Construction of the targeted and pH-sensitive paclitaxel drug delivery system RGD/PTX@ZIF-90 and anti-tumor activity research

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Abstract
Tumors area common cause of morbidity and mortality. High treatment efficiency and low drug toxicity are key for effective tumor treatment. Here, the pH-sensitive material ZIF-90 was synthesized by the liquid-phase diffusion method for loading paclitaxel (PTX), and the targeting peptide (RGD) was prepared by the solid-phase synthesis method to modify it (RGD/PTX@ZIF-90). The skeleton of RGD/PTX@ZIF-90 collapses in the acidic tumor microenvironment, thereby releasing PTX and mediating the controlled release of the drug. ZIF-90 below 300 nm was obtained by adjusting the ratio of metal ions and organic ligands in the characterization experiment. In addition, in vitro drug release experiments showed that the drug release rate was greater at pH = 5.5 than at pH = 7.4. The lethal rate of RGD/PTX@ZIF-90 to human breast cancer cells (MCF-7) was 44.5%, which was higher than the lethal rate of PTX alone (37.3%) in the cytotoxicity experiment and apoptosis experiment. Uptake experiments revealed that RGD/PTX@ZIF-90 mainly existed in the cytoplasm of MCF-7, which suggests that the drug had successfully entered the cell to achieve the therapeutic effect. The loading of the nano-medicine carrier ZIF-90 and the modification of the targeting peptide RGD significantly improve the therapeutic effect of PTX and indicate that this system could be used to treat breast cancer.

1. Introduction
As cancer is a major disease endangering human health [1], its effective control and treatment are important public health concerns [2]. Traditional treatment methods for cancer include surgery, radiotherapy, and chemotherapy, which are still first-line clinical treatment methods [3]. Although traditional anti-tumor drugs can prolong the life of some patients, they also face many challenges, such as short half-lives, low bioavailability, high drug resistance, non-specific distribution, and difficulty crossing physiological barriers [4].

Paclitaxel (PTX) is a common anti-tumor drug that is widely used in the treatment of various forms of advanced and refractory cancers [3]. It can be extracted from the bark of Taxus brevifolia or obtained using semi-synthetic methods [6]. PTX can bind to tubulin in cells, promote tubulin aggregation and inhibit its dissociation so that cells cannot divide normally, thereby leading to cell cycle arrest and apoptosis [7]. It is a broad-spectrum anti-tumor drug for the treatment of breast cancer, ovarian cancer and non-small cell lung cancer with a remarkable curative effect [8]. However, the solubility of PTX is poor [9]. PTX injection employs a mixture of polyoxymethylene castor oil and absolute ethanol as a solvent; however, the use of this non-aqueous solvent can cause severe allergic reactions [10]. Furthermore, PTX lacks targeting specificity and can easily cause systemic adverse reactions, such as neutropenia and neurological diseases [11]. Its low bioavailability and toxic side effects greatly limit its applications in medicine [12]. To circumvent these shortcomings, researchers have developed new drug delivery systems.
In recent years, the rapid development of nanotechnology, especially the emergence of new nanomaterials, has contributed new ideas and methods for the treatment of many major diseases [13]. Nano-drug carriers have shown great potential in tumor treatment and have received widespread attention [14]. An increasing number of nano-drug carriers have been used in various tumor treatments [15]. For example, Lei Zhang et al. used nanomosporous silica loaded doxorubicin for the treatment of liver cancer [16]; Yang Liu et al. used nanoprotein loaded PTX for the treatment of lung cancer [17]. Compared with traditional drug delivery systems, nano-drug delivery systems can effectively improve the pharmacokinetics and pharmacodynamic properties of drugs because of their special properties, such as size, shape, and materials, thereby enhancing their efficacy [18].

Traditional nano-drug carriers include liposomes, polymer nanoparticles, protein nanoparticles and metal nanoparticles [19]. However, these carriers have several disadvantages, such as poor stability, low drug loading and poor biocompatibility. Metal organic frameworks (MOFs) are a type of porous material composed of metal ions (or metal clusters) and organic ligands [20]. Because of their special periodic structure, high specific surface area, high adsorption and high porosity [21], MOFs have been shown to have wide application prospects in adsorption, electrochemistry and catalysis [22]. Compared with traditional nano-medicine carriers, MOFs have multiple advantages [23], such as higher drug loading; good biodegradability, avoiding the toxic and side effects caused by the accumulation of drug carriers; and the use of modification methods that can permit them to carry a variety of functional groups [24]. The zeolite imidazole ester framework (ZIF) structure is similar to inorganic zeolite [25] and has the advantages of zeolite and MOFs, such as ultra-high surface area, permanent micropores, high crystallinity and good stability [26]. As the ZIF-90 material synthesized in this article has good biocompatibility, it does not affect the normal internal environment as a drug carrier after entering the human body [27]. In addition, ZIF-90 material is also a pH-responsive MOF material [28]. When it enters the tumor area, its skeleton collapses because of the acidic tumor microenvironment [29]. This not only increases the drug release rate, but the collapsed skeleton can also be used by the organism, thereby greatly reducing harm to the organism [30]. As RGD is a peptide showing good targeting specificity, ZIF-90 modified by RGD can target tumor cells, which not only reduces the toxicity and side effects on normal cells during the administration process but also improves the therapeutic effect of the drug.

Here, we synthesized the targeting peptide RGD by solid-phase synthesis, confirmed its successful synthesis by mass spectrometry, and used high-performance liquid chromatography to separate and purify it. ZIF-90 was synthesized by the liquid-phase diffusion method, and the success of its synthesis was confirmed by scanning electron microscopy, Fourier infrared spectroscopy and x-ray diffractometry. RGD was then modified to the surface of ZIF-90 by Schiff base reaction, PTX was loaded into the pores of ZIF-90 by physical adsorption and RGD/PTX@ZIF-90 composite material was obtained. The successful synthesis of the material was verified by Fourier infrared spectroscopy. Finally, the anti-tumor activity of RGD/PTX@ZIF-90 composite material was demonstrated through a cytotoxicity experiment, apoptosis experiment and cell uptake experiment.

2. Experimental

2.1. Materials
We purchased tert-butanol, imidazole-2-carboxaldehyde (ICA), PTX and methanol from Aladdin Biochemical Technology Co., Ltd. Zinc nitrate hexahydrate (Zn(NO$_3$)$_2$·6H$_2$O) and polyvinylpyrrolidone (PVP) were purchased from Sinopharm Chemical Reagent Co., Ltd Wang resin, aspartic acid (D), glycine (G), arginine (R), 1-hydroxybenzotriazole (HOBT), 4-dimethylaminopyridine (DMAP), N,N-dimethyl methyl formamide (DMF), dichloromethane (DCM), N,N-diisopropylcarbodiimide (DIC), N,N-diisopropylethylamine (DIEA), acetic anhydride and piperidine were purchased from Gill Biochemical Co., Ltd.

2.2. Preparation of RGD/PTX@ZIF-90
The liquid-phase diffusion method was used to synthesize ZIF-90 material in a water (water/alcohol/PVP) environment [31]. The specific synthesis steps were as follows. First, 0.24 g of ICA was placed into a beaker, followed by the addition of 10 ml of distilled water for ultrasonic dissolution. Next, 0.05 g of PVP was added into the beaker, placed in an ultrasonic environment and stirred for 10 min. At the same time, 0.0282 g of zinc nitrate and 10 ml of tert-butanol were added to a beaker and stirred until they were dissolved. Finally, the solutions in the two beakers were added to the round bottom flask and stirred vigorously for 10 min in an ultrasonic environment. After the reaction, the solution was poured into a centrifuge tube and centrifuged at 10 000 r min$^{-1}$; the supernatant was removed, washed with excess methanol 3 times and then freeze-dried to obtain nano-scale ZIF-90 material.

The RGD peptide was synthesized by solid-phase synthesis. First, 1 g of Wang resin was added to the peptide reactor and soaked in DCM for 10 min. After 10 min, the solvent was removed. Next, 274 mg of D, 207 mg of HOBT and 92 mg of DMAP were placed into the reactor; with DMF used as the solvent, 1 ml of DIC was added,
and the reaction was left to run for 4 h. After the reaction, the solvent was removed and washed 6 times with methanol and DMF. Using DCM as the solvent, 2 ml of acetic anhydride and 2 ml of DIEA were added and left to react for 40 min, followed by washing using the method described above. Next, piperidine was added to the reactor for deprotection for 20 min, and the solvent was washed and removed after the reaction was complete. Next, 446 mg of G and 207 mg of HOBT were added to the reactor. Using DMF as the solvent, 1 ml of DIC was added dropwise, and the contents of the reactor were left to react for 1 h. After the reaction, the solvent was washed and removed, and a small amount of resin was saved for detection using the Kaiser method. The reaction was assumed to be successful when the solution became colorless. Piperidine was added to the reactor for deprotection for 20 min, and the next amino acid R was added in the same way described above. Finally, the crude RGD peptide was obtained, which was then separated, purified and finally freeze-dried to obtain pure RGD. A certain amount was then weighed and added to a 50 ml round-bottom flask along with 25 ml of anhydrous methanol, followed by stirring until all solids were dissolved and a clear solution was obtained. The nano ZIF-90 material obtained in the previous step was then added into the solution, and the solution was stirred at room temperature for 48 h. After the reaction, the precipitate was collected by centrifugation (10,000 rpm, 10 min), washed with methanol several times and finally dried to obtain RGD/ZIF-90.

The RGD/ZIF-90 composite material obtained above was used to load the anti-tumor drug PTX. The specific steps were as follows. First, 10 mg of PTX was dissolved in 20 ml of methanol solution with stirring. Next, 5 mg of RGD/ZIF-90 was added with stirring and left to react for 24 h. After the reaction was complete, the supernatant was removed by centrifugation, washed 3 times and dried to obtain RGD/PTX@ZIF-90.

2.3. Characterization
A S-4800 scanning electron microscope (Hitachi, Japan) was used for scanning electron microscope analysis (SEM). A Japanese Shimadzu IR Prestige-21 Fourier transform infrared spectrometer was used for infrared analysis (FT-IR). A Kantar NOVA 2000e specific surface area and pore size analyzer (United States) was used for N2-sorption isotherm (N2-sorption) analysis. A Japan Shimadzu DSC-60A automatic differential thermogravimetric measurement device was used for thermogravimetric analysis (TGA). A German Bruker D8 series x-ray (powder) diffractometer was used for x-ray powder diffraction (XRD). A Shimadzu LCMS-8030 liquid chromatography mass spectrometer was used for mass spectrometry analysis. A Shimadzu ProminenceLC20A high-performance liquid chromatograph was used for high-performance liquid chromatography (HPLC).

2.4. Drug release test
Two mg of dried RGD/PTX@ZIF-90 powder was dissolved in 2 ml of pH = 5.5 and 2 ml of pH = 7.4 PBS buffer to detect the drug release effect in different pH buffers. The above solution was added to the dialysis bag (MWCO = 1000 Da) and placed into small beakers; 20 ml of buffer solutions at each pH was then added to the beakers. Next, the beaker was placed in a shaker at 37 °C, protected from light and shaken at 100 r min⁻¹. One ml of buffer solution was then removed from the beaker, and its absorbance was measured at a wavelength of 227 nm with a UV spectrophotometer. One ml of buffer solution was then added to the beakers to ensure that the buffer solution in the beakers remained unchanged. The concentration was calculated based on the standard curve, in addition to the amount of drug released over a period of time.

2.5. Cell culture
Human breast cancer cells (MCF-7) used in the in vitro experiments were purchased from Procell Life Science and Technology Co., Ltd (Wuhan, China) and were kept at 37 °C in a 5% CO₂ humidifier incubator. DMEM high glucose medium supplemented with 10% PBS (0.01 M, pH = 7.4), 1% double antibody and 10% serum was used as the medium. When the cell confluence reached more than 90%, the cells were passaged. First, the medium was preheated in a 37 °C water bath. In the ultra-clean table, the original medium was discarded, 2–5 ml of PBS was added to wash the cells, and 1 ml of trypsin was added to digest the cells. The cells were observed to become round under the microscope and when the cells begin to break off the bottle wall, 5 ml of medium was added to terminate the digestion. The medium was then centrifuged at 1000 rpm for 5 min, and the supernatant was removed. Next, 15–20 ml of culture medium was added to resuspend the cells, and the cells were then transferred to a culture flask. The cell suspension was mixed to ensure a uniform distribution of cells. The culture bottle was placed in a 37 °C, 5% CO₂ sterile incubator for culture.

2.6. Cytotoxicity and apoptosis experiments in vitro
MCF-7 cells were used for cytotoxicity experiments. First, the MCF-7 cells were cultured to the logarithmic growth phase and washed 3 times with PBS. The cells were then trypsinized and diluted to 1 × 10⁵ cells ml⁻¹. The above cell suspension was added to a 96-well plate and placed in a constant temperature incubator. The
RGD/PTX@ZIF-90 solution was then diluted to different concentrations, and 100 μl was added to a 96-well plate at concentrations of 25, 50, 100, 200 and 400 μg ml⁻¹ PTX; PBS was used as the blank group. After culturing in the incubator for 24 h, the original culture medium was aspirated, and 100 μl of 0.009% CCK8 cell culture medium was added to each well. The medium was then placed in the incubator for 2 h, the OD value of each well was measured with a microplate reader and the cell survival rate was calculated. The cytotoxicity of the same gradient concentration of ZIF-90 and PTX was tested using the method described above.

The MCF-7 cells in the logarithmic growth phase were seeded in a 6-well plate and cultured for 24 h. After the cultivation, the old medium was removed, and the medium containing PTX and RGD/PTX@ZIF-90 was added to the 6-well plate. The concentration of PTX in each well was 25, 50, 100, 200 and 400 μg ml⁻¹, and untreated MCF-7 cells served as the blank group. After culturing for 24 h, the cells were trypsinized, collected, washed with PBS solution and resuspended in buffer. The cells were then labeled with 5 μl of Annexin V-FITC and 5 μl of propidium iodide. After 10 min, an appropriate amount of binding buffer was added to dilute the cell solution, and flow cytometry (Beckman Coulter, USA) was used to detect cell apoptosis.

2.7. Cell uptake test
MCF-7 cells were seeded on a laser confocal culture dish at a density of 1 × 10⁵ cells per milliliter, and 1 ml of the cell suspension was added to each well and cultured for 4 days. The laser confocal dish from the incubator was then removed, the culture medium was discarded and the cells were gently rinsed 3 times with PBS solution preheated at 37 °C. Next, 0.5 ml of RGD/PTX@ZIF-90 preparation labeled with FITC was added. After incubating for 24 h, the drug solution was discarded, 4 °C ice-cold PBS was added to stop uptake, and the cells were washed 3 times. After the PBS solution was discarded, the cells were fixed with 4% paraformaldehyde for 20 min and washed 5 times with cold PBS. One ml of 10 μg ml⁻¹ nuclear staining solution DAPI was added and incubated for 15 min, followed by washing 3 times with cold PBS and the addition of 200 μl of PBS. A laser confocal microscope (Leica, Germany) was used to make observations and take images.

![Figure 1. SEM images of ZIF-90 (a); DLS image of the particle size of ZIF-90 (b).](image1)
![Figure 2. Mass spectrometry analysis of RGD.](image2)
3. Results and discussion

3.1. Physical and chemical characterization

After ZIF-90 was synthesized, the ZIF-90 sample was characterized by SEM to determine its morphology. ZIF-90 is a regular hexahedral structure, and the combined material can be preliminarily determined to be ZIF-90 (Figure 1(a)). ZIF-90 of different sizes could be obtained by adjusting the ratio of organic ligand (ICA) and metal ion (Zn^{2+}). When the molar ratio of organic ligand (ICA) to metal ion (Zn^{2+}) was 50:1, the particle size of the sample measured by the particle size analyzer was approximately 200 nm. Follow-up experiments were performed under this condition.

Because the purity of the purchased RGD is not high, and our laboratory provides suitable conditions for solid-phase peptide synthesis, we conducted RGD synthesis ourselves. To confirm whether the synthesized peptide was RGD, mass spectrometry was performed. Figure 2 shows the results of the mass spectrometry analysis of RGD, which confirm that the peptide obtained by solid-phase synthesis was RGD. We then used FT-IR and XRD to determine whether the synthesized material was ZIF-90. The peak position of the C=O bond of the synthesized material did not change, indicating that it did not participate in the reaction (Figure 3(a)). The characteristic peak of the aldehyde group at 2700 cm^{-1} to 2900 cm^{-1} was not destroyed, and the peak at 1200–1400 cm^{-1} was sharp, indicating that the N of imidazole-2-carboxaldehyde underwent a coordination reaction with Zn^{2+}. In addition, the peak position of the combined material was consistent with that of the standard analog peak of ZIF-90 (Figure 3(b)). Thus, the synthesized material was ZIF-90. In addition, we performed nitrogen adsorption characterization on the synthesized ZIF-90, which showed that it is a mesoporous material that can be used to load drugs.

Figure 3. FT-IR spectra of ICA, ZIF-90, PTX@ZIF-90 and RGD/PTX@ZIF-90 (a), XRD analysis patterns of ZIF-90 and PTX@ZIF-90 at 0°–50°, 6° min^{-1} (b), TGA analysis of ZIF-90 and PTX@ZIF-90 with a nitrogen atmosphere, aeration rate of 20 ml min^{-1}, heating range of 40°C–800°C and heating rate of 10°C min^{-1}, (c). Nitrogen adsorption curve of ZIF-90 (d).
Figure 4. The drug release curve of RGD/PTX@ZIF-90 in PBS buffer with pH = 5.5 and pH = 7.4 at 37°C (a). The cytotoxicity of 25, 50, 100, 200 and 400 μg ml⁻¹ ZIF-90 to MCF-7. The toxicity of PTX and RGD/PTX@ZIF-90 to MCF-7 cells when the PTX concentration is 25, 50, 100, 200 and 400 μg ml⁻¹. PBS was used as the blank group (b).

Figure 5. FCM assay of RGD/PTX@ZIF-90 at different concentrations (25, 100 and 400 μg ml⁻¹) compared with the PTX control group.
FT-IR and XRD were used to characterize ZIF-90 when it was loaded with PTX. The aldehyde peak in the infrared spectrum of ZIF-90 remained, and the peak position of its XRD spectrum did not change (figures 3(a) and (b)). The loading of PTX did not destroy the crystal structure of ZIF-90, and the drug was loaded in the pores. FT-IR was used to determine whether RGD was modified on the material. The C=O peak was red-shifted, and the characteristic peak of the aldehyde group was absent, indicating that RGD was modified on the surface in figure 3(a). The thermal weight loss curve of ZIF-90 and PTX@ZIF-90 materials in a nitrogen atmosphere, with an aeration rate of 20 ml min$^{-1}$, heating range of 40 °C–800 °C and heating rate of 10 °C min$^{-1}$ is shown in figure 3(c). When the temperature reaches 150 °C, the solvent molecules remaining in the ZIF-90 material are decomposed. When the temperature reaches 220 °C, the PTX@ZIF-90 material begins to decompose, and the ZIF-90 material skeleton collapses at approximately 300 °C, as the melting point of PTX is approximately 220 °C. This phenomenon also indirectly indicates that the PTX is loaded on the ZIF-90 material.

**Figure 6.** Cell survival rate of the PTX group and RGD/PTX@ZIF-90 group at drug concentrations of 25, 100 and 400 μg ml$^{-1}$ through apoptosis.

**Figure 7.** Confocal microscopy images of RGD/PTX@ZIF-90.
3.2. Drug release and cytotoxicity experiments in vivo

PTX anti-tumor drugs experience different internal environments (normal blood environment and tumor cell tissue environment) during release in the body. PBS buffer solutions with $\text{pH} = 7.4$ and $\text{pH} = 5.5$ were used to simulate the normal blood environment and tumor tissue environment, respectively, to monitor the release effect of PTX drugs in different environments. The release rate of PTX was significantly greater at $\text{pH} = 5.5$ than at $\text{pH} = 7.4$ (figure 4(a)). When the release time reached 100 min, the drug release amount in the $\text{pH} = 5.5$ buffer solution reached 93%, whereas the drug release amount in the $\text{pH} = 7.4$ buffer solution reached 64%. The ZIF-90 nano-drug carrier shows pH responsiveness and can permit slow drug release.

Cytotoxicity experiments were carried out with ZIF-90, PTX and RGD/PTX@ZIF-90. The results are shown in figure 4(b). When the ZIF-90 concentration was 25, 50, 100, 200 and 400 $\mu$g ml$^{-1}$, the cell survival rate in the ZIF-90 group did not change significantly, indicating that the materials were essentially non-toxic to cells. When the PTX concentration was 25, 50, 100, 200 and 400 $\mu$g ml$^{-1}$, the drug-alone group and the RGD/PTX@ZIF-90 group were toxic to MCF-7 cells. As the concentration increased, the toxicity of the drug-alone group and the RGD/PTX@ZIF-90 group to MCF-7 cells increased. In addition, the toxicity of the RGD/PTX@ZIF-90 group to MCF-7 cells was slightly higher than that of the drug-alone group. Encapsulation of PTX can effectively improve its lethality to tumor cells.

3.3. Apoptosis and cell uptake

PTX and RGD/PTX@ZIF-90 were used for apoptosis experiments. The PTX concentration applied was 25, 100 and 400 $\mu$g ml$^{-1}$. As the PTX concentration increased, the apoptosis rate of the drug-alone group and the RGD/PTX@ZIF-90 group increased (figure 5), which is consistent with the cytotoxicity test results described above. When the concentration was 400 $\mu$g ml$^{-1}$, the apoptosis rates of the two groups were 37.3% and 44.5%. As the drug concentration changed, the apoptosis rate showed a clear upward trend, and the apoptosis rate was slightly higher in the RGD/PTX@ZIF-90 group than in the drug-alone group (figure 6). Although the difference in the rate of apoptosis between the two groups was not particularly obvious, it was also different. This can prove that the loading of ZIF-90 and the modification of RGD can improve the therapeutic effect of PTX on tumor cells.

To understand the uptake of RGD/PTX@ZIF-90 by MCF-7 cells, an uptake experiment was carried out, followed by laser confocal microscopy. The results are shown in figure 7. The blue fluorescence is the nucleus of MCF-7 cells, and the green fluorescence is RGD/PTX@ZIF-90. After 24 h of drug culture, RGD/PTX@ZIF-90 mainly existed in the cytoplasm of MCF-7 cells (figure 7), which indicates that the drug had successfully entered the cells. Therefore, RGD/PTX@ZIF-90 can accurately target MCF-7 tumor cells and achieve tumor treatment effects.

4. Conclusion

In this paper, the targeting peptides RGD and ZIF-90 were synthesized by the solid-phase synthesis method and liquid-phase diffusion method, and the two were combined by Schiff base reaction. PTX was then loaded into the pores of ZIF-90 by physical adsorption, and a pH-sensitive and targeted PTX drug delivery system RGD/PTX@ZIF-90 was obtained. Mass spectrometry, FT-IR, XRD and TGA characterization demonstrated the successful synthesis of each step of the material. In addition, cytotoxicity, apoptosis and cell uptake experiments were carried out on RGD/PTX@ZIF-90, and the results showed that encapsulation of PTX can effectively improve its therapeutic effect on tumors. PTX mainly inhibits the depolymerization of microtubules, prevents the mitosis of tumor cells and thus has a strong cytotoxic effect on tumor cells. The ability of PTX to kill tumor cells critically depends on the ability of RGD/PTX@ZIF-90 to deliver PTX to its targets in cells. As a recognized targeting polypeptide, RGD can specifically recognize tumor cells and use RGD modification to gather drugs around tumor cells. In addition, the encapsulation of PTX by ZIF-90 can prevent it from being released under normal cell environment, but when it reaches the tumor microenvironment, due to the acid-sensitive properties of ZIF-90, its skeleton collapses, thereby releasing the drug. The results of this experiment show that the RGD/PTX@ZIF-90 nano-drug carrier is mainly distributed in the cytoplasm, which is consistent with the site of PTX and conducive to its anti-tumor effect, thereby improving the therapeutic effect of PTX on tumors. Moreover, the targeting specificity and pH sensitivity of RGD/PTX@ZIF-90 make it less harmful to normal cells and also permit better drug release in tumor cells.

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