N-doped carbon nanodots@UiO-66-NH₂ as novel nanoparticles for releasing of the bioactive drug, rosmarinic acid and fluorescence imaging

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Abstract

Background and the purpose of the study The purpose of the present research was to synthesize affordable nanoparticles for simultaneous drug release and cell fluorescence imaging to decrease the costs associated with conventional treatments.

Methods In the present study, N-doped carbon nanodots@UiO-66-NH₂ nanoparticles were simply synthesized in few steps and were used as a novel carrier for rosmarinic acid (RA). Nano particles were characterized by FT-IR spectroscopy, X-ray powder diffraction (XRD), Dynamic Light Scattering (DLS) and field emission scanning electron microscopy (FE-SEM). UV/vis spectroscopy was used to study the release profile of RA drug from this novel carrier. Methylthiazolyl tetrazolium (MTT) assay was to evaluate the effect of irradiation with a (UV) lamp. Confocal laser scanning microscopy was used for fluorescence imaging of cancer cells.

Results Results of the MTT assay revealed that UiO-66-NH₂@N-CNDs nanoparticles as a drug carrier for RA, have an excellent therapeutic effect due to their high quantum yield under irradiation of UV light. On the contrary, the observed therapeutic effect was decreased under ambient light.

Conclusions UiO-66-NH₂@N-CNDs nanoparticles can be considered as promising vehicles for drug delivery due to their cost effectiveness in cancer treatment, based on the results of MTT assay. It should be emphasized that this nanocarrier can be as potential platforms for coincident drug delivery system and cell fluorescence imaging due to possessing green fluorescence and microporosity features.

Keywords UiO-66-NH₂ · Rosmarinic acid · N-doped carbon nanodot · Drug delivery · Therapeutic effect

Introduction

Rosmarinic acid (R-*o*-caffeoyl-3, 4-dihydroxyphenyllactic acid; RA) is a remarkable chemical compound belonging to the class of hydroxycinnamic acid esters. It can be found in many species of herbs and spices, mainly in the families of

Boraginaceae and *Lamiaceae* [1–3]. RA has been shown to have many properties such as an antioxidant, anti-HIV, anti-mutagenic, anti-cyclooxygenase, anti-proliferation, and anti-tumorigenic properties [4–9]. So, its delivery is important for scientific community. For example, RA encapsulated into modified chitosan microparticles and its controlled release was studied for topical delivery [10]. Recently, NMOFs are attractive interest carrier for drug delivery system because of their brilliant intrinsic properties such as the tunable pore size, tailorable chemistry, a large surface area and a large pore volume [11].

Metal–organic frameworks (MOFs), which are also known as a fascinating class of porous coordination networks, consist of variable metal connecting ions and organic bridging ligands. Due to their functional tenability, these materials have been investigated comprehensively for potential application in separation [12], catalysis [13], gas storage [14, 15], nonlinear optics [16], light harvesting [17], chemical sensing [18] and biomedicine [19–26].

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One of the most favorable applications of MOFs in human health care is drug delivery, which is relying on limitations associated with conventional therapeutics, such as poor physiological stability, nonspecific distribution and low cell membrane permeability throughout the body leading to side effects, and poor pharmacokinetics [27, 28]. Therefore, the number of diverse strategies such as organic polymers [29] and inorganic porous materials [30] has been developed to enhance the efficacy and reduce the toxicity of conventional therapeutics. The facile synthesis and biodegradable structure of NMOFs, high loading and manageable release of drugs in NMOFs allow them to perform as confident nanoplatforms intended for drug delivery compared to other nanocarriers [31].

Recently, loading of the hydrophobic antitumoral doxorubicin (DOX) in MIL-100 (Fe) nanoparticles was reported to be up to 9 wt%. The release profiles indicated that a sustained release rather than a burst release was achieved during 14 days in PBS [22, 32]. He et al. introduced C-dots@ZIF-8 as a nanocarrier for simultaneous fluorescence imaging and controlled delivery of Fluorouracil (5-Fu) [33].

In recent research, carbon nano dots (CNDs) have emerged as promising materials for biomedical applications due to their photostability, biocompatibility, and easy and low cost synthesis techniques. A very common way to improve the quantum yield of CDs is nitrogen doping [34–37], because access to its resources is easy and its action mechanism is based on a nitrogen-containing chromophore that can passivate the active positions on the surface of the C-dots [38]. So, using of N-doped carbon nanodots (N-CNDs) appear to be very effective in photo-thermal therapy. It can reduce the amount of drug used because it can selectively attack the malignant cells through obtained quantum yield by UV light. Therefore, it can reduce the expense of treating illnesses.

The purpose of the present study was inclusion of the N-doped carbon nanodots into nano-sized MOFs to prepare a dual-action platform for drug delivery and simultaneous fluorescence imaging. Hereby, we report for the first time, a novel combination of RA, N-doped carbon nanodots and UiO-66-NH₂ through a simple preparation route. Trend of drug release was investigated within 2 days by UV/vis spectroscopy. MTT assay, on the other hand, showed that when the RA is loaded onto the nanocarrier, the effective amount required is significantly reduced. This nanocarrier can absorb UV irradiation by N-doped carbon nanodots to increase the quantum yield, which in coordination with RA release can lead to the death of diseased cells. Therefore, these results can promise a bright future in cost effective treatment of diseases, especially in the case of expensive cancer drugs.

Experimental

Materials and methods

All reagents and solvents used for the present study were purchased from Merck without any further purification. FT-IR spectra were recorded in KBr pellets on an Alpha Bruker FT-IR spectrophotometer. X-ray powder diffraction (XRD) measurements were performed on an X'Pert PRO MPD from PANalytical Company with Cu K α radiation. Field emission scanning electron microscope imaging (FE-SEM) was performed on a MIRA3TESCAN-XMU by gold coating. UV-Vis absorption analysis were obtained using a Beijing Rayleigh UV-1800 UV-Vis Spectrophotometer. Confocal laser scanning microscopy (CLSM) was performed on a LEICA TCS SPE confocal microscope. Dynamic light scattering experiments (DLS) and Zeta potential measurements were made using a Microtrac analyzer. Photoluminescence (PL) spectrum was recorded on a CARY ECLIPSE fluorospectrophotometer.

Experimental procedures

Synthesis of UiO-66-NH₂ UiO-66-NH₂ NPs were synthesized according to a previously reported procedure along with minor modifications [39]. Briefly, ZrCl₄ (160 mg, 0.68 mmol) and 2-NH₂-bdc (124 mg, 0.68 mmol) were dissolved in DMF (54 mL). This mixture was placed inside the autoclave, and afterward heated at 120 °C for 24 h. The NMOFs were separated by centrifugation at 1500 rpm for 5 min. Then, the precipitate was washed in turn with DMF (2 $\times$ 8 mL) and EtOH (2 $\times$ 8 mL) by centrifugation at 1500 rpm for 3 min. The product was then exchanged by EtOH (8 mL) three times for 3 days to remove the remaining DMF solvent. Then the obtained nanoparticles were activated by heating at 80 °C overnight.

Synthesis of N-CNDs These nanoparticles were obtained by a solvothermal-synthesis method as reported previously [40]. The mixture of citric acid aqueous solution (1 g/mL) and nitric acid solution (7 M, 1 mL) was heated for 3 h at 250 °C. Then, methanol (40 mL) was added and the mixture was oven dried. Subsequently, toluene (15 mL) and ethanolamine (90 mL) were used to dissolve the viscous liquid (300 mg). The mixture was heated in an oven until a solid was remained. Later, water (10 mL) was added to the solid. Finally, dialysis against water (the solution was placed in the dialysis bag, then it was stirred in a water container for 6 h) followed by freeze drying to remove the water, resulted in the desired N-CNDs.

Synthesis of N-CNDs@UiO-66-NH₂ The activated UiO-66-NH₂ (100 mg) was mixed with a diluted solution of N-doped carbon nanodots (0.0001 wt%) at room temperature for 24 h. Then, the solid was washed with water (3 × 5 mL) by centrifugation at 1500 rpm for 3 min, and oven dried at 60 °C overnight.

Drug loading The incorporation of RA into N-CNDs@UiO-66-NH₂ was performed by mixing an ethanolic solution of RA (25 mg/ml) with N-CNDs@UiO-66-NH₂ (50 mg) at room temperature for 24 h. Afterward, nanoparticles were washed with EtOH (3 × 5 mL) by centrifugation at 1500 rpm for 3 min and were dried at 60 °C overnight.

Calibration plots of standard RA Five concentrations of RA (3, 23, 33, 43 and 53 µgml⁻¹) in PBS with pH = 7.4 and pH = 5.5 were prepared as standards. Then, calibration plots of standard drug in PBS (pH = 7.4, 5.5) obtained by UV/Vis spectrophotometer at 326 nm and 202 nm (Fig. S1), respectively.

Drug release The drug-loaded samples (UiO-66-NH₂@N-CNDs@RA, 20 mg) were dispersed in simulated body fluids (PBS) with pH = 7.4 (5 mL) and pH = 5.5 (5 mL) by stirring at 37 °C. The dissolution medium was used at predetermined time intervals (2, 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 h) to determine the drug concentration. The RA concentration was determined by measuring the absorbance of the solutions at 326 nm and 202 nm and using the appropriate calibration curve.

In vitro investigations Cell viability was evaluated by the MTT (Methylthiazolyldiphenyl-tetrazolium bromide) assay. The yellow MTT solution is diminished to purple formazan in living cells. In this research, A549 Cells (lung cancer) were used as model cell line. Cells (2 × 10⁴) were seeded in 96 well plate in complete media contained RPMI medium (Bioidea, Glutamax high glucose), antibiotics (Bioidea, 100X penicillin/ streptomycin solution, 1%), heat-inactivated fetal bovine serum (Gibco, 15%) and (5% CO₂, at 37 °C, 95% humidity) for 24 h. Afterward, medium was removed and fresh media including different concentrations of UiO-66-NH₂, UiO-66-NH₂@N-CNDs, UiO-66-NH₂@N-CNDs@RA, RA, ZrCl₄ and 2-NH₂-bdc (25, 50, 75, 100 and 150 µg/mL) were added to the wells. Meanwhile, A549 cells with equal cell numbers in complete medium were used as control. After 24 h of incubation, old medium was exchanged with fresh MTT included medium (0.5 mg/mL final concentration). The plate was incubated for 4 h and then medium was dismissed. The resulted formazan crystals in each well

were dissolved in dimethylsulfoxide (DMSO, 50 µL). The plate was incubated for 15 min at room temperature by mild shaking. The absorbance was read by an Indirect enzyme-linked immunosorbent assays (ELISAs) plate reader at 490 nm by a reference wavelength of 630 nm. Cell viability was estimated by the following (eq. 1).

$$\text{Cell Viability}(\%) = \frac{(\text{absorbance of sample})}{(\text{absorbance of control})} \times 100 \quad (1)$$

All of the mentioned steps in this section were also repeated under irradiation of UV light for 20 min after addition of nanoparticles to the wells.

Fluorescence imaging of cancer cells: The A549 cells (2 × 10⁴) were seeded onto glass cover slips in a 24 well plate in complete media contained RPMI medium (Bioidea, Glutamax high glucose), antibiotics (Bioidea, 100X penicillin/ streptomycin solution, 1%), heat-inactivated fetal bovine serum (Gibco, 15%) and (5% CO₂, at 37 °C, 95% humidity) for 24 h to allow the cells to attach. Afterwards, the remaining particles and dead cells removed by detaching the medium, then the adherent cells were washed twice with PBS. The fresh medium containing UiO-66-NH₂@N-CNDs (30 µg/mL) was replaced. After incubation for 24 h, for removing the remaining particles and dead cells, the cell monolayer on the coverslip was washed with PBS and then the cells sealed with a microscope glass slide and were observed by using CLSM.

Results and discussion

In summary, our experimental procedure involves the following steps: the hydrothermal method used to the synthesis of UiO-66-NH₂ nanoparticle and the solvothermal method employed for the synthesis of N-CNDs compound. Then, hybrid nanocomposite (UiO-66-NH₂@N-CNDs) produced by the incorporation of the N-CNDs into UiO-66-NH₂. Afterwards, RA loaded into nanocomposite. So, this drug delivery vehicle (UiO-66-NH₂@N-CNDs@RA) can employ for simultaneous drug release and cell fluorescence imaging.

The N-CNDs emit a green light when they are exposed to UV irradiation (inset of Fig. 1), which is constant with the emission peak at 473 nm in the PL spectrum (Fig. 1). Furthermore, in the FT-IR spectrum of the N-CNDs (Fig. 2 (a)) the following characteristic vibrations were observed: 3418 (O-H stretching of the absorbed water molecules) 1630 (O-H bending), 1647 (C=O), 1562 (C=C), 1281 (C-N), 2931 (aliphatic C-H stretching), and 3050 (aromatic C-H stretching) cm⁻¹.

Fig. 1 PL spectra of N-CNDs. (inset: photographs of the N-CNDs suspended in deionized water in ambient light (right) and under UV irradiation (left))

These data are consistent with its physical properties such as solubility in water, which arises from the presence of carboxylic and N-containing functional groups. In addition, PXRD pattern of the N-CNDs (Fig. 2 (b)) revealed a broad diffraction peak centered at $2\theta = 20^\circ$, which is related to the turbostratic carbon phase [40].

In the FT-IR spectrum of the UiO-66-NH₂ (Fig. S2 (a)), corresponding vibrations of N-H, C=O, C=C, C-O, and C-N functionalities were appeared at 3466, 1569, 1431, 1384, and 1254 cm⁻¹, respectively. These vibration bands were also reoccurred in similar positions in the FT-IR spectra of UiO-66-NH₂@N-CNDs and UiO-66-NH₂@N-CNDs@RA (Fig. S2 (b), (c)). The N-H stretching band of the UiO-66-NH₂ however, was overlapped with the O-H stretching band of the N-CNDs in the FT-IR spectra of UiO-66-NH₂@N-CNDs and UiO-66-NH₂@N-CNDs@RA. Appearance of the aliphatic C-H stretching bands at 2926 and 2933 cm⁻¹ in the FT-IR spectra of UiO-66-NH₂@N-CNDs@RA, and UiO-66-NH₂@N-CNDs is another proof of the correctness of the expected structures.

In order to further prove the successful synthesis of nanoparticles, powder X-ray diffraction (PXRD) measurements were taken. PXRD pattern of UiO-66-NH₂

Fig. 3 Simulated (a), and recorded (b) PXRD patterns for UiO-66-NH₂

was fully consistent with the simulated pattern generated from atomic coordinates (Fig. 3) and was well in agreement with the previously reported powder X-ray diffraction pattern [40]. Furthermore, the PXRD patterns for UiO-66-NH₂@N-CNDs and UiO-66-NH₂@N-CNDs@RA (Fig. 4) showed the anticipated reflections from both UiO-66-NH₂ and N-CNDs, which indicates that the crystalline structure of UiO-66-NH₂@N-CNDs is preserved during drug loading.

Examination of the photographs (Fig. 5) taken under UV irradiation and ambient light shows that UiO-66-NH₂ is yellow in both cases. It is also clear that when the N-CNDs are included, both UiO-66-

Fig. 2 FT-IR spectrum (a) and PXRD pattern (b) for N-CNDs

Fig. 4 PXRD patterns for UiO-66-NH₂@N-CNDs (a) and UiO-66-NH₂@N-CNDs@RA (b)

NH₂@N-CNDs and UiO-66-NH₂@N-CNDs@RA samples have a green fluorescence. This phenomenon also proves the presence of N-CNDs in the intermediate and final NMOF samples. FE-SEM imaging on the other hand (Fig. 6) showed that all of the prepared nanoparticles adopt an octahedral morphology with an average diameter of 35 ± 10 nm.

DLS size distribution measurements for UiO-66-NH₂, UiO-66-NH₂@N-CNDs and UiO-66-NH₂@N-CNDs@RA (Fig. S3), were also in agreement with the FE-SEM observations and showed that the particle size distribution was in the range of 25–45 nm. The Zeta

potential of UiO-66-NH₂ and N-CNDs@UiO-66-NH₂ were found to be -3.6 and 0 mV, respectively. It can be concluded that N-CNDs increased the zeta potential of the nano-carrier.

The RA loading efficiency (LE%) for UiO-66-NH₂@N-CNDs (MOF@N-CNDs) was calculated by Eq. (2):

$$LE\% = \frac{(\text{Weight of MOF@N-CNDs@RA}) - (\text{Weight of MOF@N-CNDs})}{(\text{Weight of MOF@N-CNDs})} \times 100 \quad (2)$$

As a result, the amount of loaded RA in UiO-66-NH₂@N-CNDs was found to be 7% according to the above eq. RA investigated as the typical drug based on its brilliant therapeutic effects such as anti-tumorigenic activity. The release of RA was studied systematically to determine the trend of its release from UiO-66-NH₂@N-CNDs@RA at 37 °C and different pH values (pH = 7.4 and 5.5) of phosphate-buffer saline (PBS) (Fig. 7). RA loaded nano-carrier exhibited a sustained release profile in neutral and acidic PBS solutions. It is clearly visible that the RA release was moderate and similar results were obtained in different pH values during the same period of time (50 h). Generally, a sustained release is much more desirable than a burst release, and RA@N-CNDs@UiO-66-NH₂ performs pretty well in this context.

It is noteworthy that the PXRD patterns of UiO-66-NH₂@N-CNDs@RA (Fig. S4) after releasing RA in PBS showed that the crystalline structure of NMOFs was preserved. Besides, the stability tests (Fig. S5) showed that UiO-66-NH₂@N-CNDs nanoparticles well tolerated the experimental conditions (stirring for 50 h in human serum and PBS at 37 °C).

In the next phase of the study, MTT assay was performed in the presence and absence of UV irradiation to examine the apoptotic effects of the drug loaded nanoparticles. Results of the MTT assay are presented in Fig. 8 and show the apoptotic effects of the nanoparticles after 24 h of incubation. An increase in the concentration from 25 to 150 µg/mL, resulted in an increase of the apoptotic effect of the nanoparticles.

Fig. 5 Photographs taken under UV light (top) and ambient light (bottom) for UiO-66-NH₂ (a, b), UiO-66-NH₂@N-CNDs (c, d), UiO-66-NH₂@N-CNDs@RA (e, f)

Fig. 6 FE-SEM images of UiO-66-NH₂ (a), UiO-66-NH₂@N-CNDs (b), UiO-66-NH₂@N-CNDs@RA (c)

On the other hand, according to the results of MTT assay presented in Fig. 9, apoptotic effects were enhanced upon increasing the concentration from 25 to

150 $\mu\text{g/mL}$, as the cells were exposed to UV light for 20 min, and the results calculated after 24 h of incubation. In addition, the apoptotic effect of UiO-66-

Fig. 7 Trend of RA release from UiO-66-NH₂@N-CNDs, in PBS with pH = 7.4 (green) and pH = 5.5 (red) at 37 °C

Fig. 8 In vitro viability of A549 cells in the presence of UiO-66-NH₂, UiO-66-NH₂@N-CNDs, UiO-66-NH₂@N-CNDs@RA, RA, ZrCl₄, 2-NH₂-bdc

Fig. 9 In vitro viability of A549 cells under uv irradiation in the presence of UiO-66-NH₂, UiO-66-NH₂@N-CNDs, UiO-66-NH₂@N-CNDs@RA, RA, ZrCl₄, 2-NH₂-bdc

NH₂@N-CNDs@RA was approximately equivalent to that of RA (Fig. 9). It can be suggested that the produced quantum yields from N-CNDs under UV light increases the apoptotic effect on the A549 cancer cell line. Thus, this drug delivery system involves excellent apoptotic effects under UV light while reducing drug intake.

The application of UiO-66-NH₂@N-CNDs in cell imaging was explored via incubation of A549 cells as an example in cell culture medium for 24 h by confocal laser scanning microscopy (CLSM). The green fluorescence of UiO-66-NH₂@N-CNDs was observed in the cytoplasm of A549 cells (Fig. 10 (b)). In contrast to Fig. 10 (a), it showed that its entrance into the A549 cells and it is as an efficient and novel vehicle for cell fluorescence imaging and drug delivery, simultaneously.

Recently, Ca-MOF, Fe-MIL-53, Fe-MIL-101, and Fe-MIL-100 were synthesized and employed for flurbiprofen (FBP) delivery [41]. UiO-66-NH₂@N-CNDs in comparison, have the advantage of

fluorescence emission. Another unique feature of the N-CNDs as an additive to the carrier is its therapeutic effects as well. Hence, UiO-66-NH₂@N-CNDs nanoparticles can be utilized as a therapeutic agent. This carrier can be considered as potential platforms for coincident drug delivery system and cell fluorescence imaging due to their cost effectiveness in cancer treatment and possessing green fluorescence. So, the smart design of UiO-66-NH₂@N-CNDs paves the way for reaching it to target cells, and to make it a hopeful vehicle in future.

Conclusions

In summary, we have devised a novel carrier based on a combination of N-CNDs and UiO-66-NH₂ for the well-known anticancer drug RA. UiO-66-NH₂@N-CNDs found application as a stable carrier for RA and as a fluorescence imaging agent. In this research RA loaded in NMOFs for first time and it was used as anticancer drug. The release of RA investigated at 37 °C and two pH (7.4, 5.5). Drug release demonstrated slow and similar speed release without burst release in examined different pH. Over time of released RA was 50 h. The results of MTT assay revealed that UiO-66-NH₂@N-CNDs as a carrier has an excellent potential therapeutic effect under UV irradiation since UiO-66-NH₂@N-CNDs can produce significant quantum yield in presence of the UV light. But, potential therapeutic effect of this carrier was decreased in ambient light. Therefore, this novel carrier can be introduced as a promising and cost effective vehicle for drug delivery in cancer treatment, while it has another unique feature, which is the ability to use in cell

Fig. 10 Fluorescence imaging: CLSM images of A549 cells incubated with RA loaded UiO-66-NH₂@N-CNDs for 24 h. **a** The differential interference contrast (DIC) image. **b** The green fluorescence showing internalized RA loaded UiO-66-NH₂@N-CNDs

fluorescence imaging due to its green fluorescence emission.

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Compliance with ethical standards

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

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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