



Mesoporous titanium dioxide@ zinc oxide–graphene oxide nanocarriers for colon-specific drug delivery

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ABSTRACT

In this project, $\text{TiO}_2@\text{ZnO}$ nanoparticles core–shell nanostructured and titanium dioxide@ mesoporous zinc oxide–graphene oxide ($\text{TiO}_2@\text{ZnO-GO}$) hybrid nanocomposites as controlled targeted drug delivery systems were synthesized by a facile sono-chemical method. We prepared a novel mesoporous and core–shell structure as a drug nanocarrier (NCs) for the loading and pH-responsive characteristics of the chemotherapeutic curcumin. The structure, surface charge, and surface morphology of NCs were studied using with X-ray diffraction, Fourier transform infrared spectroscopy, dynamic light scattering, brunauer–emmett–teller, scanning electron microscopy (SEM), and transmission electron microscopy (TEM). The SEM and TEM images of NCs show the uniform hexagonal mesoporous morphology with average grain size of about ~ 190 nm. The drug loading was very high about 16 and 19 for $\text{TiO}_2@\text{ZnO}$ and $\text{TiO}_2@\text{ZnO-GO}$, respectively. The NCs showed pH-dependent drug release behavior. Drug release from $\text{TiO}_2@\text{ZnO-GO}$ in neutral pH were higher than in acidic medium, due to anionic charge of GO nanosheet. MTT assay results showed that the curcumin-loaded NCs showed significant toxicity due to which cell viability reduced to below 50% at $140 \mu\text{g/mL}$ concentration, thereby confirming its anticancer effects. The goal of this study is the application of water-dispersed $\text{TiO}_2@\text{ZnO-GO}$ with pH-dependent release properties for design a new drug delivery carrier.

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Introduction

In 2016, over one and half million new cancer cases are diagnosed, and about six hundred thousand Americans were died of cancer the same year. Of these new cases in 2016, it is anticipated that one hundred thousands were be due to colon cancer. Indeed, colorectal cancer is the third leading reason of cancer death for both men and women [1]. However surgical removal of a primary colorectal tumor has proven to be beneficial, thirty percent of patients eventually develop a metastasis [2]. The most prevalent sites of metastasis are the liver, lungs, and draining lymph nodes [3]. Chemotherapy is one of the cancer therapy manners and many drugs such as irinotecan (CPT-11), doxorubicin (DOX), oxaliplatin (OXA), cisplatin (CP), and curcumin (CUR) have been used for chemotherapy [4–6].

CUR is the yellowish pigmentation of turmeric which is commonly used as a food flavoring and coloring agent. Its chemical formula is 1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione with a chemical structure in the keto-enol tautomerism [7, 8]. CUR is an attracting therapeutic agent from a pharmaceutical viewpoint because of its notable biological characteristics, including its antioxidant, antimicrobial, anti-inflammatory, and wound healing activities [9, 10]. It also displays potential use for the medicinal treatment of various diseases, especially cancer [11]. However, CUR suffers from some disadvantages including low water solubility under acidic or neutral conditions, high decomposition rate in an alkaline media, and photo-degradation in organic solvents which subsequently limit its clinical applications [12]. The most challenging work in the progress of colon-specific drug delivery carriers is to deal with premature drug release from the carriers before the drug can be delivered to the target. To extend the successful colon-specific drug delivery NCs, they required to be stable and protected from the harsh acidic environment of the stomach and release the drug more specifically to the colon [13, 14]. Multiple approaches have been undertaken in recent years to develop the delivery of CUR in colonic tissues. Mucoadhesive chitosan nanoparticles [15], pH-sensitive nanoparticles [16], guar gum microspheres [17], polymeric NCs, [18] and graphene [19] have improved the bioavailability of CUR to some extent in colon, even

so; these carriers did not deliver the soluble form of CUR.

Graphene (G), a two-dimensional single layer of carbon atoms in a closely packed honeycomb lattice, has attracted significant attention from scientific communities in recent years [20–22]. Graphene has been extensively studied in the last several years due to its interesting characteristics, such as significant electrical conductivity, great theoretical specific surface area and high chemical stability, excellent absorptivity, and excellent mechanical properties [23–25]. Graphene oxide (GO) is a derivative of graphene and has attracted attention of many bioapplications including cellular growth and differentiation [26], gene and drug delivery [27], and photo-thermal therapy [28]. GO can simultaneously activate toll-like receptor (TLR)-4 and -9 responses as same autophagy in macrophages [26] and colon cancer cell CT26. In addition, injection of GO alone stimulates the immune cell infiltration into the tumor bed and inhibits colon cancer growth in mice [29]. Furthermore, GO conjugated with chemotherapy drugs (DOX and CP-11) can improve the killing of MCF-7 cells that are resistant to DOX and CP [27].

Many research works are going on for the development of anticancer agents having enhanced targeted characteristics, better therapeutics and low toxicity [30–33]. Due to this, TiO_2/ZnO are regarded to be a promising substance because of its reported anticancer potential [34, 35]. TiO_2 is one of the well-known mesoporous materials. Because of biocompatibility, large surface area, and mesoporous properties of TiO_2 , some of the investigation has been developed to use nanosized TiO_2 in dye-sensitized solar cells, electrochromic display, water splitting, degradation of organics, glucose sensors and specially as carrier for drug delivery which required slow and sustained release [36–38]. Biocompatibility and nontoxicity of TiO_2 caused by combination of TiO_2 with other materials such as mesoporous zinc oxide (mZnO) produce an intelligent drug delivery system for use in pharmaceutical formulation. In this work, we report the synthesis of a mesoporous TiO_2/ZnO and $\text{TiO}_2/\text{ZnO}-\text{GO}$ by a facile sonochemical way to allow multifunctional properties to be imparted into such a nanostructure. CUR was loaded on NCs, and the loading capacity and release behavior of CUR from NCs were also tested. As expected, the prepared ($\text{TiO}_2/\text{ZnO}-\text{GO}$) have

displayed high anticancer drug loading and pH-sensitive release behavior.

Materials and methods

Material

Zinc (II) nitrate hexahydrate ($\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, $\geq 99\%$, $M_w = 290.70$ g/mol), CUR (Merck, Darmstadt, Germany, Art No. 820354), sodium hydroxide (NaOH , $M_w = 40$ g/mol), ethanol, and polyvinylpyrrolidone (PVP) surfactants were purchased from Merck. Deionized water was prepared by an ultra-pure water system (Smart-2-Pure, TKACo, Germany). GO was prepared from graphite powder using sulfuric acid (H_2SO_4 , 98%), nitric acid (HNO_3 , 98%), potassium permanganate (KMnO_4 , 5% HCl , and hydrogen peroxide (H_2O_2 , 30%), all purchased from Merck. Other solvents and chemicals were from chemical laboratory in purity grades.

Preparation of GO nanosheets

GO was synthesized from natural graphite powder by a modified Hummers method [35]. In a routine process, 1 g of graphite was added to 100 mL of concentrated H_2SO_4 , 50 mL of HNO_3 in an ice bath, and while stirring, 4 g of KMnO_4 was slowly added. The reaction mixture is stirred for 2 h at temperatures below 10°C , followed by 1 h at 35°C until a thick dough had formed. After that, it is diluted by 100 mL of deionized (DI) water in an ice bath and transferred to a 98°C oil bath and stirred for 1 h. Again, the mixture was diluted to 300 mL. Then, 20 mL H_2O_2 (30%) was added until the color of the solution changed to a light yellow. The final product was centrifuged and washed several times with 5% HCl solution, and then by DI water, until the supernatant became neutral. Finally, the final solid was dried at 60°C for 24 h, and a loose brown powder was obtained.

Synthesis of $\text{TiO}_2@\text{ZnO}$ -1 wt% GO and $\text{TiO}_2@\text{ZnO}$

At first, the TiO_2 nanoparticles were synthesized by the sol-gel method [39]. A mesoporous ZnO shell was coated on the TiO_2 nanoparticles using sonochemical method. In a typical procedure, 0.11 g of the

TiO_2 nanoparticles was dispersed in a mixed solvent of ethanol: DI (1:1), 0.21 g PVP, and NaOH solution, followed by that, 1.8 g $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ was added and exposed with ultrasound waves at room temperature for 5 h. Power and frequency of the ultrasound waves were 100 W and 20 kHz, respectively. Then, a suspension of 1 wt% of GO (prepared in mixture of 10 mL of DI and 20 mL of ethanol) was added to this solution at room temperature and stirred with magnetic stirring. The obtained ternary nanoparticles of $\text{TiO}_2@\text{ZnO}$ -GO were dried at 100°C overnight. For comparison, the same method was used to synthesize $\text{TiO}_2@\text{ZnO}$ (m was short for mesoporous) with core-shell structure without GO.

Preparation of curcumin-loaded nanocarriers

CUR-loaded NCs were obtained by precipitation method by acetone as the solvent. Briefly, 15 mg of CUR was dissolved in 5 mL of acetone. Then, this solution was injected drop-wise into 50 mL of DI solution containing 60 mg of NCs under constant mixing rates and stirred magnetically at room temperature until complete evaporation of the acetone occurred and drug loaded nanoparticles were prepared. The final nanoparticles were separated by centrifuging at 20000 rpm for 15 min. The obtained NC was dried at vacuum oven overnight.

Characterization

XRD analysis

Phase analyses of the NCs were carried out by powder XRD (Philips X' pert Pro MPD, Holland) using a graphite-filtered $\text{Cu K}\alpha$ ($k = 0.9$ nm) radiation in the 2θ range of $10-90^\circ$, at 2θ steps of 0.05° , and a wavelength of 1.54 \AA .

Particle morphology

The surface morphological properties of NCs were examined by means of scanning electron microscopy (SEM) (VEGA\\TESCAN-XMU) at an accelerating voltage of 20 kV, and transmission electron microscopy (TEM) images were obtained using a Philips CM120 microscope operating at 120 kV and linear resolution of 2.5 \AA .

FT-IR analysis

FT-IR spectrophotometer (Bruker, Tensor 27, Biotage, Germany) was used for determining chemical structure of the NCs.

Determination of surface charge

The zeta potential of the prepared NCs was determined by dynamic light scattering (DLS) using a zetasizer (Malvern Instruments, Worcestershire, UK, model Nano ZS).

BET analysis

Nitrogen adsorption/desorption isotherms of TiO_2/ZnO were measured by a BELSORP-mini II adsorption porosimeter at 77 K after being degassed at 180 °C under vacuum for 5 h. The specific surface areas were calculated using the Brunauer–Emmett–Teller (BET) method, and the pore size distributions were calculated according to the Barrett–Joyner–Halenda (BJH) method.

Determination of loading efficiency

To determine the loading efficiency of the drug in the NCs, two parameters were determined including the drug loading ratio of drug. Drug loading ratio was determined as:

$$\text{DL}\% = \frac{W_{\text{drug}}}{W_{\text{carrier}}} \times 100, \quad (1)$$

where DL% is the drug loading ratio (percent), and W_{drug} and W_{carrier} represent the weight of the entrapped drug and the total weight of the corresponding drug-entrapped carrier, respectively.

For determination of the drug loading ratio, 1 mg of the final dried NCs was dissolved in 1 mL of acetone, and the drug content was measured spectrophotometrically (Thermo Fisher Scientific, USA, Madison, model GENESYS™ 10S) at wavelengths of 420 nm.

Drug release study

In general, drug-loaded NCs are suspended in a vessel containing certain amount of release media, and then the drug release is investigated over time. Briefly, 5 mg of drug-loaded carriers were dispersed

in 20 mL phosphate-buffered saline (PBS) containing 1% (v/v) Tween 80, and the resulting suspension incubated at 37 °C. The tubes were centrifuged at 12000 rpm for 5 min to separate the particles from medium. Then, at predetermined time intervals, 1 mL of the suspension was taken out and replaced by 1 mL fresh PBS. The concentration of CUR in the suspension was determined by ultraviolet–visible spectroscopy (UV–Vis) at wavelength of 420 nm. All the release studies were carried out in triplicate. In order to study the pH-dependency of the drug release, the experiments were carried out as well as at a pH of 5.5.

Cell cytotoxicity

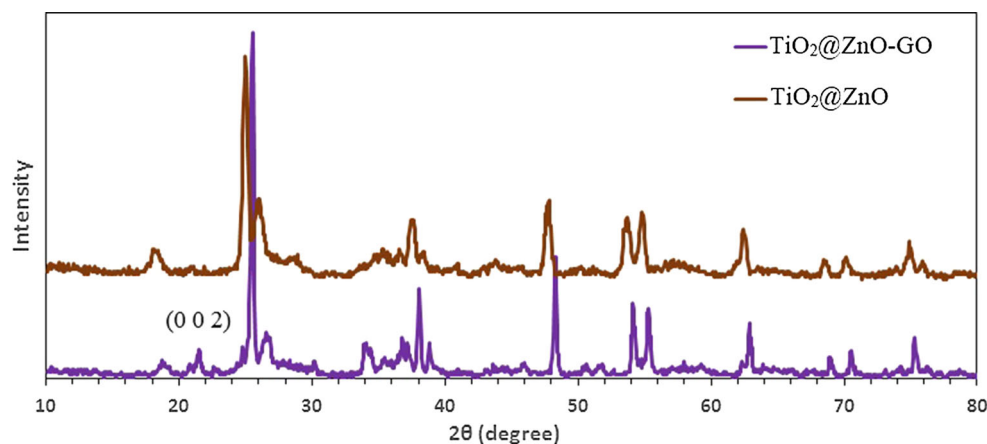
For the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) assay, 96 well plates were used, and Caco-2 cells were seeded onto plates and adhered and grown overnight in 200 μL culture medium with 10^4 cancer cells per well concentration. Then, the cancer cells were incubated with 100 μL fresh medium containing serial concentrations (0–140 $\mu\text{g}/\text{mL}$) of void CUR and same doses of CUR/ TiO_2/ZnO -GO and CUR/ TiO_2/ZnO for 24 h and a group without treatment for control. Then 20 μL of 4 mg/mL MTT solution was added to each 100 μL media of well and the plates were then incubated at 37 °C in a humidified atmosphere containing 95% air and 5% CO_2 for 3 h. Following the incubation, the MTT solution was eliminated, and 100 μL of dimethyl sulfoxide (DMSO) was added to each well for dissolution of the formazan crystals. The plates were shaken for 10 min on a plate shaker to obtain adequate solubility. After the shaking, absorbance readings of each well were done at 570 nm (single wavelength) by a multi-scan plate reader made in the UK. All experiments were repeated three times for statistical analysis. The final results were expressed as mean \pm S.D.

Results and discussion

XRD

The Bragg diffraction peaks of the two NCs, shown in Fig. 1, agreed well with those of the pure synthesized hexagonal ZnO [40], at 2θ values of 31.9°, 34.6°, 36.4°, 47.7°, 56.8°, 63.0°, and 68.1° which were indexed to be

Figure 1 XRD pattern of nanocarriers.



(1 0 0), (0 0 2), (1 0 1), (1 0 2), (1 1 0), (1 0 3), and (1 1 2) planes, respectively. and the peaks of $2\theta = 25.6^\circ$, 30.1° , 38.0° , 48.7° , and 54.1° can be indexed to the crystal faces of (1 0 1), (1 2 1), (0 0 4), (2 0 0), and (1 0 5) of TiO_2 , respectively. Due to the low amount of graphene oxide in the composite, the (0 0 2) peak of the corresponding to an interlayer distance of GO nanosheets around 21° has slight intensity and shown in the inset Fig. 1 [41].

Particle morphology

Figure 2a, b shows the SEM image of $\text{TiO}_2@\text{ZnO}-\text{GO}$ (a) and $\text{TiO}_2@\text{ZnO}$ (b). TiO_2 nano particles are used as a template to produce fine ZnO powders. Last researches indicate that suitable amount of TiO_2 can effectively suppress grain growth and phase transformation of ZnO [42]. With this approach, we can produce uniform nanoparticles. It can be seen in

Fig. 2a that the graphene nanosheets are fully exfoliated and almost decorated with nearly spherical $\text{TiO}_2@\text{ZnO}$ nanoparticles. Figure 2b illustrates the SEM images of $\text{TiO}_2@\text{ZnO}$ nanoparticles. It is evident from the Fig. 2b that the core-shell nanoparticles have a clear hexagonal phase with an average size of 190 nm. Figure 3 shows TEM images of $\text{TiO}_2@\text{ZnO}$ core-shell nanoparticles, which show the agglomeration of particles with different shapes (both spherical and hexagonal shape can be observed). From TEM images, the average particle size was estimated to be around 190 nm for nanoparticles, which is consistent with the SEM results.

FT-IR analysis

FT-IR spectra of the NCs are shown in Fig. 4. Nevertheless, the significant bands that characterize the formation of $\text{TiO}_2@\text{ZnO}$ are located at 470 and 657

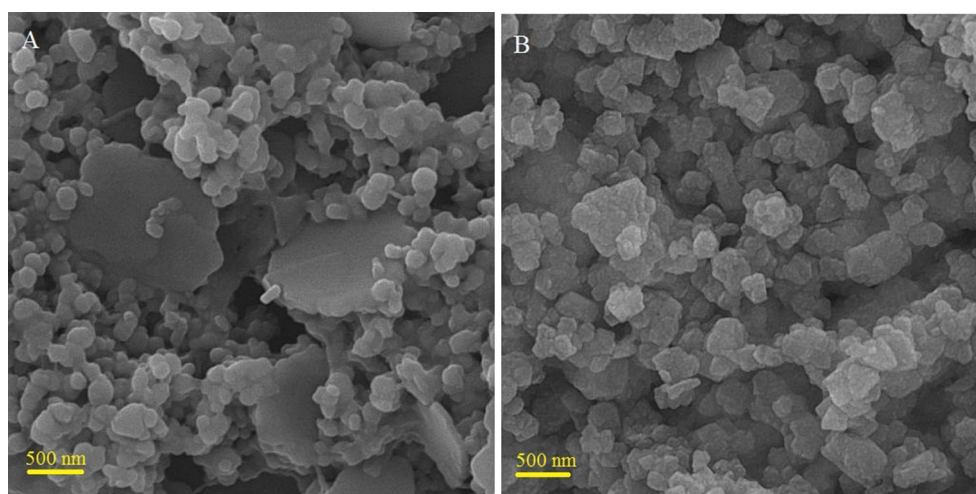


Figure 2 SEM images of $\text{TiO}_2@\text{ZnO}-\text{GO}$ (A) and $\text{TiO}_2@\text{ZnO}$ (B).

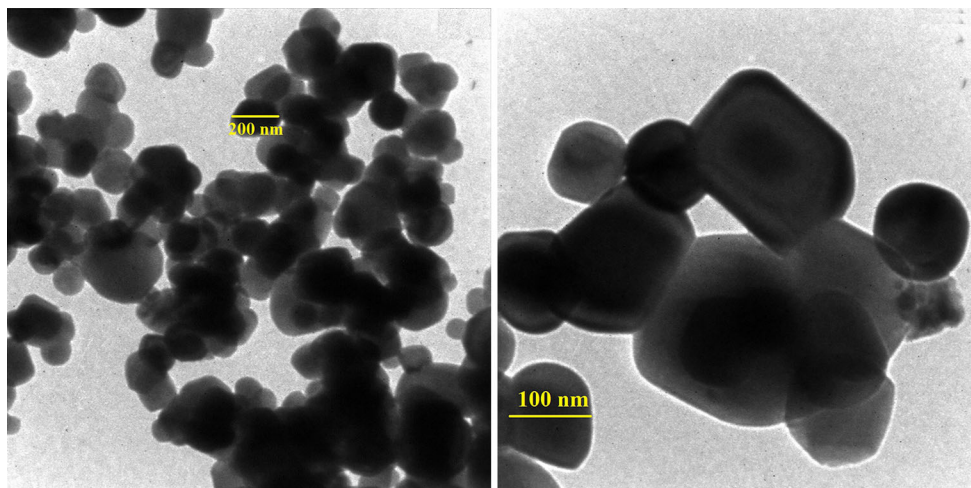
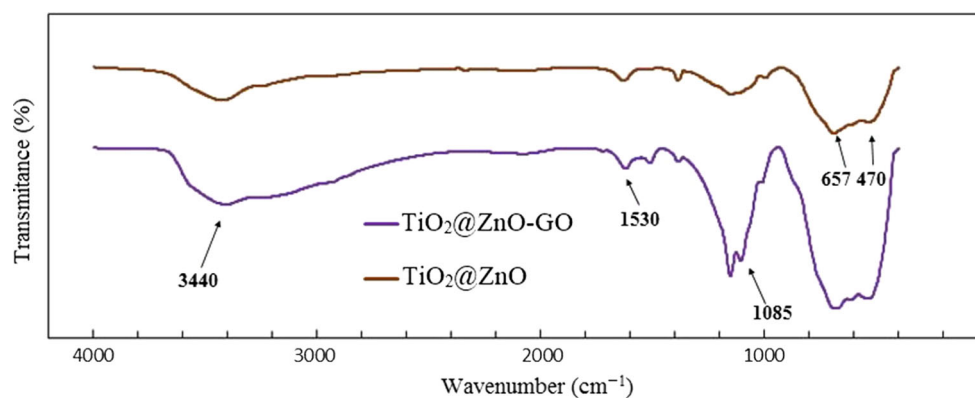


Figure 3 TEM images of $\text{TiO}_2@\text{ZnO}$.

Figure 4 FT-IR curve of nanocarriers.



Wavenumber (cm^{-1}), which are associated with the vibrations of Zn–O and Ti–O bonds, respectively [43, 44]. The peaks at 1085 , 1530 cm^{-1} were attributed to the stretching vibrations of C–O and C–H bonds, respectively [45]. In the case of the GO nanosheets, the absorption peak appeared at 3440 cm^{-1} in the IR spectra. This confirmed the presence of –OH groups in its nanostructure.

Surface charge of nanocarrier

The zeta potential of the aqueous suspension of NCs was also measured. Figure 5 shows zeta potential for $\text{TiO}_2@\text{ZnO}$ -GO determined in the PBS buffer solution at pH 7.4 and 5.5, respectively. As shown in Fig. 5, zeta potential of CUR-loaded NCs at pH 7.4 and 5.5 was found to be about -15.8 and -0.31 mv. It is clear that at the pH 7.4 where our results showed a negative zeta potential due to carboxyl group of graphene oxide are ionized. At lower pH, the

carboxyl group of graphene oxide are in deionized form which could form a proper condition for π – π stacking bond between drug and nanocarrier [46]. Surface charge is important in decisive whether the nanoparticles will cluster in blood flow or will stick to or interact with oppositely charged cell membrane. The plasma and blood cells constantly had a negative charge; nanoparticles with slight negative surface charge can minimize nonspecific contact with these components through electrostatic interactions [33, 47].

BET analysis

The nitrogen adsorption/desorption isotherms and pore size distribution profiles of $\text{TiO}_2@\text{ZnO}$ are presented in Fig. 6. It can be seen, sample have microporous structure. The BET surface area and total pore volume of $\text{TiO}_2@\text{ZnO}$ were calculated to be 31.59 m^2/g and 0.084 cm^3/g , respectively. As we

Figure 5 Zeta potential of $\text{TiO}_2@\text{ZnO}-\text{GO}$ at PH 5.5 (a) and PH 7.4 (b).

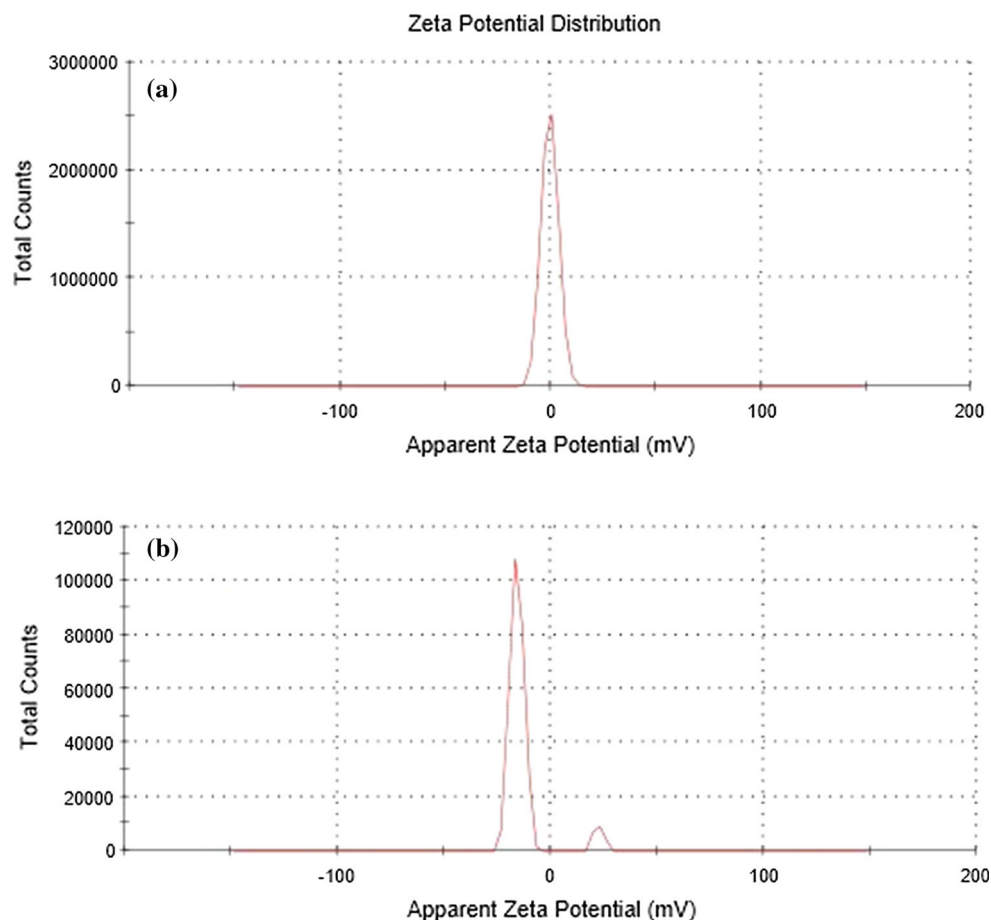
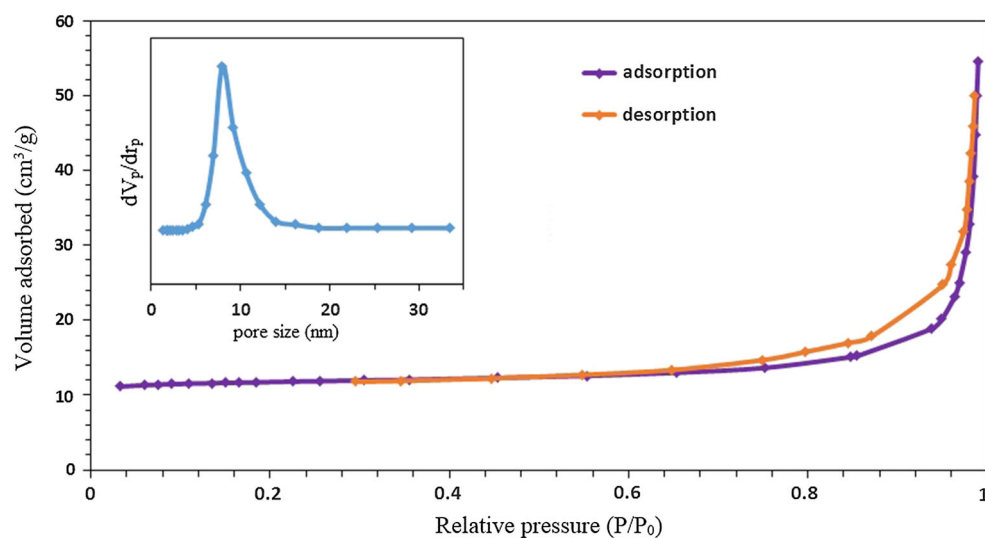


Figure 6 N_2 adsorption/desorption and pore size distribution of $\text{TiO}_2@\text{ZnO}$.



knew, the surface areas and pore volumes increased systematically with utilizing TiO_2 . Similar trends were observed after loading or mixing TiO_2 with ZnO [48]. Researches showed that surface area of pure

ZnO is about $11 \text{ m}^2/\text{g}$ [49], so with this approach, surface area would be significantly higher than pure ZnO .

Drug loading and release study

The effect of $\text{TiO}_2@\text{ZnO}$ and $\text{TiO}_2@\text{ZnO}-\text{GO}$ on the loading and release of CUR were investigated in detail in this section. Figures 7 and 8 show a schematic diagram of CUR loading and release for NCs. The amounts of CUR incorporated as pure drug in these NCs are listed in Table 1. It is observed that the loading of CUR in the NCs increases when utilizing $\text{TiO}_2@\text{ZnO}-\text{GO}$ instead of $\text{TiO}_2@\text{ZnO}$. This could be attributed to the strong $\pi-\pi$ stacking interaction between GO and drugs, which allows the penetration of drug molecules into the NCs [46]. Figure 9 illustrates in vitro drug release profile of CUR-loaded in NCs at pH 5.5 and 7.4. The results revealed the bare curcumin release percents attainable after a period of 12 h in PBS pH 7.4 and 5.5 were 86 and 88%, respectively. As expected, percentage of CUR released from the NCs slightly increased as the pH value increased from 5.5 to 7.4. The drug release curve Fig. 9 clearly illustrates that at the 12-h, there is a 19 and 28% CUR release from $\text{TiO}_2@\text{ZnO}$ to GO matrix which reached at 29s and 49% at pH 5.5 and 7.4, respectively, after six days. Sustained release of curcumin can be attributed to the entrapment of curcumin in mesoporous of NCs. The release is faster in neutral pH than acidic pH which can be attributed to deprotonation of residual carboxyl groups in GO of the $\text{TiO}_2@\text{ZnO}-\text{GO}$ at higher pH, creating a repulsion force between the NC and the drug. Therefore, more amount of drug will be diffused out. In addition in neutral medium, the breaking of

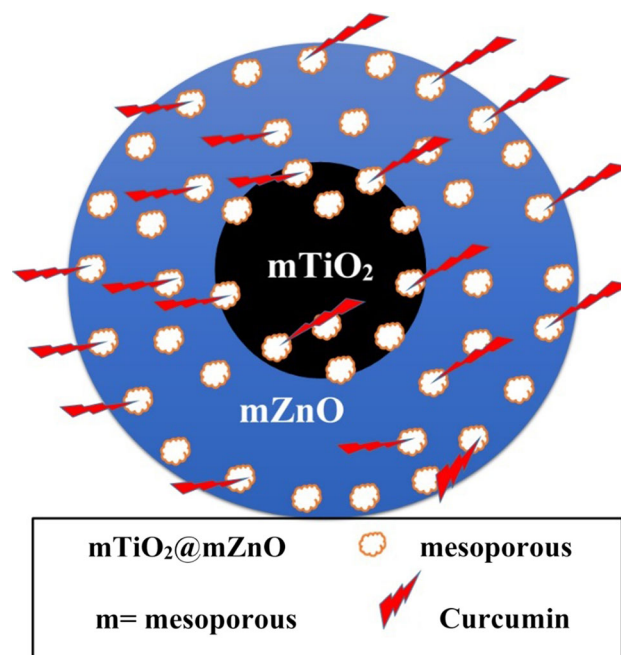


Figure 8 Schematic illustration of CUR in NCs.

Table 1 Drug loading of nanocarriers

Sample	Nanocarrier (μg)	Initial drug (μg)	DL%
$\text{TiO}_2@\text{ZnO}$	60000	15000	16.40
$\text{TiO}_2@\text{ZnO}-\text{GO}$	60000	15000	19.79

hydrogen bonding between the GO and CUR facilitated the release of the drug and thus increased the cumulative release. As expected, considerable initial

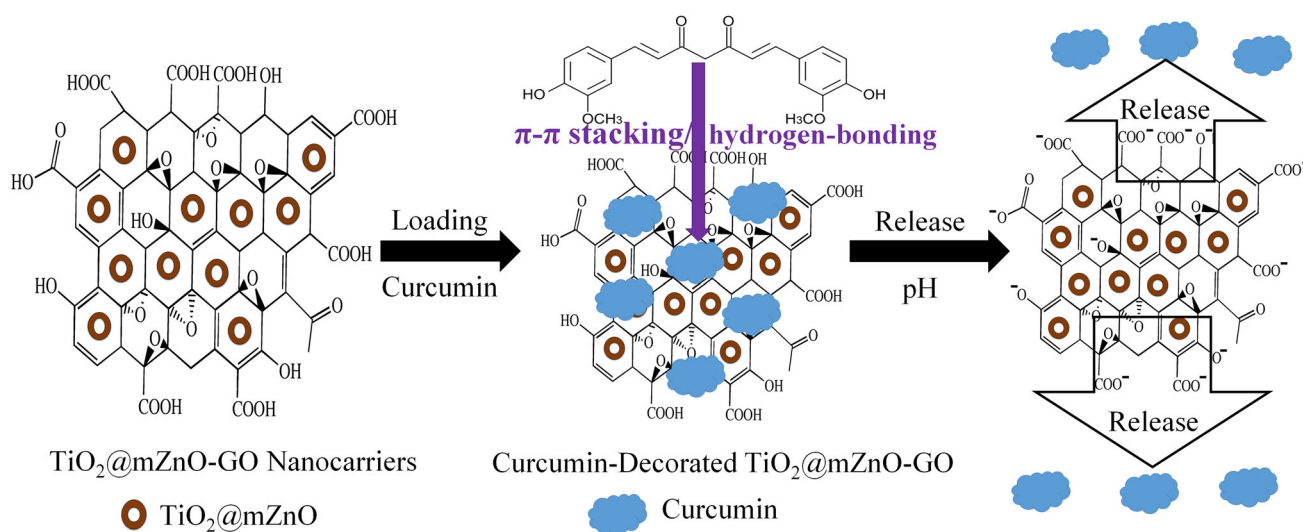


Figure 7 Schematic illustration of loading and release of CUR.

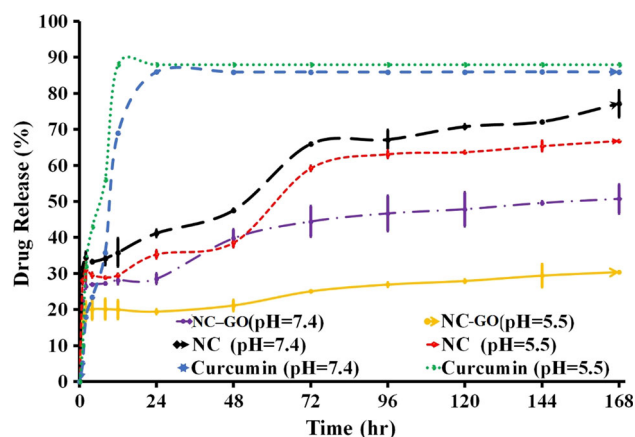


Figure 9 Release profiles at different pH values.

burst curcumin release was observed from the NCs due to desorbing curcumin from surface of NCs. This phenomenon could be useful for delivering drug to colon because after about 6 h the NCs reach to colon, therefore significant drug release should be happen during this period of time. In other hand, CUR released from NCs that could expose ZnO to cancer cells and bare ZnO makes this synergistic effect. These results reveal that $\text{TiO}_2\text{@ZnO-GO}$ could be used as colon-specific drug delivery carriers that would show pH-dependent drug release behavior [50].

Study on cancerous cell's viability after CUR loaded $\text{TiO}_2\text{@ZnO}$ and $\text{TiO}_2\text{@ZnO-GO}$ NCs treatment

The in vitro anticancer effects of CUR-loaded NCs against human epithelial colorectal adenocarcinoma cells (Caco-2) (pH 6.2–6.9) estimated using a MTT assay (Fig. 10). MTT results illustrated that the Curcumin-loaded NCs showed significant toxicity due to which cell viability reduced to below 50% at 140 $\mu\text{g}/\text{mL}$ concentration, thereby confirming its anticancer effect. The data exhibit that cell toxicity is directly proportionate to CUR-loaded NCs concentration. The concentration at which cell growth was inhibited by 50% (IC_{50}) was specified by the standard curve method and is shown in Table 2. Higher toxicity of $\text{TiO}_2\text{@ZnO}$ and $\text{TiO}_2\text{@ZnO-GO}$ than CUR-loaded NCs can be imputed to the presence of ZnO nanoprecipitation on the cells. In particular, ZnO when reduced from bulk to nanoscale has been shown to exhibit inherent preferential cytotoxicity against cancer cells in vitro [51, 52]. Also, the cytotoxicity assay showed relatively higher toxicity of the $\text{TiO}_2\text{@ZnO}$ than $\text{TiO}_2\text{@ZnO-GO}$ against Caco-2 cancer cell lines. Therefore, GO reduced toxicity of ZnO nanoparticle. On other hand, curcumin-loaded NCs showed lower toxicity in the test revealed that adsorbed curcumin on surface of ZnO nanoparticles covered their surface and this method can reduce toxicity of ZnO nanoparticles. And due to lower

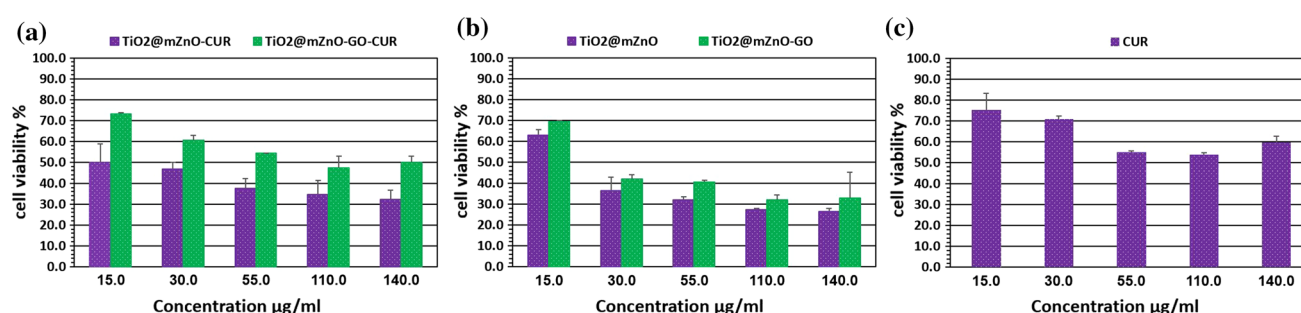


Figure 10 MTT assay for **a** CUR-loaded NCs, **b** bare NCs, and **c** void CUR on Caco-2 after incubation at 24 h. X-axes in figure are related to concentration of CUR and NCs, and y-axes show percentage of cell viability.

Table 2 Comparison of IC_{50} values for various concentration of void CUR and NCs at 24 h against Caco-2 cell line as determined by the MTT assay (the data unit is based on micromolar [$\mu\text{g}/\text{mL}$])

Type of treatment	$\text{TiO}_2\text{@ZnO-CUR}$	$\text{TiO}_2\text{@ZnO-GO-CUR}$	$\text{TiO}_2\text{@ZnO}$	$\text{TiO}_2\text{@ZnO-GO}$	CUR
IC_{50}	17.41	89.46	10.43	40.33	113.28

release of drugs in acidic environment like stomach, this method can protect normal cells of stomach against toxicity of ZnO. In other hand, when the physiological pH was increased (at colon), CUR released from NCs and bare ZnO makes this synergistic effect. Also, the comparable anticancer activity of NCs and curcumin revealed that curcumin retained its anticancer activity even after being loaded into NCs.

Conclusion

Novel $\text{TiO}_2@\text{ZnO}-\text{GO}$ NC was synthesized as a pH-sensitive carrier for colon-targeted drug delivery. The SEM and TEM studies revealed that the prepared NCs had a diameter about 190 nm and hexagonal in shape. The $\text{TiO}_2@\text{ZnO}-\text{GO}$ showed pH-dependent drug release behavior due to the presence of large amount of carboxylic acid group in the GO network. The release of CUR from the $\text{TiO}_2@\text{ZnO}-\text{GO}$ was dependent on pH of the medium. It was found that the rate and amount of CUR released from the $\text{TiO}_2@\text{ZnO}-\text{GO}$ are higher in pH 7.4. MTT results showed that the curcumin-loaded NCs showed significant toxicity due to which cell viability reduced to below 50% at 140 $\mu\text{g}/\text{mL}$ concentration, thereby confirming its anticancer effects. These results demonstrate that $\text{TiO}_2@\text{ZnO}-\text{GO}$ could be a drug delivery system to deliver the drug more specifically to the colon.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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