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·论著·

靶向治疗用 Fe_3O_4 及其白蛋白包被磁性纳米粒子的制备

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摘要:**目的** 制备用于肿瘤靶向治疗的 Fe_3O_4 及其白蛋白包被的磁性纳米粒子。**方法** 采用部分还原法制备 Fe_3O_4 纳米粒子,通过微乳化方法制备了白蛋白包被的 Fe_3O_4 磁性纳米颗粒。**结果** Fe_3O_4 粒径为 10 nm 左右,X - 射线粉末衍射分析显示 Fe_3O_4 纳米磁性微粒是典型的尖晶石构型;白蛋白包被的磁性纳米粒子直径在 200 nm 左右。**结论** Fe_3O_4 及其白蛋白包被的磁性纳米粒子适于用于肿瘤靶向治疗的进一步研究。

关键词: 靶向治疗;磁性纳米粒子;白蛋白包被;制备
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Preparation Fe_3O_4 Nanoparticles and HSA - Coated Magnetite Nanoparticals for Tumor Target Therapy

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Abstract: **Objective**: To prepare Fe_3O_4 magnetite nanoparticles and HSA - coated magnetite particles for the purpose of regional target therapy. **Methods**: To adopt partial reduction method to prepare the Fe_3O_4 nanoparticles: 100 ml 0.01 mol/L Na_2SO_3 was added dropwise into 100 ml 0.06 mol/L $FeCl_3$ solution under nitrogen gas flow. 10 %(V %) ammonia was added dropwise with rapid stirring until pH of the reaction solution reach 8. Heated at 70 ℃ with water bath for 15 min. Preparation of HAS - coated magnetite particles: To use microemulsion approach, with oleic acid as oil phase, mixture of HSA and magnetite solution as water phase and sp - 85 as emulsion agent. **Results**: Fe_3O_4 magnetite particles with about 10 nm in diameter and X - ray power diffraction show that the nanoparticles is γ - Fe_2O_3. HAS - coated Fe_3O_4 magnetite nanoparticles is characterized by TEM with diameter no more than 200 nm. **Conclusions**: Fe_3O_4 magnetite nanoparticles and HSA - coated magnetite particles is suitable for researching of regional target therapy.

Key words: Preparation; Target Therapy; Magnetic Nanoparticle; HAS - coated;
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1 Introduction

Cancer is one of the most threatening disease for human and now day chemotherapy is still the most common method for cancer treatment. Although chemotherapeutic drugs are very effective, their potency leads to many undesirable and even toxic side effects. Replacing the systemic delivery of chemotherapeutic drugs with regional cancer treatment approaches is one way of overcoming side effects. Furthermore, the therapeutic efficiency can be improved since higher drug concentrations at the tumor sites are possible when using regional therapy. Besides the chemotherapy, internal radiotherapy is also commonly used and it needs more precise targetry because a therapeutic radiopharmaceutical given systematically would cause more serious side effect than chemotherapeutic method. Although radioisotope - labeled monoclonal antibodies (Mabs) are expected site - specific, relatively small concentration of therapeutic agent is delivered.

In the search for a more generally applicable drugs targeted - delivery method for cancer therapy, magnetically controlled target chemotherapy have been proposed[1]. In this approach, a physical method of capturing magnetically responsive particles present in a patient's ability to bind, transport and later release a chemotherapeutic drug. Tumor targeting of magnetic particles have been tested, to date, in only a few clinical trials[2]. At the same time the possibility of using magnetic particles as carrier of radioisotope is also studied.

In this paper we prepared HSA - coated magnetic nanoparticle as radioisotope carrier. The advantages of the magnetic nanoparticles are that: It is magnetically responsive and can target the tumor site under external magnetic field; The particles are biologically compatible and have no harm to human body during metabolites; Under the external magnetic field radionuclide therapy can be enhanced[3]; More over nanoparticals have their own's targeting property themselves. For example, intravenously injected colloidal particles can be targeted to the lung, liver, spleen, bone marrow, or provided with long circulation properties through judicious choice of size and surface characteristics[4,5]. Similar results have been obtained for lymphatic delivery[6,7].

The aim of this paper is to prepare Fe_3O_4 magnetite nanoparticles and HSA - coated magnetic nanoparticle, which is the precondition for further studying its targeting behavior in vivo.

2 Experimental

2.1 Materials

Water is purified using super - purity water machine (U. S. A PALL). All chemicals are AR grade from Shanghai Regent Company (China) except for ^{188}R4, which is obtained from Kexing pharmaceutical company.

2.2 Preparation of Fe_3O_4 nanoparticles

We adopt partial reduction method to prepare the nanoparticles, with ferric sulfate $6Fe^{3+} + SO_3^{2-} + 18NH_3 \cdot H_2O \rightarrow 2Fe_3O_4 \downarrow + SO_4^{2-} + 18NH_4^+ + 9H_2O$ as iron source, ammonia as alkaline source and sodium sulfite as reducing agent. The experimental process is that: 100 ml 0.01 mol/L Na_2SO_3 was added dropwise in to 100 ml 0.06 mol/L $FeCl_3$ solution under nitrogen gas flow. 10 % (V %) ammonia was added dropwise with rapid stirring until pH of the reaction solution reach 8. Heated at 70 ℃ with water bath for 15 min. Then the precipitated magnetite is immobilized with a permanent magnet and the aqueous supernatant decanted and discarded. Washed the particles with ethanol and water respectively for several times and dried under vacuum.

2.3 Preparation of HSA - coated magnetic nanoparticles

We use microemulsion approach, with oleic acid as oil phase, mixture of HSA and magnetite solution as water phase and sp - 85 as emulsion agent, for the preparation. In detail, weigh 250 mg HSA and 80 mg magnetic nanoparticles, then mix them into 1ml water; 0.4 ml sp - 85 was mixed with 40 ml oleic acid. The mixtures of above two solution was ultrasonated for 15 min, then adding dropwise into 130 ℃ oleic acid rapidly, stirring at 1350 rpm for 20 min. The

particles were extracted with ether, washing with acetone for three times and drying under vacuum.

3 Results and Discussion

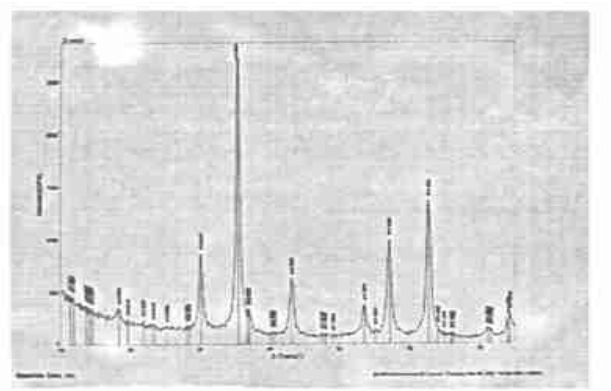

Fig 1 Fe_3O_4 nanoparticles X-ray power diffraction map

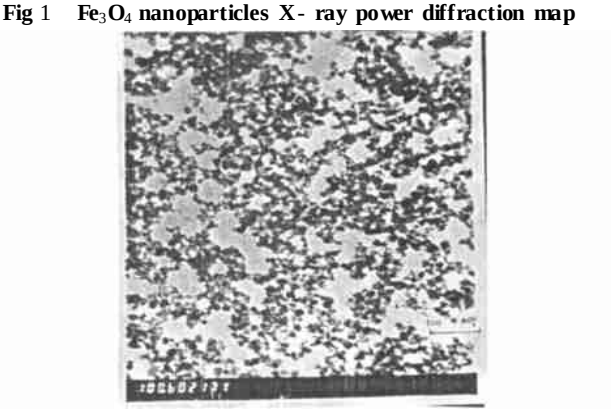

Fig 2 TEM micrograph of Fe_3O_4 nanoparticles

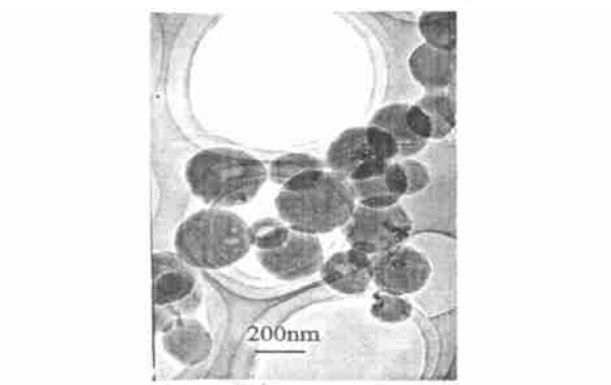

Fig 3 EWM micrograph of HSA-coated magnetite

There are many literatures reporting various methods for preparation of magnetite nanoparticles. By partial reduction method, from TEM result, we prepare the magnetite particles with about 10 nm in diameter and X-ray power diffraction show that the nanoparticles is γ-Fe_2O_3. The advantage of partial reduction method is that there needs no nitrogen gas protection. But we found that the morphology of the particles is irregular and many show needle shape if there is no nitrogen bubbled. The slurry of the particles is stable for several months with no dispersant added.

HAS-coated magnetite is characterized by TEM with diameter no more than 200 nm. But the experimental conditions must be controlled strictly.

4 Conclusion

The microemulsion method can be used for preparation of HSA-coated magnetic particles with diameter no more than 200 nm.

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