Magnetic Drug-loaded Microcapsules Intergrating Photothermal and Targeted Therapy

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Abstract. Compared with single chemotherapy, collaborative treatment can significantly improve the cure rate of malignant tumors, reduce the use of chemotherapy drugs and avoid the damage to the organs. The combination of photothermal therapy and chemotherapy has also become the most common treatment in recent years. In this article, we synthesized a kind of mesoporous silica with a large specific surface area and pore volume to encapsulate the Fe\textsubscript{3}O\textsubscript{4} nanoparticles. Owing to the unique magnetic and photo thermal properties of Fe\textsubscript{3}O\textsubscript{4} nanoparticles, the combination of PTT-chemo targeted therapy has been achieved and greatly reduces the side effects of the drugs on the human body. This novel particle will create a broader application in the future.

1. Introduction

Cancer has been a serious problem on account of its increasing death rate [1-3]. There is an urgent need to explore new way for early cancer detection and therapy [4]. Up to now, chemotherapy is still one of the main treatments for malignant tumors, but it is not the best choice. Photothermal therapy (PTT) is considered to be the most promising treatment because of its high efficiency, non-invasive [5], remote control characteristics and negligible drug resistance. It represented that get high temperature in low power to ablating tumor cells, at the same time, it could prevent damage of normal tissue cells [6-8]. The combination of PTT and chemotherapy have several merits, such as utilizing near-infrared light which reduce side effects and improve therapeutic efficacy. [9-10].

Fe\textsubscript{3}O\textsubscript{4} nanoparticles are widely used in drug delivery systems due to their excellent superparamagnetic and bio-degraded properties. In this particle, mesoporous silica was used to encapsulate magnetic nanoparticles and the model drug (Doxorubicin, DOX for short) as a drug carrier Fe\textsubscript{3}O\textsubscript{4}@SiO\textsubscript{2}-DOX. The external magnetic field is used to lead the drug to the tumor location to achieve the effect of targeted therapy. Furthermore, combined the photo thermal characteristics of Fe\textsubscript{3}O\textsubscript{4} nanoparticles, the drug carrier Fe\textsubscript{3}O\textsubscript{4}@SiO\textsubscript{2}-DOX would achieve the properties of chemotherapy and targeted therapy, which could greatly increase the accumulation in the tumor site. Therefore, the drug carrier of Fe\textsubscript{3}O\textsubscript{4}@SiO\textsubscript{2} has a wide range of research prospects.
2. Synthesis experiment of Fe$_3$O$_4$@SiO$_2$ nanoparticles

2.1. Synthesis of Fe$_3$O$_4$ nanoparticles

Solution 1: 3.6g anhydrous sodium acetate was dissolved in 15 ml of ethylene glycol solution, and stirred slowly at 40°C. Solution 2: 1.35g FeCl$_3$·6H$_2$O was dissolved in 15 ml of ethylene glycol solution. After ultrasonic dissolution, 0.75 g polyethylene glycol (molecular weight of 2000) was added. The solution 2 was added to solution 1 and stirred for 0.5h. Then, the mixture was transferred the solution to PTFE reactor and heat at 200°C for 8h; then the solution was naturally cooled down to room temperature. The product was collected by magnetic separation, being washed several times with deionized water and ethanol. Finally, the Fe$_3$O$_4$ nanoparticles were collected after been dried at 80°C for 8h.

2.2. Synthesis of Fe$_3$O$_4$@SiO$_2$ nanoparticles

Solution 3: The obtained Fe$_3$O$_4$ nanoparticles (0.1g) were dissolved into 25ml deionized water, dispersed by ultrasonic; Solution 4: 0.25g CTAB was added into 100ml ethanol solution, and then dissolved by ultrasonic. The solution 4 was added to solution 3 and heated at 80°C for 10min. Then, 1.5 ml TEA (triethanolamine) was added to the mixture and stirred for 10min. After that, 5 ml TEOS was added dropwise at the rate of 1 ml/min and stirred for 6h. The product was collected by centrifugation and then washed with ethanol several times. Finally, the centrifugal sediment was dried at 80°C for 8h, which is the Fe$_3$O$_4$@SiO$_2$ nanoparticles.

3. Results and Discussion

3.1. Morphological Characterization of Fe$_3$O$_4$@SiO$_2$

![Figure 1. Morphological Characterization of Fe$_3$O$_4$@SiO$_2$. (a), (b) The SEM images; (c) The TEM images](image)

As illustrated in the scanning electron microscopy (SEM, Fig.1 a, b) of Fe$_3$O$_4$@SiO$_2$. The nanoparticles were spherical and had good dispersion. In addition, the average diameter of Fe$_3$O$_4$@SiO$_2$ was 300-400 nm. Fig.1(c) was the morphologies of Fe$_3$O$_4$@SiO$_2$ that were investigated by transmission electronic microscopy (TEM) images, Fe$_3$O$_4$@SiO$_2$ with Fe$_3$O$_4$ core were obtained. The core-shell structure was obvious and Fe$_3$O$_4$ nanoparticles occupied about 60% of the microspheres. The thickness of the mesoporous silica shell was 80nm approximately.
3.2. BET characterization of Fe$_3$O$_4$@SiO$_2$

Table 1. Analysis of Fe$_3$O$_4$@SiO$_2$ pore size and specific surface area

| Parameter                                      | Value     |
|------------------------------------------------|-----------|
| BET surface area (m$^2$/g)                    | 51.9059   |
| average pore diameter (nm)                    | 8.43567   |
| Single point adsorption total pore volume of pores(cm$^3$/g)(<14.63657nm) | 0.10946   |

![Figure 2. N$_2$ absorption–desorption isotherms](image)

To explored the Fe$_3$O$_4$@SiO$_2$ pore size and specific surface area , as shown in Fig. 2, the two curves in the figure were the desorption and adsorption isotherms. Fe$_3$O$_4$@SiO$_2$ had a rough surface area of 51.9m$^2$/g. At the same time, the existence of hysteresis loop illustrated that the material had mesoporous and average pore diameter was 8nm approximately. So, Fe$_3$O$_4$@SiO$_2$ could be used for loading anticancer drugs for treatment.

3.3. Drug release measurement and Cytotoxicity analysis

Fe$_3$O$_4$@SiO$_2$ was dissolved in PBS buffer at different pH (M1: pH=5.0, M2: pH=7.2, M3: pH=8.0), respectively. Then stirred vigorously for 24h in the dark for drug loading. To verify the sustained release effect of Fe$_3$O$_4$@SiO$_2$, the DOX release of Fe$_3$O$_4$@SiO$_2$ (DOX) was studied in PBS buffer solutions. At specific time points, the content of DOX in the solution was quantified by a UV–vis spectrophotometer at a wavelength of 480 nm.
According to the DOX standard equation \[ m = \frac{1}{2} \cdot \text{DOX} \cdot \text{DOX} \cdot V \] to calculate the drug loading rate was calculated about 51.2%. The high drug loading rate indicated that Fe₃O₄@SiO₂ had pore structure to achieve better drug loading effect. The DOX release behaviour of Fe₃O₄@SiO₂ (DOX) in PBS buffer at different pH values was shown in Fig.3. Approximately 60% of DOX were released 10h and Fe₃O₄@SiO₂ (DOX) could achieve sustained release in acidic medium.

To verify sample safety, cell experiment was done for 1 day and 3 days to co-cultivation of Fe₃O₄@SiO₂ with the cells. Generally, cytotoxicity values between 80% and 120% could be considered safety. From the Fig 4, it could be seen that the cytotoxicity of the material concentration of 100ug and 50ug was safe, but the material concentration was 25ug, which was significantly different for three days, so the sample might be infected by bacteria.

### 3.4. The photo thermal properties of Fe₃O₄@SiO₂

To investigate the photo thermal conversion effect, Fe₃O₄@SiO₂ nanoparticles were irradiated with an 808 nm laser (1 W/cm²) in vitro. As shown in Fig. 5, the temperature could reach 49 ℃ within 20min in vitro. The internal temperature rised rapidly in vivo, and the temperature had increased 57.5℃ at 13 min, the highest temperature could reach to 75℃.
On the other hand, Fe$_3$O$_4$@SiO$_2$ nanoparticles were injected into mice to investigate the photo thermal conversion effect in vivo and then the mice were exposed to an 808nm laser. Fig.6 was a schematic diagram of temperature at 10 min and 12 min in vivo, respectively. It can be clearly seen that the temperature had increased significantly in the mice body under the irradiation with an 808 nm laser (1 W/cm$^2$). In summary, Fe$_3$O$_4$@SiO$_2$ had excellent photo thermal conversion.

![Figure 6. Temperature diagram in vivo at 10 min and 12 min](image)

4. Conclusion
In this study, Fe$_3$O$_4$ nanoparticles were synthesized and successfully wrapped with mesoporous silica to form Fe$_3$O$_4$@SiO$_2$ with core-shell structure. The larger specific surface area and pore volume of these novel particles provided a location for DOX load, while drug is continuously released at a uniform rate, and sustained release behaviour of the model drug DOX was achieved. On the other hand, the particles had high biological safety. Finally, combining the photo thermal characteristics of Fe$_3$O$_4$, the particles had achieved the combination of PTT-chemo-targeted therapy, which could give the anticancer drugs with tumor-targeting and greatly reduce the side effects of the drugs on the human body.

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