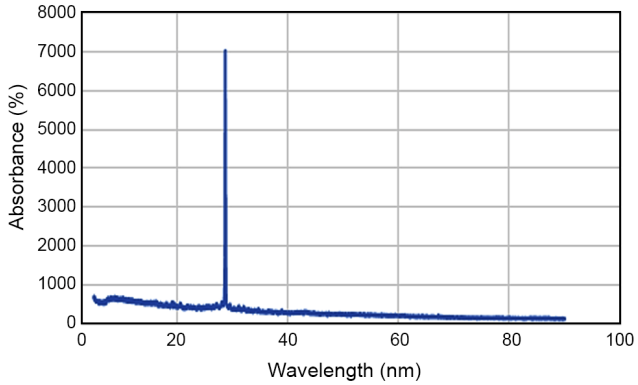

Fig. 5. Graph of UV-Vis spectroscopy of Graphene oxide-5-fluorouracil

to 5-FU [23, 24].

To further ensure the correct synthesis of Graphene oxide and 5-FU-GO, XRD evaluation was used. The GO UV–Vis's assimilation spectra have appeared in Fig. 4.

The corresponding spectrum at an angle of 2θ = 12° shows a clear diffraction pattern, which is related to Graphene oxide, and another diffraction pattern can be seen at 2θ = 43°, which is related to graphite. This peak shows that the graphite is not completely oxidized. The results obtained by the one-step oxidation of graphite are consistent with the results of previous studies.[25]. The reduction process of Graphene oxide was evaluated by UV-Vis spectroscopy (Fig. 5).

The self-evident retention peak at 234 nm was attributed to the π–π* move of the Graphene C=C bonds. In expansion, the 300 nm bear peak was credited to the π –π* move of the Graphene oxide C=O bonds on the carboxyl or the carbonyl group. The two characteristic assimilation peaks were demonstrated to be effective arrangements of GO [24]. The morphology of created microbeads was examined utilizing SEM. The morphologies of GO and 5-FU-GO were characterized by SEM (Fig. 6). The GO is a flat structure with wrinkles on the surface, outlining that it could be a planar two-dimensional structure (Fig. 6 right). Compared with GO, the estimate of 5-FU-GO was marginally expanded, but still appeared a lamellar structure (Fig. 6 left). The 5-FU-GO picture appeared that the materials did not total or alter with the beginning lamellar structure of GO remaining intaglio (Fig. 6 left). The results of scanning electron microscopy show the high stability of 5-fluorouracil supported by Graphene oxide, which is similar to the results of the Pan et al. study.[24, 26]. 5-FU has been adsorbed onto the GO nano transporter through covalent interactions. The 5-FU calibration curve was y= 63.115 x + 19.873 (r = 0.9989), with

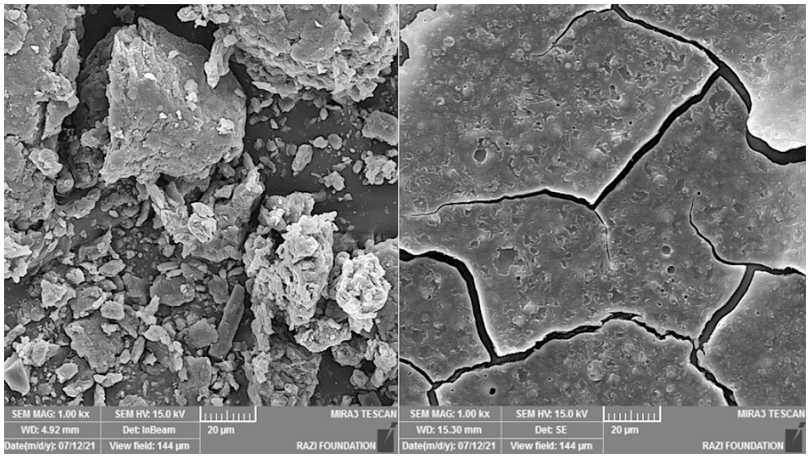

Fig. 6. Scanning electron microscope image of Graphene oxide (right), and scanning electron microscope image of 5-Fluorouracil-Graphene oxide (left)

a range of 6.5~250 µg/mL. The encapsulation ratio (EE) and the efficacy of the drug load (DL) were determined by unrelated drug levels to assess the yield of the drug load. The come about appeared that the EE expanded with the increment within the concentration of the drug and the most elevated EE was 83.2%. Consistent with the equation, the LE was 34.7%, or 499.52 µg of 5-FU can be adsorbed over 1 mg of GO. Therefore, GO could be a promising drug carrier that can fulfill a huge drug burden. The conceivable mechanisms of the high load capacity of 5-FU on the GO can be clarified through taking after clarifications. many forms of hydrogen bonds exist between the 5-FU carrier and GO, counting –COOH in GO and –NH– in 5-FU, –COOH in GO and-in 5-FU C=O, –OH in GO and –NH– in 5-FU, –OH in GO and –C=O in 5-FU, –COOH and 5-FU in GO –F in GO, –COOH in GO and –F in 5-FU, these hydrogen bonds make 5-FU-GO steady in the arrangement. The in vitro aggregate discharge of 5-FU from the 5-FU-GO at the temperature of 25, 37, 40, 45, and 50°C in 1.2,5, 10, and 7.4 PBS is arrangement. The release behavior of 5-FU was found to be affected by environmental pH. In the pH 7.4 buffer, drug release was moderate and sustained, with approximately 70.84% of the total sedative release after 72 hours. In contrast, the amount of sedative released at pH 7.4 was generally less than at pH 1.2 and pH 5 at the same time points. The total static stacking released from 5-FU-GO is approximately 90.29% and 85.75%, which can be achieved at pH 1.2 and pH 5, respectively. This could be attributed to the π-π interaction and hydrogen bonding between 5-FU and GO. The lower pH cases the higher degree of protonation of hydrogen bonds. Thus, the quality of hydrogen bonding was controlled by pH, resulting in the release of 5-FU. This pH-sensitive drug delivery scaffold plays an important role in antitumor drugs and can influence the release of drugs into tumor cells.[27,28]. The results related to the effect of Graphene oxide on MCF-7 cells are shown in (Fig. 7).

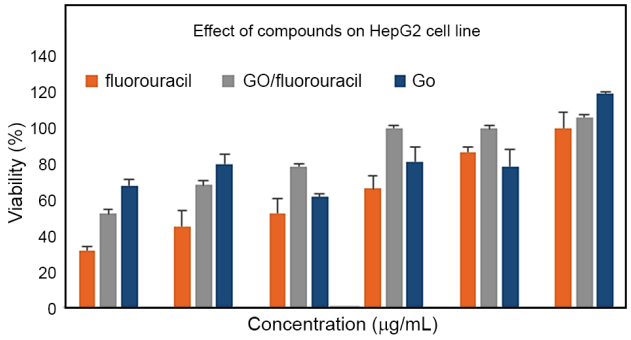

Fig. 7. The viability of different concentrations of 5-FU, -GO, and 5-FU -GO in Hep G2 cells

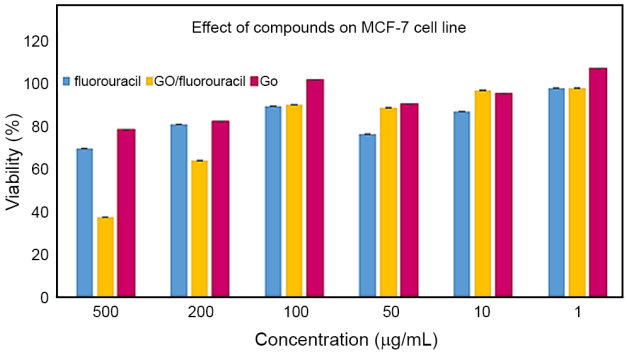

Fig. 8. The viability of different concentrations of 5-FU, -GO, and 5-FU -GO in MCF-7 cells

GO shows significant toxicity in different concentrations on the Hep G2 cell. 5-FU has also shown that it has cytotoxic power in different concentrations. After adding 5-FU to GO, its inhibitory effect increases with increasing concentration, which indicates that the nanocarrier can deliver antitumor drugs. By examining the effect of GO on MCF7 cells (Fig. 8), it was shown that in most cases, the effect of GO alone is from 5-FU and the combination of GO and 5-FU, which indicates the low effectiveness of nanocarriers in this concentration. The IC50 value of GO-5-FU was 542.88, which is higher than 5-FU alone, the reason for this can be the binding capacity of GO-5-FU, which increases apoptosis and the inhibitory effect of 5-FU on cells. As a result, the duration of the effect of GO-5-FU on cells is longer than 5-FU alone, which causes a better inhibition of cell growth which is similar to the study of Penn et al. in China and Edi Hashmi et al in India [24, 29].

COCCLUSION

In this study, Graphene oxide was synthesized as a carrier of 5-FU anticancer drug. The gotten nanocarrier had a round shape with micro-sized distance across. The DL and EE of 5-Fu expanded clearly with the increment of GO substance, which is able decrease the

number of dosages required. With the increase of GO substance, the starting burst was drastically smothered, and the nanocarrier shown supported discharge behavior of 5-Fu, which is able upgrade medicate utilization. In expansion, the gotten GO-Fu aerogel is delicate to pH value, which will be valuable for drug discharge within the focused-on tumor locales. These findings open a modern approach for the development of medicate carriers based on characteristic polysaccharides for maintained and stimuli-sensitive drug discharge.

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Declarations

Ethical Approval

This investigation didn't belong to human and/ or animal studies

Competing interests

There is no competing interest

Authors' contributions

Zahra javidi worked in laboratory for the synthesis and biological activity evaluation.

Mohammad kazem mohammadi and nooredin goodarzian wrote the manuscript.

Elham tahanpesar was the advisor for results description.

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Availability of data and materials

In this manuscript we used free Microsoft data analysing databases.

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