Fabrication of a pH-Responsive Magnetic Nanocarrier Based on Carboxymethyl Cellulose-Aminated Graphene Oxide for Loading and In-Vitro Release of Curcumin

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Abstract
In this study, a pH-responsive magnetic drug delivery system was prepared by cross-linking of CoFe2O4/graphene oxide to carboxymethyl cellulose (CMC) biopolymer with adipic acid dihydrazide (ADH) and then investigated for loading and release of a poorly water-soluble anti-cancer drug, curcumin (CUR). The CoFe2O4/GO-ADH-CMC bio-nanocomposite was characterized by FE–SEM/EDX, TEM, FT–IR, XRD, TGA, VSM, and zeta-potential techniques. The highest amount of drug loading was achieved as 23.7 mg g⁻¹ at 323 K, pH 6.0, and 120 mg L⁻¹ CUR concentration. The study of adsorption isotherms revealed that the Sips model was best fitted to the equilibrium data (R² > 0.997 and RMSE < 0.48), which indicated the contribution of both chemisorption and physisorption in drug loading. Furthermore, the release profile of CUR from drug-loaded CoFe2O4/GO-ADH-CMC was studied in mimicking the endosomal (pH = 5.6) and physiological (pH = 7.4) conditions. After 24 h, the maximum cumulative releases were found to be 86 and 38% at pH = 5.6 and 7.4, respectively. Also, the Peppas-Sahlin kinetic model was followed for the release data. The MTT assay exhibited good biocompatibility of the CoFe2O4/GO-ADH-CMC. The results implied that CoFe2O4/GO-ADH-CMC magnetic bio-nanocomposite might be utilized as a potentially safe carrier with the continuous and slow release of CUR.
Graphical Abstract

Keywords  Biopolymer · Adsorption · Smart nanocarrier · Sustained release · Release kinetics · Drug delivery
Introduction

Nanoscience and nanotechnology have found substantial applications in targeted drug delivery for cancer treatment over the past two decades, primarily to maximize therapeutic benefits (effectiveness) and minimize toxicity (safety) [1]. Drug systems containing nanomaterials have offered several superiorities over macro systems. Nanomaterial-containing drug delivery systems based on biodegradable and biocompatible intelligent polymers have been used as promising, sustainable, and safe candidates for the continuous release of anti-cancer drugs. These smart drug delivery systems (SDDS) are superior to conventional drug delivery systems (CDDS) [2–4]. Due to their controlled drug release profile in response to specific physiological stimuli and targeted drug delivery to specific organs and tissues. Moreover, they can reduce the number of doses by maintaining their stability, thereby diminishing the side effects associated with CDDS. Drug release stimuli can be internal and related to the natural tissue response (such as hypoxic activity, temperature, or enzymatic activity), external (such as a magnetic field, or ultrasound), or a combination of both. Among SDDS, pH-responsive polymers (such as alginate, carboxymethyl chitosan, Poly(N,N-dimethylaminoethylmethacrylate), poly(propyleneimine), poly(vinyl-imidazole), and carboxymethyl cellulose (CMC)) have received much attention [5–7].

CMC is a water-soluble anionic polysaccharide derived from natural cellulose, which can be obtained by substituting the hydroxyl groups of cellulose with the –COOH groups [8]. Thanks to its hydrophilicity, biocompatibility, biodegradability, and low toxicity, CMC has found wide application in pH-responsive drug carriers [9]. The pH variations can alter the acidic form (–COOH) in the CMC to its alkaline form (–COO−), considerably altering the rate of CMC swelling at different pH levels. However, the use of CMC in controlled drug delivery systems is restricted as its low mechanical strength may cause drug burst release. The incorporation of minerals such as GO and metal oxides into the CMC gel can improve its mechanical strength along with stability [10, 11].

In recent years, graphene-based materials have been conjugated with polysaccharides as biopolymers for upgrading the aqueous dispersibility, bioavailability, drug loading capacity, and controllable release rate as well as decreasing the toxicity and activation of the immune response to suit their applications as smart drug delivery systems [12]. Rao, et al. designed a pH-sensitive system using GO-CMC conjugate loaded with doxorubicin (DOX). In-vitro studies demonstrated that the GO-CMC/DOX had great anti-tumor activity and was safer compared to the single DOX administration [13]. Rasoulzadeh and Namazi prepared biodegradable CMC/GO hydrogels via physically crosslinking with FeCl3·6H2O as a delivery device for sustained release of DOX [14]. The swelling ratio of the hydrogel was significantly different at various pH values, suggesting that the hydrogel was highly sensitive to pH. Sun et al. designed pH-sensitive bio-nanocomposite beads, which were a hybrid built of ZnO nanoparticles, CMC, and chitosan (CS) biopolymers for colon-specific release of 5-fluorouracil (5-FU) [15]. Dhanavel et al. prepared 5-FU and Cur co-encapsulated CS/RGO nanocomposites. The results confirmed the efficacy of the system toward the inhibition of growth of the HT-29 colon cancer cells. Also, a better cytotoxicity was observed in co-delivery compared to individual delivery of drugs [16]. Pooresmaeil et al. investigated the encapsulation of ibuprofen (IBU)-loaded mesoporous magnetic GO inside CMC nanogels as a coating agent. CMC/MG@SiO2-IBU exhibited pH-sensitive swelling behavior. The significant advantage of CMC nanogels in drug delivery was the ability to release the IBU in a controlled manner in the colon medium that minimized the side effects of the drug [17].

CoFe2O4 nanoparticles (NPs) have found various biomedical uses in drug delivery, magnetic resonance imaging (MRI), and disease diagnosis. Thanks to their high magnetic anisotropy and moderate magnetism, the placement of CoFe2O4 NPs on graphene oxide nanosheets can result in an SDDS to maximize the therapeutic effects of the drug on the target tissue by effective driving of the drug carrier into the tumor tissue under the magnetic field [18].

Chemotherapy drugs such as 5-FU [16], camptothecin [19, 20], DOX [21, 22], CUR [23–27] can be loaded onto pH-sensitive polymer nanocomposites. CUR is the bioactive substance of turmeric, which can be obtained from the rhizome of Curcuma longa. Numerous clinical studies have been conducted using CUR as the main therapeutic agent. The anticancer potential of CUR has been proven against a variety of cancer types, including gastrointestinal, hematologic, breast, ovarian, prostate, lung, colon, sarcoma, and brain tumors. For instance, Anirudhan et al. reported a nano cellulose containing folic acid (FA) as a targeting ligand for pH-controlled delivery of CUR [28]. The biocomposite showed an apparent longer-term growth-suppression influence on the breast cancer cell lines (MDA MB-231) along with a satisfactory sustained-release behavior compared with free CUR. CUR inhibits tumor formation through a combination of mechanisms involving anti-oxidant, anti-inflammatory, anti-angiogenesis, cell inhibitory, and proapoptotic activities exerted by regulating the genes and molecules involved in these pathways [28, 29].

By taking into account the aforementioned contents, the main aim of this was to develop a pH-responsive magnetic bio-nanocomposite comprising GO, CoFe2O4, and CMC and evaluate its ability for controlled drug delivery agent. For this purpose, CUR was loaded on the CoFe2O4/
GO-ADH-CMC. To the best of our knowledge, this bio-nanocomposite as a carrier for CUR delivery application has not been reported. Factors affecting drug loading rate, adsorption kinetics, adsorption isotherm, and drug release behavior were studied considering related theoretical models. Furthermore, the release profile of the drug was examined at different pH values (physiological pH and endosomal pH), which confirmed the pH responsiveness and sustained release of the carrier. Finally, biocompatibility of the carriers was compared on normal and breast cancer cells.

Materials and Methods

Materials

The CUR drug (chemical formula = C21H20O6 and molecular weight = 368.385 g mol⁻¹; λmax = 424 nm) was provided by ExirNanoSina Co. (Iran, Tehran). Iron (III) chloride hexahydrate (FeCl₃·6H₂O, ≥ 98%), Cobalt (II) chloride hexahydrate (CoCl₂·6H₂O, ≥ 97%), Polyvinylpyrrolidone ((C₈H₁₇N₃·HCl, ≥ 98.0%), Adipic acid dihydrazide (ADH, NH₂NHCO(CH₂)₄CONHNH₂, ≥ 98%), Sodium carboxymethyl cellulose (CMC, average Mw ~ 90,000), and all other substances were purchased from Sigma Aldrich (USA) and used as received, without further purification.

Preparation of the Magnetic CoFe₂O₄/GO-ADH-CMC

Expandable graphite was used as the raw material to synthesize graphene oxide via the ultrasound-assisted Hummers method [30]. The CoFe₂O₄/GO composite was prepared by the co-precipitation of CoFe₂O₄ magnetic NPs on GO nanosheets [18, 31]. Typically, 0.67 g PVP, 0.81 g CoCl₂·6H₂O, and 1.6 g FeCl₃·6H₂O were dissolved into a 150 mL solution containing 250 mg of fully-dispersed GO and followed by magnetic stirring in an inert atmosphere at 333 K for 30 min. Then, the temperature rose to about 353 K, and ammonia solution (32%, v/v) was added slowly under vigorous magnetic stirring to raise the mixture solution pH to around 10.5. The reaction continued for another 120 min. After cooling down to room temperature, the obtained black CoFe₂O₄/GO was collected using a magnet, washed three times with deionized water/ethanol to remove the excess base, and finally dried at 50 °C under vacuum.

To prepare aminated magnetic graphene oxide, 100 mg CoFe₂O₄/GO was dispersed in 40 mL of deionized water by ultra-sonication for 60 min and followed by the addition of 50 mg EDC along with 150 mg NHS which are completely dissolved in 20 mL deionized water. After 60 min of reaction, 100 mg ADH was added, and the mixture was stirred overnight at ambient temperature. In the presence of EDC.HCl and NHS, the COOH group of GO could form a reactive intermediate, which combined with the amino group of ADH to form GO-ADH. The as-prepared CoFe₂O₄/GO-ADH was magnetically separated, washed to remove the excess reactants, and dried under vacuum [13].

For binding the amino group of ADH to the carboxyl group of CMC, 50 mg CoFe₂O₄/GO-ADH was dispersed in 10 mL of water by ultra-sonication for 30 min. Afterward, 15 mg CMC, 38 mg EDC, and 113 mg NHS were poured into 15 mL deionized water, and the mixture was agitated overnight at 20 °C. After filtration, the magnetic gel product was freeze-dried to obtain the CoFe₂O₄/GO-ADH-CMC bio-nanocomposite. The reaction process is demonstrated in Fig. 1.

Instrumental Analyses

The morphology, structure, and average size of the samples were monitored with a field emission-scanning electron microscope (FE-SEM, MIRA 3 TESCAN, Czech, 15 kV) and a transmission electron microscope (TEM, Zeiss model EM 10C, Germany). The Fourier Transform Infrared spectra (FT-IR) were recorded on a spectrophotometer (Avatar, Thermo, USA) in the range of 4000–400 cm⁻¹ using KBr pellets. Crystallographic structures of the samples were examined by an X-ray diffractometer (PW1730, Philips, Netherlands) at room temperature using Cu/Kα radiation at 40 kV and 30 mA in the range of 9°–70°. Thermogravimetric analysis (TGA) was carried out on the TGA instrument (Q600, TA, USA) for thermal degradation of materials at a heating rate of 20 °C/min, from 25 to 600 °C under N₂ flow. The magnetic property was characterized by using a vibrating sample magnetometer (VSM, MDK model LBKFB, Meghnatis Daghigh Kavir, Iran) from −14 to 14 kOe at room temperature. The zeta potential of the samples was measured at 25 °C by using a zeta potential analyzer. The CUR concentration was measured using a UV–Vis spectrophotometer (UV-2100, Japan).

Adsorption Experiments

A stock solution of the drug (500 mg L⁻¹) was prepared by dissolving a calculated amount of CUR in the required amount of aqueous ethanol (96% v/v), and the working concentrations of the drug solution were prepared by dilution with deionized water. The structure of CUR is shown in Fig. S1 in the supplementary material. The initial and remaining CUR concentrations were determined according to the Beer-Lambert plot (absorbance versus concentration plot), obtained by using UV/Vis spectrophotometers. The adsorption batch experiments consisted of varying the solution
Fig. 1 Schematic illustration of the synthesis route of CoFe$_2$O$_4$/GO-ADH-CMC
pH (2.5–8.0), time of contact (5–90 min), adsorbent dosage (0.25–1.0 g L\(^{-1}\)), drug initial concentration in solution (2–120 mg L\(^{-1}\)), and temperature (298–323 K) [32]. For each batch experiment, the known amount of adsorbent dosage was added into the Erlenmeyer flask containing a 20 mL drug solution with a fixed concentration. The flask was protected with aluminum foil from light. The initial pH of the CUR solution was adjusted by adding NaOH (0.01 M) or HCl (0.1 M). The suspension was stirred on a shaker with a shaking speed of 200r/min for a certain time at the controlled temperature. The adsorbent was separated from the suspension by the magnet, and CUR concentration in the resulting supernatant was estimated at 424 nm wavelength. The adsorption capacity at a specific time, \(t\), was referred to as \(q_t\) (mg g\(^{-1}\)) and was assessed by the Eq. (1):

\[
q_t = \frac{(C_0 - C_t) V}{m}
\]

where \(C_0\) (mg L\(^{-1}\)) is the CUR concentration in the solution before adsorption, and \(C_t\) (mg L\(^{-1}\)) represents the CUR concentration of the suspension when the adsorption proceeds at a certain time; \(V\) (L) and \(m\) (g) stand for the CUR solution volume and the adsorbent mass.

### In-Vitro Release Experiments

#### The CUR Loading

For the preparation of the drug carrier, 0.2 g of CoFe\(_2\)O\(_4\)/GO-ADH-CMC (CoFe\(_2\)O\(_4\)/GO) was suspended in 50 mL CUR solution in aqueous ethanol (96\% v/v) with a concentration of 500 mg L\(^{-1}\), followed by adjusting the pH level to 6.0. After a continuous shaking for 60 min in the dark at room temperature and 300 rpm, the resulting carrier was taken out and washed to remove the unloaded drug. The amount of free CUR in the supernatant was analyzed by a UV–Vis spectrophotometer.

#### The CUR Release

For the in-vitro drug release study, the CUR-loaded CoFe\(_2\)O\(_4\)/GO-ADH-CMC (CUR-loaded CoFe\(_2\)O\(_4\)/GO), obtained from the loading step, was transferred into a dialysis bag with a molecular weight cut off (MWCO) of 14 kDa. The bag was tightened and soaked in 50 mL of phosphate-buffered saline (PBS; pH 7.4 and 5.6) at 37 °C for 24 h. At a predetermined time interval, 3 mL of the solution was withdrawn, and the same amount of fresh buffered solution was replaced to keep the solution volume constant. The release test was taken in triplicates, and the fraction of the drug released at time \(t\), \(M_t/M_\infty\) (%), was determined using Eq. (2).

\[
\frac{M_t}{M_\infty} = \frac{C_t}{C_0} \times 100
\]

where \(M_t\) and \(M_\infty\) represent the released drug at time \(t\) and the total loaded drug, respectively; \(C_0\) and \(C_t\) are the quantity of CUR released and quantity of CUR loaded at time \(t\).

### Cell Experiments

MTT assays were performed to evaluate the biocompatibility of the prepared materials. Breast adenocarcinoma (MDA-MB 231) cells and normal breast cells (MCF 10A) were grown in 96-well plates, and incubated with various concentrations (6–96 μg mL\(^{-1}\)) of CoFe\(_2\)O\(_4\)/GO-ADH-CMC (or CoFe\(_2\)O\(_4\)/GO) for 24 h at 37 °C in a CO\(_2\) incubator. The solution in each well was removed and then 200 μL of MTT solution (5 mg mL\(^{-1}\)) was introduced. After 4 h of incubation, the MTT-containing medium was replaced with 200 μL of DMSO so as to dissolve the insoluble formazan crystals. A microplate plate reader was used to measure the solution absorbance at 570 nm.

### Results and Discussion

#### Structural Characterizations

The shape and appearance of the GO, CoFe\(_2\)O\(_4\)/GO, and CoFe\(_2\)O\(_4\)/GO-ADH-CMC were characterized by FE-SEM at low and high magnifications, as shown in the upper and middle panels of Fig. 2, respectively. It can be seen that GO has an apparent lamellar structure with many wrinkles [14]. CoFe\(_2\)O\(_4\)/GO has a rough surface compared to GO because spherical cobalt ferrite NPs are densely deposited on the GO surface and its edges. The surface roughness of the fabricated bio-nanocomposite decreased after CoFe\(_2\)O\(_4\)/GO was modified by ADH and CMC. This can be due to the crosslinking of CMC with GO sheets, which makes a partially smooth surface in CoFe\(_2\)O\(_4\)/GO-ADH-CMC [14]. The EDX spectra in the bottom panels of Fig. 2 show the C, O, Co, Fe, and N elements are present in the CoFe\(_2\)O\(_4\)/GO-ADH-CMC nanocomposite.

The representative TEM images of CoFe\(_2\)O\(_4\)/GO-ADH-CMC, Fig. 3, illustrate thin, wrinkled sheets of GO with a relatively large distribution of CoFe\(_2\)O\(_4\) in the range of 10–200 nm. Moreover, almost no free CoFe\(_2\)O\(_4\) was observed outside of the GO, confirming the in situ nucleation of NPs on the GO [18, 33].

The FT-IR analysis was used to illuminate the surface functional groups of prepared materials. Figure 4a represents the infrared spectra of the GO, CoFe\(_2\)O\(_4\)/GO, CoFe\(_2\)O\(_4\)/GO-ADH, and CoFe\(_2\)O\(_4\)/GO-ADH-CMC. The GO spectrum included a sharp peak at 3437 cm\(^{-1}\) attributed to the
stretching vibrations of the O–H functional groups as well as the inter-/intra- molecular hydrogen interactions with a number of peaks at 2924, 1710, 1635, 1269, and 1074 cm\(^{-1}\), which are related to the stretching vibrations of aromatic C–H of CH\(_2\), aromatic C=C, C=O, CO–H, and deformation vibration of C–O, respectively [14, 18]. With the formation of the CoFe\(_2\)O\(_4\)/GO, some changes were observed in the intensity or positions of peaks in the spectrum. For example, the peak at 3437 cm\(^{-1}\) became weak and shifted to 3411 cm\(^{-1}\) and a new absorption band appeared at 607 cm\(^{-1}\) due to the asymmetric bending mode (Fe–O) of the CoFe\(_2\)O\(_4\) [34]. When the GO was functionalized with ADH, two characteristic peaks of 3200 and 1620 cm\(^{-1}\) related to the N–H stretching vibration and amide bond were detected. After the reaction of the amino group at the terminal of CoFe\(_2\)O\(_4\)/GO-ADH with the carboxyl group of CMC through the crosslinking agent, the intensity of the peak at 1620 cm\(^{-1}\) increased due to the formation of the amide bond. The peaks at 3440 cm\(^{-1}\) and 3200 cm\(^{-1}\) were respectively resulted from the stretching vibration of O–H in GO and CMC, and N–H in ADH structure. In addition, the presence of CMC in CoFe\(_2\)O\(_4\)/GO-ADH-CMC could be confirmed by the three absorption bands at 1601, 1409, and 1066 cm\(^{-1}\), which are caused by asymmetric and symmetric stretching vibrations of carboxylate groups as well as stretching of C–O on the polysaccharide skeleton of CMC, respectively [35].

The XRD analysis of GO, CoFe\(_2\)O\(_4\)/GO, and CoFe\(_2\)O\(_4\)/GO-ADH-CMC within the 2\(\theta\) range of 9°–70° are illustrated in Fig. 4b. The XRD pattern of GO shows a sharp diffraction peak at 9.7° [36, 37]. For the CoFe\(_2\)O\(_4\)/GO, five new peaks, 30.04°, 35.80°, 43.66°, 53.8°, 57.6°, and 63.10°, appeared for component CoFe\(_2\)O\(_4\) NPs indexed to (220), (311), (400),...
A new broad diffraction peak observed at 22.44° in the XRD pattern of CoFe₂O₄/GO-ADH-CMC is associated with the partly crystalline structure of CMC, confirming its existence as a CoFe₂O₄/GO-ADH coating layer [39].

TG analysis was carried out to investigate the thermostability of GO, CoFe₂O₄, and CoFe₂O₄/GO-ADH-CMC, and the results are shown in Fig. 4c. CoFe₂O₄ displayed high thermal stability, containing only a slight mass loss (about 8%) for the whole measured range (25 to 600 °C), corresponding to the dehydroxylation of the CoFe₂O₄. GO had a 57% mass loss when the temperature rose to 600 °C. After ADH and CMC modification, the mass loss of CoFe₂O₄/GO-ADH-CMC was 50% within the same temperature range. The lower mass loss of the composite compared to GO implies that the addition of CoFe₂O₄ and the formation of interactions between CMC and GO could enhance the thermostability of the whole system [15, 40]. The chemically cross-linking process between CMC and GO through ADH as the crosslinking agent could improve the thermostability of the composite [2]. Moreover, the hydrogen bonding interactions, between hydroxyl and carboxyl groups on
the surface of GO and appropriate groups present in the structure of CMC and ADH could result in a delay in the polymer degradation [11]. The TG curve of CoFe2O4/GO-ADH-CMC had three stages at 25–150 °C, 150–400 °C, and 400–600 °C, which could be assigned to the loss of physically adsorbed water, the decomposition of liable oxygen-containing functional groups of GO, carbonyl, and amine groups of ADH, together with partial degradation of the CMC chain, and the decomposition of final waste of the polysaccharide CMC, followed by the pyrolysis of the carbon skeleton, respectively [2].

The VSM analysis was applied to assess the magnetic property of the nanocomposite at room temperature (300 K). Figure 4d displays the magnetization (M vs. H) plot of CoFe2O4/GO-ADH-CMC. The M-H curve passes through the origin and does not include any hysteresis. This “S” like behavior of the nanocomposite reveals its superparamagnetic essence, which is a requirement for biological applications since it prevents aggregation when the external magnetic field is switched off [33]. The saturation magnetization value was measured to be 6.6 emu g⁻¹, lower than the commonly reported value for pristine CoFe2O4 NPs [18], indicating the presence of a non-magnetic nature of GO and CMC coating layer in the bio-nanocomposite.
Affecting Parameters on the Adsorption of CUR

The adsorption experiments of CUR were aimed to examine the effect of the main process parameters on the drug loading through adsorption. The pH of the solution is a key parameter in CUR loading that affects both the ionization degree of the soluble drugs and the surface charge of the adsorbent. Figure 5a shows the adsorption capacity for CUR versus the pH solution in a range from 2.5 to 8 with a CUR concentration of 20 mg L⁻¹ and the adsorbent dosage of 10 mg after shaking for 120 min. The adsorption capacity was enhanced with increasing the pH from 2.5 to 4, peaked at 31.6 mg g⁻¹ at pH 4, and strongly decreased at the neutral and basic pH (≥ 7). It should be noted that at a higher initial pH (≥ 8), the CUR was highly unstable to chemical degradation.

CUR is a weak Brönsted acid, with three labile protons and therefore has three pKa values of 7.7 to 8.5, 8.5 to 10.4, and 9.5 to 10.7 [41]. In acidic and neutral media (i.e., pH 3–7), CUR appears either in neutral or in a partially protonated form. However, in basic solutions (i.e. pH > 7), CUR exists in anionic forms and behaves as an electron donor [42]. According to the zeta potential results, the pHpzc of CoFe₂O₄/GO-ADH-CMC was estimated to be 2.9 (Fig. 5b), implying that at pH < 2.9, the surface of the adsorbent was positively charged, and negatively charged at pH > 2.9 [43]. The small value of the point of zero charge (pzc) for the adsorbent may be assigned to the presence of abundant oxygenated functional groups (such as hydroxyl, carboxyl, and carbonyl groups of CMC biopolymer and GO nanosheets) on the adsorbent surface [44]. The electrostatic attraction between the negatively charged moieties on the CoFe₂O₄/GO-ADH-CMC surface and protonated CUR with the positive charge causes the maximum adsorption capacity at pH 6. On the contrary, deprotonation of the hydroxyl group of CUR, which occurs at pH higher than 7, leads to the electrostatic repulsion between negatively charged adsorbent surface and anionic forms of CUR, thereby decreasing the adsorption capacity of CUR, as seen in Fig. 5a. Also, the adsorption mechanism might be ascribed to the H-bonding, π–π stacking, and hydrophobic interaction between CUR and CoFe₂O₄/GO-ADH-CMC [45]. The plausible interactions between CUR and the prepared composite were illustrated in Fig. S2. Finally, pH 6 was chosen as optimal for subsequent studies.

Other factors affecting the amount of drug loading are contact time and adsorbent dosage, which were evaluated in...
the range of 5 to 90 min and 0.25 to 1.0 g L\(^{-1}\), respectively, in this study. In each experiment, the CoFe\(_2\)O\(_4\)/GO-ADH-CMC was added to the CUR solution (20 mL) with an initial concentration of 20 mg L\(^{-1}\) and shaken at room temperature. Regarding the results, represented in Fig. 5c, the adsorption capacity declined from 50.2 to 16.9 g L\(^{-1}\) with the adsorbent dosage increased from 0.25 to 1.0 g L\(^{-1}\) at 60 min owing to the reduction in the total surface area of the adsorbent as a consequence of CoFe\(_2\)O\(_4\)/GO-ADH-CMC stacking [46, 47]. On the other hand, the initial rate of CUR loading increased with the prolongation of the contact time. In the beginning, the adsorption rate of the drug was very fast, on account of the availability of free adsorptive sites and the high possibility of collision of CUR with the CoFe\(_2\)O\(_4\)/GO-ADH-CMC surface. After that, the loading rate slowed down because of the saturation of active binding sites on the adsorbent. Eventually, equilibrium occurred, and no further adsorption was observed [48].

The effects of drug initial concentration and temperature on the drug loading were investigated at varied CUR concentrations from 2 to 120 mg L\(^{-1}\) and controlled temperatures from 298 to 323 K. In each experiment, the 0.02 g of CoFe\(_2\)O\(_4\)/GO-ADH-CMC was put into 20 mL of CUR solution, and shaken for 90 min. As Fig. 5d indicates, the adsorption capacity slightly increased from 20.29 to 23.66 mg g\(^{-1}\) with the rise in temperature from 298 to 323 K once the CUR concentration was 120 mg L\(^{-1}\). That means the adsorption process was endothermic. It might be due to the improving solubility and diffusion of CUR to the adsorptive sites. The obtained results also indicated that the adsorption capacity was enhanced by increasing drug concentration due to augmentation in the driving force for mass transfer of CUR from the solution to the surface of the CoFe\(_2\)O\(_4\)/GO-ADH-CMC at a higher initial concentration [48].

**Adsorption Kinetics and Isotherms**

The non-linear form of pseudo-first-order (PFO), pseudo-second-order (PSO), and intra-particle diffusion (IPD) models [49, 50] was adopted to analyze the adsorption kinetic data of CUR onto the CoFe\(_2\)O\(_4\)/GO-ADH-CMC at three dosages of 0.25, 0.5, and 1.0 mg L\(^{-1}\). The kinetic equations of the PFO and PSO models are as follows, respectively:

\[
q_t = q_e \left(1 - e^{-kt}\right)
\]

(3)

\[
q_t = \frac{k_2q_e^2t}{1 + k_2q_et}
\]

(4)

where \(k_1\) (min\(^{-1}\)) and \(k_2\) (g mg\(^{-1}\) min\(^{-1}\)) are the rate constant of the two kinetic models, respectively; \(q_e\) (mg g\(^{-1}\)) denotes the amount of the CUR adsorbed at equilibrium.

The IPD model reveals the diffusion mechanism of adsorption kinetics. The mathematical equation of the IPD model can be expressed as below (Eq. (5)):

\[
q_t = k_it^{1/2} + C
\]

(5)

where \(k_i\) (mg g\(^{-1}\) min\(^{-1/2}\)) is the IPD rate constant and \(C\) (mg g\(^{-1}\)) denotes the boundary layer thickness, respectively.

The relevant kinetic parameters, obtained from the non-linear curve fitting of dynamic experimental data (\(q_t\) versus \(t\)), are outlined in Table 1. The appropriateness of the fitted kinetic models was evaluated using the regression coefficient \((R^2)\) along with the root mean square error (RMSE). The RMSE function is principally the sum of the squares of the differences between the experimental data and model-calculated values [51]. As presented in Table 1, the \(R^2\) values for the PSO kinetic model were slightly higher than those for the two other models. In addition, the PSO model had the lowest RMSE for all the adsorbent dosages. It means that the adsorption kinetic pattern of CUR onto CoFe\(_2\)O\(_4\)/GO-ADH-CMC was consistent with the PSO model. This finding implies that chemisorption is the most likely rate-limiting step in the adsorption process [52–54]. However, given that the \(R^2\) values of the PFO and IPD models were also reasonable, it can be concluded that CUR adsorption onto the bio-nanocomposite may occur via complex mechanism pathways such as chemisorption, physisorption, and pore diffusion [55, 56]. Besides, by incrementing the adsorbent dosage from 0.25 to 1.0 mg L\(^{-1}\), the \(k_i\) value for PSO equation increased from 0.0012 to 0.0044 (Table 1), which represents the faster equilibrium of adsorption is attained at a high dosage of CoFe\(_2\)O\(_4\)/GO-ADH-CMC.

| Kinetics models | Parameters | Adsorbent dosage (g L\(^{-1}\)) |
|-----------------|------------|-------------------------------|
|                 |            | 0.25 | 0.5 | 1.0 |
| Pseudo-first-order | \(k_1\) (min\(^{-1}\)) | 0.065 | 0.116 | 0.241 |
|                 | \(q_{e,cal}\) (mg g\(^{-1}\)) | 51.51 | 30.32 | 16.24 |
|                 | \(R^2\) | 0.9973 | 0.9975 | 0.9979 |
|                 | RMSE | 0.4929 | 1.3226 | 0.6849 |
| Pseudo-second-order | \(k_2\) (mg g\(^{-1}\) min\(^{-1}\)) | 0.0012 | 0.004 | 0.023 |
|                 | \(q_{e,cal}\) (mg g\(^{-1}\)) | 60.97 | 34.34 | 17.48 |
|                 | \(R^2\) | 0.9995 | 0.9997 | 0.9998 |
|                 | RMSE | 0.9156 | 0.3786 | 0.2175 |
| Intra-particle diffusion | \(k_i\) (mg g\(^{-1}\) min\(^{-1/2}\)) | 4.79 | 2.44 | 0.87 |
|                 | \(C\) (mg g\(^{-1}\)) | 11.89 | 12.64 | 10.89 |
|                 | \(R^2\) | 0.9956 | 0.9956 | 0.9987 |
|                 | RMSE | 2.8013 | 1.7504 | 0.5426 |
The non-linear form of Langmuir, Freundlich, Temkin, Dubinin-Radushkevich, and Sips models [57] was adopted to analyze the adsorption equilibrium data of CUR onto the CoFe$_2$O$_4$/GO-ADH-CMC (at three temperatures of 298, 308, and 323 K) and CoFe$_2$O$_4$/GO (at the temperature of 323 K).

The isotherm equations of the Langmuir and Freundlich models can be expressed as follows, respectively:

$$ q_e = \frac{q_{\text{max}}KLC_e}{1 + KLC_e} $$  \hspace{1cm} (6)

$$ q_e = K_Fe^{1/n} $$  \hspace{1cm} (7)

where $q_{\text{max}}$ (mg g$^{-1}$) is the Langmuir maximum adsorption capacity; $K_L$ (L mg$^{-1}$) and $K_F$ (L$^2$ mg$^{-2}$ g$^{-1}$) are the constant of Langmuir and Freundlich isotherms, respectively; $1/n$ is the characteristic of the adsorption intensity.

The Temkin isotherm is given by the following Eq. (8):

$$ q_e = \frac{RT}{B} \ln (A_T C_e) $$  \hspace{1cm} (8)

where $A_T$ (L mg$^{-1}$) is the equilibrium binding constant and $b$ (J mol$^{-1}$) is a constant related to the heat of adsorption; $T$ (K) and $R$ (8.314 J mol$^{-1}$ K) are the absolute temperature and the ideal gas constant, in the respective order.

The Dubinin-Radushkevich isotherm is represented by the following Eq. (9):

$$ q_e = q_{\text{D-R}}e^{-Bc^2} $$  \hspace{1cm} (9)

where $B$ (mol$^2$J$^{-2}$) is Dubinin–Radushkevich isotherm constant and $q_{\text{D-R}}$ (mg g$^{-1}$) denotes the theoretical saturation capacity; $c$ is Polanyi potential defined as $c = RT\ln[1 + 1/C_e]$; $B$ is the constant of the adsorption energy, as. The average free energy, $E$(mol$^{-1}$) is obtained from $B$ as $E = 1/(2B)^{1/2}$.

The Sips isotherm is a three-parameter model combining the Langmuir and Freundlich isotherms. It represents the multilayer adsorption characteristic of Freundlich isotherm at a low equilibrium concentration of adsorbate, while converting to Langmuir monolayer isotherm at high adsorbate concentration [58]. The Sips isotherm is described based on the Eq. (10):

$$ q_e = \frac{q_{\text{ms}}K_S C_e^{\frac{1}{nS}}}{1 + K_S C_e^{\frac{1}{nS}}} $$  \hspace{1cm} (10)

where $q_{\text{ms}}$ (mg g$^{-1}$) and $K_S$ (mg$^{-1/nS}$L$^{1/nS}$) are the Sips maximum adsorption capacity and Sips equilibrium constant, in the respective order; $1/n_S$ is the Sips exponent pertaining to the heterogeneity factor.

Plots of the non-linear fittings related to the above five isotherms along with the experimental data are illustrated in Fig. 6. The relevant fitting results are presented in Table 2. Amongst five nonlinear models, the Sips isotherm described the adsorption system the best, as reflected by the largest $R^2$ and the smallest RMSE values for all temperatures. This may be referred to the contribution of both chemisorption and physisorption in drug loading, which was affirmed by studying the kinetic models [59]. Furthermore, because of the low $R^2$ and high RMSE values, the Freundlich and Dubinin-Radushkevich models showed less agreement with the experimental data, implying that the adsorption of CUR could not be described well by these two models.

The Sips isotherm exponent ($1/n_S$) values were between 0 and 1, which meant that the Langmuir isotherm was more suitable to describe the adsorption of CUR onto the CoFe$_2$O$_4$/GO-ADH-CMC than the Freundlich isotherm, which was also verified by both $R^2$ and RMSE values. Based on the observed isotherm parameters, it can be deduced that a substantial amount of monolayer adsorption and a minor amount of multilayer adsorption of CUR took place on the surface of bio-nanocomposite owing to its surface heterogeneity [53, 60].

The values of $q_{\text{max}}$, calculated for CoFe$_2$O$_4$/GO-ADH-CMC using the Langmuir model were 19.9, 20.86, and 22.80 mg g$^{-1}$ at the temperatures of 298 K, 308 K, and 323 K, respectively. However, CoFe$_2$O$_4$/GO exhibited a lower $q_{\text{max}}$ value (17.46 mg g$^{-1}$) at 323 K under the same conditions of adsorbent dosage, contact time, and pH. The results indicate that the addition of ADH and CMC provides a higher adsorption capacity for CoFe$_2$O$_4$/GO-ADH-CMC bio-nanocomposite due to the increase in the surface binding groups. Furthermore, the value of the Langmuir isotherm constant ($K_L$) was higher for CoFe$_2$O$_4$/GO-ADH-CMC than for CoFe$_2$O$_4$/GO, specifying the increase in the affinity for CUR by providing new bonds on the surface of the CoFe$_2$O$_4$/GO-ADH-CMC. The $1/n$ parameters obtained by the Freundlich isotherm were smaller than one at all temperatures, representing the favorability of the CUR adsorption process [61]. With increasing the adsorption temperature in the range of 298 to 323 K, the values of $A_T$ constant, corresponding to the equilibrium binding energy, for the Temkin model increased from 61.44 to 202.66 L mg$^{-1}$, indicating the endothermic essence of the adsorption process of CUR onto CoFe$_2$O$_4$/GO-ADH-CMC [61].

**In-Vitro Drug Release Kinetics**

pH-sensitivity is a highly remarkable feature for a drug delivery system considering the acidic pH of the tumors in contrast with the neutral pH of the whole body, which can lead to a controlled-release behavior of the drug [21]. To verify the pH responsiveness of the carrier for drug delivery, the cumulative release behaviors of CUR-loaded CoFe$_2$O$_4$/GO and CUR-loaded CoFe$_2$O$_4$/GO-ADH-CMC at
the temperature of 37 °C in the PBS under two pH conditions (pH 5.6 (endosomal pH) and 7.4 (physiological pH)) were investigated, and the relevant plots ($M_t/M_{\infty}(\%)$ versus $t$) were shown in Fig. 7a.

Under physiological conditions (pH 7.4), the release behavior of CoFe$_2$O$_4$/GO-ADH-CMC was relatively slow, and the total released amount of CUR was only about 38% in 24 h. During the same period, the released amount of CUR from CoFe$_2$O$_4$/GO-ADH-CMC rapidly increased at the slightly acidic medium (pH 5.6), and the release amount reached 86%, which was much higher than that at pH 7.4. The possible reason for this phenomenon might be correlated with the presence of pH-responsive CMC blocks in the drug carrier. In the medium with a higher pH than pK$_a$ (∼4.3) of CMC, carboxyl groups convert to negatively charged carboxylate ions (−COO$^-$), resulting in the electrostatic repulsion between the biopolymer chains that leads to the polymeric network swelling. It is noteworthy that the swelling rate in the acidic medium is less than in the neutral medium [17]. Because, in the acidic medium, carboxyl groups can exist in the protonated form. H-bonding between the carboxylic and hydroxyl groups on CMC causes the shrinking of the polymer structure and facilitates the release of the drug [14, 62]. Thus, when arriving acidic cancerous tissue, CUR-loaded CoFe$_2$O$_4$/GO-ADH-CMC could undergo triggered-release of the drug. From Fig. 7a, it is also visible that under neutral solution conditions, CoFe$_2$O$_4$/GO released the drug rapidly and 55% of the CUR was released in the first 6 h. However, after the coating of CoFe$_2$O$_4$/GO with the CMC layer, drug release took place in a controlled way and approximately 35% of CUR was released (at pH 7.4), indicating that CMC could act as a degradable capsule and prevent the burst releases of CUR. These findings show that the CoFe$_2$O$_4$/GO-ADH-CMC could be a hopeful controlled pH-responsive drug delivery system for cancer therapy.

The non-linear form of the first order, Higuchi, Korsmeyer–Peppas, and Peppas–Sahlin kinetic models were adopted to analyze the obtained release pattern of drug from CUR-loaded CoFe$_2$O$_4$/GO and CUR- loaded CoFe$_2$O$_4$/GO-ADH-CMC in PBS at pH 5.6 and 7.4 up to 6 h (Fig. 7b–e). While the first-order kinetic model is widely used to describe drug delivery systems in which the release profile is...
controlled predominantly by the concentration of the loaded drug, the Higuchi model is applied to clarify the drug release from the insoluble matrix and involves dissolution and diffusion [7, 63]. The equations of the first order and Higuchi model can be expressed in Eqs. (11) and (12), respectively:

\[
\frac{M_t}{M_\infty} = q_0 (1 - e^{-k_1 t})
\]

\[
\frac{M_t}{M_\infty} = k_H t^{1/2}
\]

where \(q_0\) is the amount of CUR released at the initial time; \(k_1\) and \(k_H\) represent the constants of the first-order and Higuchi.

The Korsmeyer–Peppas model is common for describing the drug release from a polymeric system. Korsmeyer–Peppas and Peppas–Sahlin kinetic models are represented by Eqs. (13) and (14), respectively [64]:

\[
\frac{M_t}{M_\infty} = k_{KP} t^n
\]

\[
\frac{M_t}{M_\infty} = k_1 t^n + k_2 t^{2n}
\]

where \(k_{KP}\) is the constant of the Korsmeyer–Peppas model. Also, \(k_1\) and \(k_2\) denote the rate constants of the Peppas–Sahlin model, and \(n\) is the release exponent.

The release kinetic parameters along with the regression coefficient values, obtained from the non-linear curve fitting of release experimental data, are listed in Table 3. The highest value of the regression coefficient \((R^2 > 0.998)\) was observed for the Peppas-Sahlin model, revealing that the release data satisfactorily were fitted by the Peppas-Sahlin model. The value of the diffusion exponent \((n)\) from the Korsmeyer–Peppas model was in the range of 0.60 to 0.69. Therefore, the release of CUR obeys non-Fickian transport behavior (anomalous releasing), which is associated with the operation of both molecular diffusion and polymer corrosion releasing mechanisms [62, 65].

| Isotherm models | Parameters | CoFe\(_2\)O\(_4\)/GO-ADH-CMC | CoFe\(_2\)O\(_4\)/GO |
|-----------------|------------|-------------------------------|---------------------|
|                 | Temperature (K) | 298 | 308 | 323 | 323 |
| Langmuir        | \(q_0\) (mg g\(^{-1}\)) | 19.91 | 20.86 | 22.80 | 17.46 |
|                 | \(K_L\) (L mg\(^{-1}\)) | 1.46 | 2.189 | 2.68 | 0.12 |
|                 | \(R^2\) | 0.9989 | 0.9989 | 0.9977 | 0.9960 |
|                 | RMSE | 0.5176 | 0.5488 | 0.8744 | 0.7536 |
| Freundlich      | \(K_F\) (mg L\(^{-1}\) g\(^{-1}\)) | 9.64 | 10.57 | 11.87 | 3.74 |
|                 | \(1/t\) | 0.18 | 0.17 | 0.17 | 0.33 |
|                 | \(R^2\) | 0.9785 | 0.9793 | 0.9822 | 0.9749 |
|                 | RMSE | 2.3507 | 2.4320 | 2.4488 | 1.8960 |
| Temkin          | \(A_T\) (L mg\(^{-1}\)) | 61.44 | 104.19 | 202.66 | 2.93 |
|                 | \(b_t\) (J mol\(^{-1}\) g mg\(^{-1}\)) | 1004.62 | 1044.46 | 1077.4 | 1729.60 |
|                 | \(R^2\) | 0.9923 | 0.9929 | 0.9946 | 0.9988 |
|                 | RMSE | 1.4059 | 1.4226 | 1.3494 | 1.0175 |
| Dubinin-Radushkevich | \(q_{DR}(mg g\(^{-1}\)) | 19.14 | 20.17 | 22.11 | 14.90 |
|                 | \(B\) (mol J\(^{-1}\) L\(^2\) g\(^{-1}\)) | 1.09 | 0.58 | 0.43 | 30.26 |
|                 | \(E\) (kJ mol\(^{-1}\)) | 2.14 | 2.94 | 3.41 | 0.41 |
|                 | \(R^2\) | 0.9895 | 0.9924 | 0.9912 | 0.9931 |
|                 | RMSE | 1.6455 | 1.4768 | 1.7162 | 0.9922 |
| Sips            | \(q_{sp}(mg g\(^{-1}\)) | 20.26 | 21.30 | 23.64 | 15.89 |
|                 | \(K_S\) | 1.31 | 1.74 | 1.80 | 0.07 |
|                 | \(1/n_S\) | 0.85 | 0.82 | 0.71 | 0.69 |
|                 | \(R^2\) | 0.9994 | 0.9996 | 0.9995 | 0.9985 |
|                 | RMSE | 0.3883 | 0.3167 | 0.4267 | 0.4705 |
Fig. 7 Cumulative drug release (%) plots of CUR-loaded CoFe$_2$O$_4$/GO-ADH-CMC and CUR-loaded CoFe$_2$O$_4$/GO (a) in 0.9 g L$^{-1}$ PBS of two pH values (5.6 and 7.4) at 37 °C; Release kinetic models of CUR-loaded CoFe$_2$O$_4$/GO-ADH-CMC (a, b) and CUR-loaded CoFe$_2$O$_4$/GO (c, d) in PBS of pH 5.6 and 7.4 at 37 °C

First-order, Higuchi, Korsmeyer-Peppas, Peppas-Sahlin
In-Vitro Cell Viability

Breast adenocarcinoma (MDA-MB 231) cells and normal breast cells (MCF 10A) were incubated with various concentrations (6–96 μg mL⁻¹) of CoFe₂O₄/GO-ADH-CMC, CoFe₂O₄/GO for 24 h, and the cell viability was obtained using the MTT assay. As demonstrated in Fig. 8a and b, with the increase of the concentrations of the nanocomposites, the cell viabilities decreased. Both nanocomposites bear more cytotoxicity against MDA-MB 231 than MCF 10A cell lines. Moreover, for CoFe₂O₄/GO-ADH-CMC at the highest concentration of 96 μg mL⁻¹, the viability of MCF 10A cells was found to be 85%, which was slightly higher than the corresponding value for CoFe₂O₄/GO, which was about 81%. This means that modification with CMC can somewhat improve the biocompatibility of the CoFe₂O₄/GO and reduce its cytotoxicity against the normal cells.

Conclusions

A pH-responsive system was prepared through the cross-linking of CoFe₂O₄/graphene oxide to carboxymethyl cellulose for potential application in drug delivery. The maximum adsorption capacity of CUR was 23.64 mg g⁻¹ for CoFe₂O₄/GO-ADH-CMC, which was relatively higher than the non-functionalized CoFe₂O₄/GO with the value of 15.69 mg g⁻¹. The in-vitro CUR release from the resultant carrier composed of CMC polymer was pH-dependent and followed a non-Fickian transport behavior (anomalous releasing) which is associated with the operation of both molecular diffusion and polymer corrosion releasing mechanisms. For CoFe₂O₄/GO-ADH-CMC, the total amount of CUR released was about 86% under neutral conditions, whereas only 38% of CUR was released in slightly acidic conditions after 24 h. The higher availability of the CUR at pH 5.6 than at pH 7.4 is valuable in chemotherapy and suggests that the CUR-loaded CoFe₂O₄/GO-ADH-CMC may be a promising

| Kinetics models    | Parameters          | CoFe₂O₄/GO-ADH-CMC | CoFe₂O₄/GO |
|-------------------|---------------------|--------------------|-----------|
|                   | pH value            | 5.6                | 7.4       | 5.6       | 7.4       |
| First-order       |                    | 0.25               | 0.24      | 0.32      | 0.33      |
|                   | kₗ(min⁻¹)           | 102.45             | 46.07     | 30.03     | 64.22     |
|                   | qₗ(mg·g⁻¹)          | 0.9991             | 0.9989    | 0.9997    | 0.9983    |
|                   | R²                  | 31.38              | 13.81     | 10.53     | 22.78     |
|                   |                    | 0.9899             | 0.9877    | 0.9941    | 0.9906    |
| Higuchi           | kₙ(min⁻¹/²)         |                    |          |           |           |
|                   | R²                  |                    |          |           |           |
| Korsmeyer-Peppas  | Kₚ₉(min⁻¹)          | 24.73              | 10.64     | 9.13      | 19.59     |
|                   | n                   | 0.67               | 0.69      | 0.61      | 0.61      |
|                   | R²                  | 0.9967             | 0.9959    | 0.9967    | 0.9936    |
| Peppas-Sahlin     | Kₚ₉(min⁻¹)          | 22.99              | 9.62      | 8.79      | 18.45     |
|                   | n                   | 1.03               | 1.08      | 0.95      | 1.01      |
|                   | R²                  | 0.9995             | 0.9987    | 0.9932    | 0.9987    |

Fig. 8 The viability (%) of a MDA-MB 231 and MCF 10A (b) cells incubated with CoFe₂O₄/GO-ADH-CMC or CoFe₂O₄/GO under concentration of 6–96 μg mL⁻¹ for 24 h at 37 °C

In-Vitro Cell Viability

Breast adenocarcinoma (MDA-MB 231) cells and normal breast cells (MCF 10A) were incubated with various concentrations (6–96 μg mL⁻¹) of CoFe₂O₄/GO-ADH-CMC, CoFe₂O₄/GO for 24 h, and the cell viability was obtained using the MTT assay. As demonstrated in Fig. 8a and b, with the increase of the concentrations of the nanocomposites, the cell viabilities decreased. Both nanocomposites bear more cytotoxicity against MDA-MB 231 than MCF 10A cell lines. Moreover, for CoFe₂O₄/GO-ADH-CMC at the highest concentration of 96 μg mL⁻¹, the viability of MCF 10A cells was found to be 85%, which was slightly higher than the corresponding value for CoFe₂O₄/GO, which was about 81%. This means that modification with CMC can somewhat improve the biocompatibility of the CoFe₂O₄/GO and reduce its cytotoxicity against the normal cells.

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candidate for the continuous and slow release of CUR in cancer treatment.

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**Declarations**

**Conflict of interest** The authors declare that they have no competing interest.

**References**

1. Zhao X, Bai J, Yang W (2021) Stimuli-responsive nanocarriers for therapeutic applications in cancer. Cancer Biol Med 18:319
2. George A, Shah PA, Shrivastav PS (2019) Natural biodegradable polymers based nano-formulations for drug delivery: a review. Int J Pharm 561:244–264. https://doi.org/10.1016/J.IJPHARM.2019.03.011
3. Soleimani K, Derakhshankhah H, Jaymand M, Samadian H (2021) Stimuli-responsive natural gums-based drug delivery systems for cancer treatment. Carbohydr Polym 254:117422. https://doi.org/10.1016/J.CARBPOL.2020.117422
4. Tian B, Liu Y, Liu J (2021) Smart stimuli-responsive drug delivery systems based on cyclodextrin: a review. Carbohydr Polym 251:116871. https://doi.org/10.1016/J.CARBPOL.2020.116871
5. Alsheli M (2020) Polymeric nanocarriers as stimuli-responsive systems for targeted tumor (cancer) therapy: recent advances in drug delivery. Saudi Pharm J 28:255–265. https://doi.org/10.1016/J.JPS.S.2020.01.004
6. Priya James H, John R, Alex A, Anoop KR (2014) Smart polymers for the controlled delivery of drugs: a concise overview. Acta Pharm Sin B 4:120–127. https://doi.org/10.1016/J.APSB.2014.02.005
7. Nguyen CT, Vu MQ, Phan TT et al (2020) Novel pH-sensitive hydrogel beads based on carrageenan and fish scale collagen for allopurinol drug delivery. J Polym Environ 28(6):1795–1810. https://doi.org/10.1007/S10924-020-01727-6
8. Suddique A, Cheong IW (2021) Recent advances in three-dimensional bioprinted nanocellulose-based hydrogel scaffolds for biomedical applications. Korean J Chem Eng 38(1):2171–2194. https://doi.org/10.1007/S11814-021-0926-X
9. Thennakoon TM, Ching YC, Chuah CH et al (2020) pH-responsive poly(lactic acid)/sodium carboxymethyl cellulose film for enhanced delivery of curcumin in vitro. J Drug Deliv Sci Technol 58:101787. https://doi.org/10.1016/J.JDDST.2020.101787
10. Wang R, Shou D, Lv Q et al (2017) pH-Controlled drug delivery with hybrid aerogel of chitosan, carboxymethyl cellulose and graphene oxide as the carrier. Int J Biol Macromol 103:248–253. https://doi.org/10.1016/J.IJBIOMAC.2017.05.064
11. Gao F, Wu X, Wu D et al (2020) Preparation of degradable magnetic temperature- and redox-responsive polymeric/Fe3O4 nanocomposite nanogels in inverse miniemulsions for loading and release of 5-fluorouracil. Colloids Surfaces A Physicochem Eng Asp 587:124363. https://doi.org/10.1016/J.COLSU RFA.2019.124363
12. Makvandi P, Ghomi M, Ashrafizadeh M et al (2020) A review on advances in graphene-derivative/polysaccharide biocomposites: therapeutics, pharmacogenomics and toxicity. Carbohydr Polym 250:116952. https://doi.org/10.1016/J.CARBPOL.2020.116952
13. Rao Z, Ge H, Liu L et al (2018) Carboxymethyl cellulose modified graphene oxide as pH-sensitive drug delivery system. Int J Biol Macromol 107:1184–1192. https://doi.org/10.1016/J.IJBIOMAC.2017.09.096
14. Rasoulzadeh M, Namazi H (2017) Carboxymethyl cellulose/graphene oxide-bio-nanocomposite hydrogel beads as anticancer drug carrier agent. Carbohydr Polym 168:320–326. https://doi.org/10.1016/J.CARBPOL.2017.03.014
15. Zare-Akbari Z, Farhadnejad H, Furughi-Nia B et al (2016) pH-sensitive bionanocomposite hydrogel beads based on carboxymethyl cellulose/ZnO nanoparticle as drug carrier. Int J Biol Macromol 93:1317–1327. https://doi.org/10.1016/J.IJBIOMAC.2016.09.110
16. Dhanavel S, Revathy TA, Sivaranjani T et al (2019) 5-Fluorouracil and curcumin co-encapsulated chitosan/reduced graphene oxide nanocomposites against human colon cancer cell lines. Polym Bull 77(77):213–233. https://doi.org/10.1007/S00289-019-02374-X
17. Pooresmaeili M, Javanbakht S, Behzadi Nia S, Namazi H (2020) Carboxymethyl cellulose/mesoporous magnetic graphene oxide as a safe and sustained ibuprofen delivery bio-system: Synthesis, characterization, and study of drug release kinetic. Colloids Surfaces A Physicochem Eng Asp 594:124662. https://doi.org/10.1016/J.COLSU RFA.2020.124662
18. Wang G, Ma Y, Wei Z, Qi M (2016) Development of multifunctional cobalt ferrite/graphene oxide nanocomposites for magnetic resonance imaging and controlled drug delivery. Chem Eng J 289:150–160. https://doi.org/10.1016/J.CEJ.2015.12.072
19. Oprea M, Voicu SI (2020) Recent advances in composites based on cellulose derivatives for biomedical applications. Carbohydr Polym 247:116683. https://doi.org/10.1016/J.CARBPOL.2020.116683
20. Almeida A, Linares V, Mora-Castaño G et al (2021) 3D printed systems for colon-specific delivery of camptothecin-loaded chitosan micelles. Eur J Pharm Biopharm 167:48–56. https://doi.org/10.1016/J.EJPB.2021.07.005
21. Lim C, Cho EB, Kim D (2019) pH-triggered intracellular release of doxorubicin from polysacpartamide-encapsulated mesoporous silica nanoparticles. Korean J Chem Eng 36:166–172. https://doi.org/10.1007/S11814-018-0185-7
22. Abbasali M, Asnefnejad A, Khorasani MT, Saadatabadi AR (2021) Fabrication of carboxymethyl chitosan/poly(e-caprolactone)/doxorubicin/nickel ferrite core-shell fibers for controlled release of doxorubicin against breast cancer. Carbohydr Polym 257:117631. https://doi.org/10.1016/J.CARBPOL.2021.117631
23. Karimi S, Namazi H (2021) Synthesis of folic acid-conjugated glycodendrimer with magnetic β-cyclodextrin core as a pH-responsive system for tumor-targeted co-delivery of doxorubicin and curcumin. Colloids Surf A Physicochem Eng Asp 627:127205. https://doi.org/10.1016/J.COLSURFA.2021.127205
24. Zakerikhoob M, Abbasi S, Yousefi G et al (2021) Curcumin-incorporated crosslinked sodium alginate-g-poly(N-isopropyl acrylamide) thermo-responsive hydrogel as an in-situ forming injectable dressing for wound healing: In vitro characterization and in vivo evaluation. Carbohydr Polym 271:118434. https://doi.org/10.1016/J.CARBPOL.2021.118434
25. Ayyanaar S, Kesavan MP, Sivaraman G et al (2019) A novel curcumin-loaded PLGA micromagnetic composite system for controlled and pH-responsive drug delivery. Colloids Surf A Physicochem Eng Asp 573:188–195. https://doi.org/10.1016/J.COLSURFA.2019.04.062
26. de Oliveira AC, de Lima GRF, Klein RS et al (2021) Thermo- and pH-responsive chitosan/gellan gum hydrogels incorporated with the β-cyclodextrin/curcumin inclusion complex for efficient
curcumin delivery. React Funct Polym 165:104955. https://doi.org/10.1016/J.REACTFUNCTPOLYM.2021.104955

27. Anagha B, George D, Maheswari PU, Begum KMMS (2019) Biomass derived antimicrobial hybrid cellulose hydrogel with green ZnO nanoparticles for curcumin delivery and its kinetic modelling. J Polym Environ 279(27):2054–2067. https://doi.org/10.1007/S10924-019-01495-Y

28. Anirudhan TS, Manjusha V, Chitra Sekhar V (2021) A new biodegradable nano cellulose-based drug delivery system for pH-controlled delivery of curcumin. Int J Biol Macromol 183:2044–2054. https://doi.org/10.1016/J.IJBIOMAC.2021.06.010

29. H. Sarkar F, Li Y, Wang Z, Padhye S (2010) Lesson learned from nature for the development of novel anti-cancer agents: implication of isoflavone, curcumin, and their synthetic analogs. Underline 16:1801–1812. https://doi.org/10.2174/13816120791208956

30. Krishnamoorthy K, Kim GS, Kim SJ (2013) Graphene nanohsests: Ultrasound assisted synthesis and characterization. Ultrason Sonochem 20:644–649. https://doi.org/10.1016/J.ULTSONCH.2012.09.007

31. Rokni SE, Shiriazi HSM, Miraliniaghi M, Moniri E (2020) Efficient adsorption of anionic dyes onto magnetic graphene oxide coated with polyethyleneimine: Kinetic, isotherm, and thermodynamic studies. Res Chem Intermed. https://doi.org/10.1007/s11164-020-04090-2

32. Shaftaati M, Miraliniaghi M, Shiriazi RHSM, Moniri E (2020) The use of chitosan/Fe3O4 grafted graphene oxide for effective adsorption of rifampicin from water samples. Res Chem Intermed 46:5231–5254. https://doi.org/10.1007/s11164-020-04259-9

33. Gupta J, Prakash A, Jaiswal MK et al (2018) Superparamagnetic iron oxide-reduced graphene oxide nanohybrid-a vehicle for targeted drug delivery and hyperthermia treatment of cancer. J Magn Magn Mater 448:332–338. https://doi.org/10.1016/J.JMMM.2017.05.084

34. Ansari H, Miraliniaghi M, Azizinezhad F (2019) CoFe2O4/chitosan magnetic nanocomposite: Synthesis, characterization and application for adsorption of acidic yellow dye from aqueous solutions. Cellul Chem Technol 53. https://doi.org/10.35812/cellulosechemtechnol.2019.53.20

35. Gholamali I, Yadollahi M (2020) Doxorubicin-loaded carboxymethyl cellulose/Starch/ZnO nanocomposite hydrogel beads as an anticancer drug carrier agent. Int J Biol Macromol 160:724–735. https://doi.org/10.1016/J.IJBIOMAC.2020.05.232

36. Khorshidi P, Shirazi RHSM, Miraliniaghi M et al (2020) Adsorption and in-vitro release studies of metformin hydrochloride. J Polym Environ 283(28):1106–1116. https://doi.org/10.1007/S10924-019-01646-1

37. Aliyari E, Fathi AA, Alvand M et al (2021) β-Cyclodextrin-grafted magnetic graphene oxide nanocomposites in ultrasound-assisted dispersive magnetic solid-phase extraction for simultaneous preconcentration of lead and cadmium ions. Res Chem Intermed 475(47):1905–1918. https://doi.org/10.1007/S11164-021-04412-Y

38. Homayonfard A, Miraliniaghi M, Shiriazi RHSM, Moniri E (2018) Efficient removal of cadmium (II) ions from aqueous solution by CoFe2O4/chitosan and NiFe2O4/chitosan composites as adsorbents. Water Sci Technol 78:2297–2307. https://doi.org/10.2166/wst.2018.510

39. Salama A, El-Sakhawy M, Kamel S (2016) Carboxymethyl cellulose based hybrid material for sustained release of protein drugs. Int J Biol Macromol 93:1647–1652. https://doi.org/10.1016/J.IJBIOMAC.2016.04.029

40. Sun X, Shen J, Yu D, Kun OX (2019) Preparation of pH-sensitive Fe3O4@C/carboxymethyl cellulose/chitosan composite beads for diclofenac sodium delivery. Int J Biol Macromol 127:594–605. https://doi.org/10.1016/J.IJBIOMAC.2019.01.191

41. Priyadarshini KI (2014) The chemistry of curcumin: from extraction to therapeutic agent. Molecules 19:20091–20112. https://doi.org/10.3390/MOLECULES191220091

42. Lee W-H, Loo C-Y, Behawo M et al (2013) Curcumin and its derivatives: their application in neuropharmacology and neuroscience in the 21st century. Curr Neuropharmacol 11:338. https://doi.org/10.2174/1570159X11311040002

43. Ansari MJ, Jaisim SA, Bokov DO et al (2022) Preparation of new bio-based chitosan/Fe2O3/NiFe2O4 as an efficient removal of methyl green from aqueous solution. Int J Biol Macromol 198:128–134. https://doi.org/10.1016/J.IJBIOMAC.2021.12.082

44. Yadav S, Ashana S, Singh AK et al (2021) Adsorption of cationic dyes, drugs and metal from aqueous solutions using a polymer composite of magnetic β-cyclodextrin/activated charcoal/Na alginate: Isotherm, kinetics and regeneration studies. J Hazard Mater 409:124840. https://doi.org/10.1016/J.JHAZMAT.2020.124840

45. Koupaei Malek S, Gabris MA, Hadi Jume B et al (2018) Adsorption and in vitro release study of curcumin form polyethyleneglycol functionalized multi walled carbon nanotube: kinetic and isotherm study. DARU J Pharm Sci 27(27):9–20. https://doi.org/10.1007/S40199-018-0232-2

46. Karimiradost S, Moniri E, Miraliniaghi M (2019) Thermodynamic and kinetic studies sorption of 5-fluorouracil onto single walled carbon nanotubes modified by chitosan. Korean J Chem Eng 36:1115–1123. https://doi.org/10.1007/s11814-019-0292-0

47. Saheed JO, Da OhW, Latip AFA, Suah FBM (2022) Mesoporous chitosan/activated charcoal powder and bead modified in 1-butyl-3-methylimidazolium acetate for the adsorption of acid blue 25 from an aqueous solution. J Chem Technol Biotechnol. https://doi.org/10.1002/JCTB.7027

48. Khan S, Aazam ES, Jain SK (2020) Synthesis and characterization of β-cyclodextrin/poly(1-naphthylamine) inclusion complex and in-vitro release studies of metformin hydrochloride. J Polym Environ 283(28):1106–1116. https://doi.org/10.1007/S10924-021-01646-1

49. Ahmed HA, Mubarak MF (2021) Adsorption of cationic dye using a newly synthesized CaNiFe2O4/chitosan magnetic nanocomposite: kinetic and isotherm studies. J Polym Environ 296(29):1835–1851. https://doi.org/10.1007/S10924-020-01989-0

50. Gad YH, Ali HE, Hegazy AES (2021) Synergistic effect of titanium dioxide (TiO2) and ionizing radiation on thermal and mechanical properties of carboxymethyl cellulose (CMC) for potential application in removal of basic dye from wastewater. J Polym Environ 291(29):3887–3899. https://doi.org/10.1007/S10924-021-02153-Y

51. Tabatabaiee Bafrooee AA, Moniri E, Ahmad Panahi H et al (2021) Ethylenediamine functionalized magnetic graphene oxide (Fe3O4@GO-EDA) as an efficient adsorbent in Arsenic(III) decontamination from aqueous solution. Res Chem Intermed 474(47):1397–1428. https://doi.org/10.1007/S11164-020-04368-5

52. He J, Ni F, Cui A et al (2020) New insight into adsorption and co-adsorption of arsenic and tetracycline using a Y-immobilized graphene oxide-alginate hydrogel: adsorption behaviours and mechanisms. Sci Total Environ 701:134363. https://doi.org/10.1016/J.SCITOTENV.2019.134363

53. Bulin C, Zhang B, Guo T et al (2021) Graphene oxide–starch composite as an efficient adsorbent for removing Cu(II): removal performance and adsorption mechanism. Res Chem Intermed 479(47):3825–3852. https://doi.org/10.1007/S11164-021-04887-7

54. Guo T, Bulin C, Zhang B et al (2021) A highly efficient adsorbent based on starch-graphene oxide architecture for scavenging aqueous Pb(II): isotherms, kinetics, thermodynamics and interaction mechanism. J Polym Environ 30(30):569–584. https://doi.org/10.1007/S10924-021-02227-X
55. Sherlala AIA, Raman AAA, Bello MM, Buthiyappan A (2019) Adsorption of arsenic using chitosan magnetic graphene oxide nanocomposite. J Environ Manage 246:547–556. https://doi.org/10.1016/J.JENVMAN.2019.05.117

56. Miao J, Wang F, Chen Y et al (2019) The adsorption performance of tetracyclines on magnetic graphene oxide: a novel antibiotics absorbent. Appl Surf Sci 475:549–558. https://doi.org/10.1016/j.apsusc.2019.01.036

57. Mita C, Bunea I, Roman T, Humelnicu D (2021) Cross-linked and functionalized acrylic polymers: efficient and reusable sorbents for Zn(II) ions in solution. J Polym Environ 297(29):2261–2281. https://doi.org/10.1007/S10924-020-02005-1

58. Xia J, Gao Y, Yu G (2021) Tetracycline removal from aqueous solution using zirconium-based metal–organic frameworks (Zr-MOFs) with different pore size and topology: adsorption isotherm, kinetic and mechanism studies. J Colloid Interface Sci 590:495–505. https://doi.org/10.1016/J.JCIS.2021.01.046

59. Alkurdi SSA, Al-Juboori RA, Bundschuh J et al (2021) Inorganic arsenic species removal from water using bone char: A detailed study on adsorption kinetic and isotherm models using error functions analysis. J Hazard Mater 405:124112. https://doi.org/10.1016/J.JHAZMAT.2020.124112

60. Murugesan A, Divakaran M, Raveendran P et al (2019) An eco-friendly porous poly(imide-ether)s for the efficient removal of methylene blue: adsorption kinetics, isotherm, thermodynamics and reuse performances. J Polym Environ 275(27):1007–1024. https://doi.org/10.1007/S10924-019-01408-Z

61. Emik S, Işık S, Yildirim E (2021) Simultaneous removal of cationic and anionic dyes from binary solutions using carboxymethyl chitosan based IPN Type resin. J Polym Environ 296(29):1963–1977. https://doi.org/10.1007/S10924-020-02016-Y

62. Anirudhan TS, Christa J (2020) Temperature and pH sensitive multi-functional magnetic nanocomposite for the controlled delivery of 5-fluorouracil, an anticancer drug. J Drug Deliv Sci Technol 55:101476. https://doi.org/10.1016/J.JDDST.2019.101476

63. Supare K, Mahanwar P (2022) Starch-chitosan hydrogels for the controlled-release of herbicide in agricultural applications: a study on the effect of the concentration of raw materials and crosslinkers. J Polym Environ 2022:1–14. https://doi.org/10.1007/S10924-022-02379-4

64. Yuan Y, Xu X, Gong J et al (2019) Fabrication of chitosan-coated konjac glucomannan/sodium alginate/graphene oxide microspheres with enhanced colon-targeted delivery. Int J Biol Macromol 131:209–217. https://doi.org/10.1016/J.IJBIOMAC.2019.03.061

65. El-Zeiny HM, Abukhadra MR, Sayed OM et al (2020) Insight into novel β-cyclodextrin-grafted-poly (N-vinylcaprolactam) nanogel structures as advanced carriers for 5-fluorouracil: equilibrium behavior and pharmacokinetic modeling. Colloids Surf A Physicochem Eng Asp 586:124197. https://doi.org/10.1016/J.COLSURFA.2019.124197

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