



Research Article

Nanovesicles of cholesterol-free enable malignant tumor-specific magnetic resonance imaging

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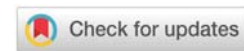
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Abstract

There are many patents for magnetic nanoparticles as tumor magnetic resonance imaging enhancers, but the gadolinium complexes commonly used in the clinic are difficult to target the diseased tissues, while nanoliposomes are ideal carriers for anti-tumor drugs. Owing to that the commonly used liposome particle size is too large, poor stability, the Cholesterol was used to increase the stability of nanoparticles or reduce their diameter. This foreign cholesterol may also have toxic side effects on patients. And the existing liquid film process cannot be large-scale production. The aim of this paper is to overcome the shortcomings of the prior art, then put forward a new method for preparing cholesterol-free tumor magnetic resonance imaging enhancer based on nano liposome encapsulation was proposed. We can obtain tumor magnetic resonance imaging enhancers with low toxicity and a good ability to cross biofilm. Finally, the facile fabrication was proved according to applications.

Introduction

For many tissue lesions, magnetic resonance imaging technology relies on the developer to improve the image clarity, especially for the diagnosis of tumor, without the developer, the clear image of the lesions cannot be obtained. The developed tumor MRI (Magnetic resonance imaging) imaging agents can be divided into four categories: Metal salt, metal chelates biomacromolecule preparation and microparticle preparation [1-5]. Among, magnetic nanoparticles have been used as magnetic resonance imaging agents, For example, Li Xiaojuan's team of Chongqing Medical University proposed the preparation method of magnetic resonance developer of

chitosan coated Fe₃O₄ magnetic nanoparticles [6], in addition, the preparation method of gadolinium loaded chitosan nanoparticles as magnetic resonance imaging contrast agent proposed by Zhang Li of Shandong University [7]. However, there are some problems in these disclosed preparation methods of developer, for example, biocompatibility is not high, it is easily engulfed by macrophages, it does not have ideal internal circulation characteristics in blood, it is not easy to accumulate in specific tissues, at the same time, gadolinium complexes commonly used in clinic are usually toxic, and it is difficult to enter the lesion cells [8-10]. The drug encapsulated by nano liposome has good biocompatibility, low toxicity, the treatment effect is good, after surface targeted modification,

it has the characteristics of active targeting tumor [11-16]. Therefore, nanoliposome is an ideal carrier for antitumor drugs, it has been used in clinical treatment, nano liposomes can be used to encapsulate magnetic complex to prepare improved developer [17-24]. However, in the research of Li Jing team [25] of Hunan Provincial People's Hospital and Wei Xin team [26] of Xinhua Hospital Affiliated to Medical College of Shanghai Jiaotong University on the application of liposome encapsulated tumor developer, the size of liposome is too large, poor stability, cholesterol is used to increase the stability of nanoparticles or reduce the diameter of nanoparticles, this foreign cholesterol may also bring side effects to patients, and the existing liquid membrane method cannot be mass-produced [27-35]. So the market needs to be cheap, low toxicity, and the ability to cross the biofilm is good, aiming at the defects of the existing technology, in this paper, we propose a method to prepare cholesterol free tumor MRI imaging agent based on nano liposome.

Materials and methods

Technical proposal

The preparation method of cholesterol free nano magnetic resonance developer was proposed, first, the solution A containing soluble protein is mixed with the solution B containing phospholipid to obtain the lipoprotein suspension D, then, only protein suspension D and solution C containing soluble metal salts and / or soluble metal chelates were filtered by hydrophobic nanofiltration, react at 50 °C for A period of time, then, the organic solvent in the reaction product of the reaction is evaporated by A rotary evaporator, the colloid F was obtained, then the colloid was dispersed in pure water, nano emulsion G was obtained, cooling and drying of nano emulsion, finally, A fluffy powder is obtained, it is a cholesterol free tumor magnetic resonance imaging agent F encapsulated by nano liposomes.

Preparation steps

The specific preparation process and raw material combination are shown in Figure 1, which can be divided into eight steps.

The first step, the soluble protein was mixed with pure water at the mass ratio of 2.7-7.2:100, vortex 1-15 min, the scroll speed is 600-6000 rpm, the soluble protein is dissolved in pure water, solution A is obtained by dissolution, the soluble protein can be one or more mixtures of water-soluble animal protein, water-soluble plant protein, water-soluble fungal protein, water-soluble bacterial protein and water-soluble recombinant protein expressed by bacteria, the water-soluble animal protein can be any one or more mixtures of serum albumin, globulin, egg protein, casein, water-soluble protein of silkworm pupa, sericin and egg white protein, the water-soluble plant protein can be any one or more mixtures of water-soluble soybean protein, black soybean protein, rice protein, corn protein, wheat protein, ginseng water-soluble protein, mulberry leaf protein and protein lifting solution containing plant protein, the water-soluble bacterial protein and water-soluble fungal protein can be any one or more mixtures of water-soluble Rhizobium protein, the water-soluble recombinant protein expressed by the bacteria can be expressed by recombinant human serum albumin and / or soluble protein expressed by Escherichia coli.

In the second step, the solid-liquid ratio of lecithin and organic solvent was 1.5-4:100, and the vortex speed was 600-6000 rpm for 1-15 min; Or the mixture of phospholipid and organic solvent was treated with ultrasonic for 1-15 min, the ultrasonic frequency was 5-150 Khz, the ultrasonic power was 5-1800 w, the phospholipid was dissolved in organic solvent, and the solution B was obtained. The phospholipid can be phospholipid glyceride or sphingomyelin, and the organic solvent can be any one or more mixtures of cyclohexane, chloroform, benzene, ether and petroleum ether.

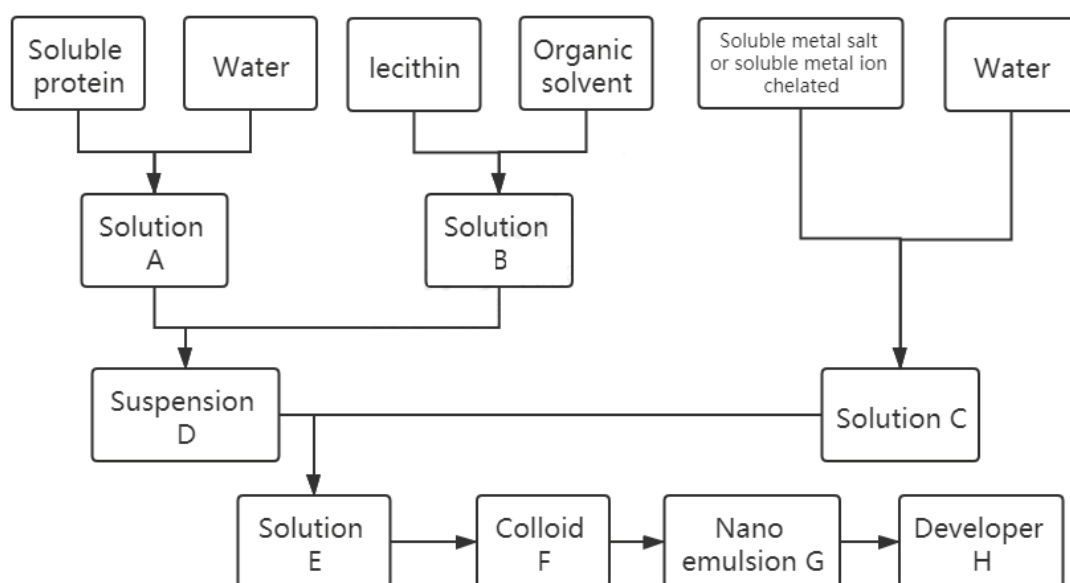


Figure 1: Preparation process of nano liposome magnetic resonance imaging agent.

In the third step, the soluble metal salt or soluble metal ion chelate was added into the pure water, the vortex was vibrated for 1-15min, and the vortex speed was 600-6000 rpm; Or the soluble metal salt and / or soluble metal ion chelate were added into pure water and treated with ultrasonic for 1-15min. The ultrasonic frequency was 5-15 KHz and the ultrasonic power was 5-1800 w. After dissolution, solution C was obtained, and the concentration of metal ions in solution C was 1-100mg / ml. The soluble metal salt can be any soluble salt of Ti^{3+} , Ni^{2+} , Fe^{3+} , Fe^{2+} , V^{4+} , CO^{3+} , Cr^{3+} , Mn^{2+} , Cu^{2+} , PR^{3+} , Gd^{3+} , Eu^{3+} , Dy^{3+} or a mixture of soluble salts of more than one metal ion, and the metal ion chelate can be any soluble salt of Ti^{3+} , Ni^{2+} , Fe^{3+} , Fe^{2+} , V^{4+} , C_0^{3+} , Cr^{3+} , Mn^{2+} , Cu^{2+} , Pr^{3+} , Gd^{3+} , Eu^{3+} , Dy^{3+} . A soluble chelate of any one ion or a mixture of soluble chelates of more than one metal ion, and the mixture of the soluble metal salt and soluble metal ion chelate can be mixed with the soluble salt of any one or more of the metal ions Ti^{3+} , Ni^{2+} , Fe^{3+} , Fe^{2+} , V^{4+} , Co^{3+} , Cr^{3+} , Mn^{2+} , Cu^{2+} , Pr^{3+} , Gd^{3+} , Eu^{3+} , Dy^{3+} and one or more of them A mixture of soluble chelates of more than one metalion.

In the fourth step, solution a was added to solution B, the mass ratio of soluble protein in solution a to lecithin in solution B was 25-100:14-41, the vortex vibration was 3-15min, the vortex speed was 600-6000 rpm, and then the ultrasonic treatment was carried out for 10-60min, the ultrasonic frequency was 5-150 KHz, and the ultrasonic power was 5-1800 w to obtain lipoprotein suspension D.

In the fifth step, solution C was added to the lipoprotein suspension, the mass ratio of metal ions in solution C and lipoprotein in lipoprotein suspension D was 1.9-6.8:38-154, the vortex vibration was 5-15 min, the vortex speed was 600-6000 rpm, and then the suspension E was obtained by ultrasonic treatment for 10-30 min, the ultrasonic frequency was 5-150 KHz, and the ultrasonic power was 5-1800 w.

In the sixth step, the suspension e was stirred at 40-60 °C for 1-10h, the stirring speed was 250-500rpm, and then the organic solvent of suspension E was evaporated by rotary evaporator to obtain colloidal substance F.

The seventh step is to add colloid F into the pure water according to the mass ratio of 1:5-10 and disperse the colloid in pure water by ultrasonic vibration, and obtain nano emulsion G.

In the eighth step, the nano emulsion is freeze-dried at -50 degrees Celsius to get the powder and the final product is obtained. The liposome encapsulated cholesterol free tumor magnetic resonance developer H.

Experiment and result analysis

In order to verify the effect of the preparation method of nano liposome encapsulated cholesterol tumor MRI developer proposed in this paper, three different raw material combinations were selected for three implementation cases. As shown in Table 1, the preparation method in this paper was used for preparation, and the final product enhancer was analyzed for laboratory data.

Particle size stability analysis

The particle size stability of magnetic resonance developer is an important index to measure the contrast agent. The particle size of nano magnetic resonance developer directly affects the effect of magnetic resonance enhancement. The finished product of implementation case 1 is iron containing nano liposome tumor magnetic resonance imaging agent. First, it is refrigerated at 4°C in dark, and then dissolved in water after 30 days and 180 days. The particle size is determined. The results are shown in Figure 2, Table 2.

It can be seen from Figure2 and Table2 that the particle size of the iron containing nano tumor magnetic resonance developer in case 1 of this paper is basically unchanged after 30 days of storage, especially after 180 days of cold storage. The measurement results show that the particle size is still maintained at 80-90nm, indicating that the magnetic resonance developer prepared by this method has good stability. The particle size is not easily changed, and can be stored for a long time.

Table 1: Raw material combination table of nanoliposomes.

	Experimental case 1	Experimental case 2	Experimental case 3
Solution A raw material	Serum protein ,pure water	Soy protein, pure water	Recombinant human serum albumin, pure water
Solution B raw material	Lecithin, cyclohexane	Cephalin, chloroform	Sphingomyelin, ether
Solution C raw material	Fe_3O_4 magnetic fluid, pure water	Gadolinium trichloride hexahydrate, pure water	C1.potassium ferrocyanide, pure water C2.ferric chloride, manganese dichloride, pure water
Final product	Magnetic resonance imaging agent of iron nanoliposome for tumor	Gadolinium nanoliposome as a tumor MR imaging agent	Magnetic resonance imaging agent of nanoliposome containing iron and manganese

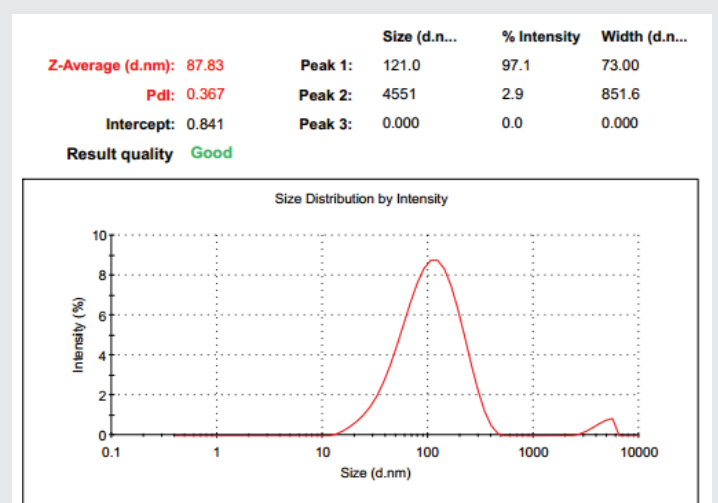


Figure 2: Particle size distribution map of magnetic resonance imaging agent containing iron nanoparticles for tumor (180 days later).

Analysis of image enhancement effect

The finished product of case 2 is gadolinium nanoliposome tumor magnetic resonance imaging agent. The nanoliposome is adjusted to different concentrations for in vitro tumor magnetic resonance imaging. The imaging situation, distribution, metabolic process and effect of the liposome are observed in Figure 3.

As shown in Figure 3, from top to bottom in Figure 3 is the in vitro tumor magnetic resonance imaging obtained by using water and adjusting the gadolinium containing nano liposome tumor magnetic resonance imaging agent in case 2 of this paper to 20 mg/ml, 10 mg/ml, 5 mg/ml, 2.5 mg/ml and 1.25 mg/ml respectively. In Figure 3, the two circles on the left are the T1 weighted imaging results measured in parallel, and the two circles on the right are the T2 weighted imaging results measured in parallel. It can be seen from Figure 3 that the nano liposome tumor MRI developer prepared by the text has a good T1 and T2 weighted image enhancement effect on tumor MRI.

Analysis of efficacy persistence

The finished product of case 3 is the iron and manganese nanoliposome tumor MRI developer. It can be seen from Figures 4,5 that the enhancement agent has the strongest image enhancement effect on the tumor within 2-10 h, with the maximum gray value, the brightness of gray-scale image is the highest, and the pseudo color image is the reddest, maintaining a high tracer effect. After 12 hours, the gray value of tumor decreased significantly, and after 24 hours, no tracer was observed in vivo. The results show that the nano magnetic resonance imaging agent prepared by this method is

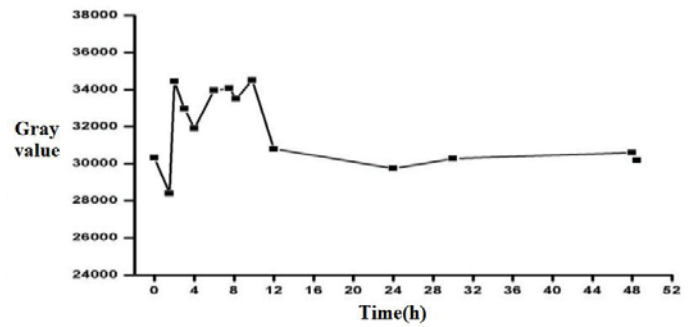


Figure 5: Gray value of enhancement effect of tumor nanometer magnetic resonance imaging enhancer *in vivo*.

suitable for clinical application in vivo, and the retention time is appropriate. It can be quickly discharged from the body after 24 hours, and there is no residue in the human body.

Conclusions

The preparation method proposed in this paper changes the existing preparation process of nano liposomes by reverse phase evaporation method. A cholesterol free tumor magnetic resonance imaging agent encapsulated by nano liposomes was prepared by using phospholipid and water-soluble protein as main raw materials, paramagnetic metal ions as chelating agent and stabilizer of liposomes, and cholesterol free biomembrane simulation assembly method.

The self-made method has the advantages of simple process, good tumor MRI enhancement effect, avoiding the introduction of cholesterol which is easy to cause arteriosclerosis, coronary heart disease and other injuries to human body, overcoming the problems of poor stability and difficult large-scale industrial production of traditional nano liposome preparation method, suitable for clinical application in vivo, and can be quickly discharged out of the body without residue. The prepared MR imaging agent has the advantages of low cost, low toxicity and good ability to cross biofilm, which has a good application prospect.

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Table 2: Stability of tumor magnetic resonance imaging agent containing iron nanoliposomes.

Index	30day	180day
Particle size/nm	77.88	87.83

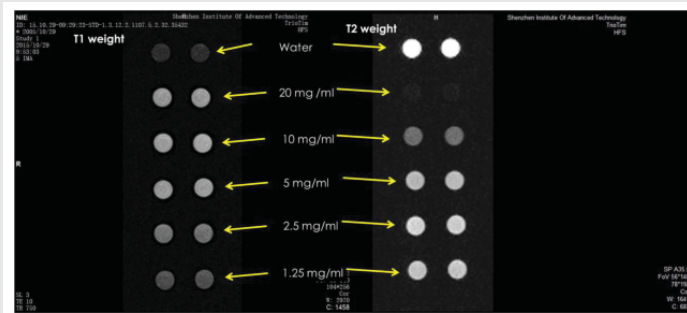


Figure 3: Enhanced effect of tumor magnetic resonance imaging *in vitro*.

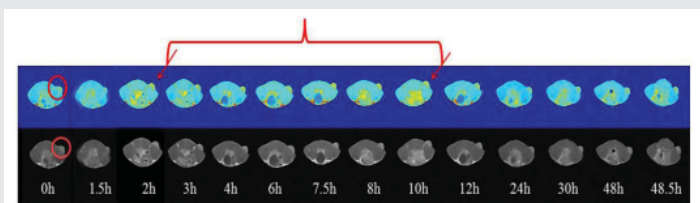


Figure 4: Enhancement effect of tumor nanometer magnetic resonance imaging enhancer *in vivo*.



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