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Magnetic cylindrical ordered mesoporous nanocarriers for targeted drug delivery

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ABSTRACT

An MCM-41 type magnetic cylindrical ordered mesoporous silicon dioxide (M-COMSD) nanocarrier for targeted drug delivery has been synthesised. Pharmaceutical drug molecules have been loaded into the mesoporous framework of the M-COMSD. In vitro (Hale cells) and in vivo (mice) drug storage and release experiments of the nanocarrier have been performed. The results of the M-COMSD system demonstrate that this material could play a significant role in developing a new generation of controlled-release nanocarriers.

1. Introduction

Since MCM-41 type mesoporous nanomaterials were synthesised in 1992 [1,2], they have become more and more popular in the family of mesoporous silicate materials. Several attractive features, such as stable mesoporous structures, large surface areas, tunable pore sizes and volumes [2], and easily modified surface properties that can be organically functionalised, have categorised MCM-41 type mesoporous silica materials as ideal nanocarriers. In addition, drug delivery is one of the most promising biomedical applications of nanotechnology. Maria Vallet-Regi [3] and Shaobin Wang [4] have summarised the recent advances of mesoporous materials for drug delivery. Drugs such as Doxil and Abraxane have already been approved for clinical use in cancer chemotherapy [5]. A good nanocarrier is characterised by its ability to circulate in blood for long periods of time as well as deliver drugs with minimal side effects [6]. Mesoporous silica nanocarriers can offer many advantages as a drug vehicle [7].

In the current research, drugs, DNA and siRNA have been directly grafted onto the surface of magnetic ferrite nanoparticles or nano-silicon particles. Other groups have made magnetic fluid [8,9], magnetic polymer carriers [10–12], liposomes [13–17], nanotubes [18–21] and silicon nanoparticles [22,23] for this application. However, the following problems remain for these carriers: the drug loading capacity and biological compatibility are limited, they are not easily moved by metabolic sequences, and they exhibit toxicity for both tumours and cells [5,10]. Studies on drug delivery carriers have shown that the nanocarriers with a diameter of less than 400 nm will be effective in vivo [24] and would be even more efficient in tumours when less than 200 nm [25,26]. In the field of gene therapy, a therapeutic gene will not be effective until it can penetrate the cell nucleus. This means that carriers need to be endocytosed by cells in order to be effective. Meanwhile, to improve the efficiency of expression, the vector's surface needs to be modified [27]. Additionally, some studies have shown that a long cylindrical shape can improve the carriers' circulation in the human body [28].

Herein, we report on a novel magnetic cylindrical ordered silicon dioxide material. We analyse its structure, drug storage ability and in vitro and in vivo properties. Our group focuses on the application of the nanocarrier, with a special focus on the field of biomedicine, such as for cancer treatment, as cancer remains one of the most devastating diseases in the world with more than 10 million new cases every year [29]. In recent reports, mortality has decreased in the past several years [30], owing to a better understanding of tumour biology and improved diagnostic devices and treatments. Targetted drug delivery technologies [5] are promising for cancer treatments. Magnetic targeted drug delivery

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systems, which are based on the inclusion of magnetic particles, are very attractive. This method may allow for a "zero-order release" profile before reaching the targeted cells or tissues. In this study, we demonstrate that Hela cells can efficiently uptake the M-COMSD nanocarriers. Further, this novel material has been shown to be an effective self-metabolic magnetic target in vivo.

2. Experiment

2.1. Synthesis of MCM-41 long, cylindrical magnetic nanocarriers

The cylindrical magnetic ordered mesoporous silicon dioxide (M-COMSD) nanocarriers, with specific functional groups, were designed and fabricated, as described in our patent [31]:

2.1.1. Preparation of the magnetic COMSD

Using nanoparticle Fe_3O_4 (15–20 nm, purchased from Nanjing Emperor Nano Material Co., Ltd., China) as the core and mesoporous silicon dioxide as the shell, we synthesised the magnetic cylindrical ordered-mesoporous silicon dioxide (M-COMSD) using a double surfactant system.

2.1.2. Preparation of the Fe_3O_4 core

Fe_3O_4 particles (2 g) were washed using hydrochloric acid (HCl, 0.1 mol/L, 100 ml each time) three times and then separated using a magnet. The Fe_3O_4 particles and 100 ml sodium citrate solution (0.5 mol/L) were then added to a flask. The solution was stirred for 4 h, ultrasonically dispersed for 10 min, separated using a magnet, washed using 100 ml of pure water three times and then separated again using a magnet.

2.1.3. Preparation of the core–shell Fe_3O_4@SiO_2 mesoporous particles

4.6 g CTAB and 2.3 g F127 were added as double surfactants into 60 ml of ethanol and ultrasonically dispersed for 10 min. The solution was then moved to a flask, while stirring, and 1 g of the fabricated Fe_3O_4 core particles were added into the flask, while continuing stirring. Finally, 20 g of hydrochloric acid (PH = 2.5) was added before adding 8.15 ml of TEOS, dropwise. After 4 h, 5 ml of NH_4OH (25 wt.%) was added. The resultant particles were separated using a filter, cleaned with ethanol three times and dried at room temperature for 12 h first and then at 60 °C for 12 h. Finally, the as-prepared products were calcined in air at 550 °C for 6 h.

2.1.4. Grafting functional groups

The M-COMSD and silane, with amino functional groups, were hydrolysed in xylene under reflux for 2 h, and the precipitates were separated by filtration, washed with deionised water twice and then dried in an oven at 60 °C for 24 h. The dry, functionalised M-COMSD are used to store the drug in the next step.

2.2. Drug release experiments

2.2.1. Drug storage

Doxorubicin (DOX) (purchased from Sigma, 99%) was dissolved in anhydrous ethanol. M-COMSD (1 g) was added to 25 ml of the doxorubicin anhydrous ethanol solution, yielding a solution concentration of 40 mg/ml, at room temperature. The loading amount was measured to be approximately 0.35 g of DOX/g of the carrier. The vials were sealed to prevent the evaporation of the ethanol, and the mixture was then stirred for 24 h. The product was filtered and dried under a vacuum at 60 °C. The sample was named M-COMSD@DOX.

2.2.2. Drug release

A total of 100 mg of M-COMSD@DOX was immersed in 100 ml of phosphate buffer solution (PBS, pH 7.4) at 37 °C while stirring at 100 rpm. The release medium (1.0 ml) of the sample was removed for analysis using a syringe at given time intervals and replaced with the same volume of fresh preheated PBS. The extracted medium was analysed using UV/Vis spectroscopy at a wavelength of 232 nm.

2.3. In vitro experiments

Hela tumour cells were maintained in T75 flasks using DMEM (Dulbecco's modified Eagle's medium) supplemented with 10% equine serum, 2 mg glutamine, 100 mg/ml penicillin, 100 mg/ml streptomycin and 1 mg/ml gentamycin. Using conventional culture techniques (37 °C, 5% CO_2), cells were split every 2–3 days. On the day before transfection, there were 5×10^5 cells in each 96-well plate.

The second step was to prepare the signed nanocarrier. We ultrasonically dispersed 50 mg of the M-COMSD in 1 ml of a curcumin solution, and then maintained the solution in darkness for 24 h.

The last step was to ultrasonically shake the solution for 2 min and then add 2 μl of the solution to each well.

2.4. In vivo experiments

We mixed the amino-functionalised M-COMSD with LSS670. LSS670 is an infrared excitation fluorescent dye that binds with amino groups. The sample was named as M-COMSD@LSS670. We then diluted the M-COMSD@LSS670 with a saline solution, ultrasonically dispersed the solution for 2 min and injected it into the tail vein of the mice. The injection time was 13:15 pm. We took the first photo at 13:23 pm. A small magnet was then affixed to the right side of the abdomen of the mice. The magnet was removed at 13:30 pm and then placed near the same abdominal area. The second photo was taken at 13:32 pm. Because the mouse was still under anaesthesia, we took the third photo at 13:37 pm. Then, we removed the magnet at 13:55 pm and took the fourth photo at 14:54 pm. The fifth photo was taken at 15:08 pm, and the sixth was taken at 15:18 pm. The seventh photo was taken at 15:27 pm, and the eighth photo was taken at 14:00 pm the next day.

3. Characterisation

Whole body images were acquired using a Kodak 4000MM Whole-Mouse Image Station. Excitation and emission filters were 720 and 790 nm, respectively. The excitation light was from an UV lamp with a 10× zoom lens and an exposure time of 0.17 s. The small-angle X-ray diffraction pattern was obtained on a Stoe Stadi powder diffractometer equipped with a curved germanium (1 1 1) monochromator and linear PSD using Cu Kα radiation (1.5405 Å) in transmission geometry. Transmission electron microscopy (TEM) was performed using a FEI electron microscope operated at an acceleration voltage of 200 kV. The UV/Vis absorption spectra were measured using a Shimadzu UV-1650PC spectrophotometer. N_2 adsorption–desorption isotherms were obtained on a Quantachrome Autosorb-1C apparatus at −196 °C under a continuous adsorption condition.

4. Result and discussion

4.1. MCM-41 nanocarriers

The M-COMSD's TEM images are shown in Fig. 1. These two images indicate that they possess an ordered mesoporous