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Mesoporous silica nanoparticles as potential carriers for enhanced drug solubility of paclitaxel

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ABSTRACT

In this study, paclitaxel (PTX), a typical chemotherapeutic agent with poor water-solubility, was selected as the model drug to evaluate the feasibility of mesoporous silica nanoparticles (MSN) to load a hydrophobic drug in different solvents. A sol-gel method was used to synthesize MSN. Drug loading was carried out in three different solvents: dichloromethane, ethanol and dimethyl sulfoxide (DMSO) via a solvent evaporation method, and their effects on drug loading were examined. We further studied the effects of drug loading period and mass ratio of drug to carrier on drug loading capacity of MSN, as well as the in vitro drug release was analyzed. Moreover, the cytotoxic effect of PTX loaded MSN on liver carcinoma (HepG2) cells was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The related materials were characterized by scanning electron microscope (SEM), transmission electron microscope (TEM), dynamic light scattering (DLS), fourier transform infrared spectrometer (FTIR), small-angle x-ray scattering (SAXS), wide-angle x-ray diffraction (XRD) and N_2 adsorption-desorption analyses. The results demonstrated a highly improved solubility of PTX by using MSN as drug carriers compared to free PTX. In addition, drug loading content increased as the solvent polarity parameter decreased or the drug/carrier mass ratio increased. Compared with the blank MSN, the PTX loaded MSN could produce a significant cytotoxicity on HepG2 cells. Our results indicated that MSN could be very potential drug delivery carriers for poorly water soluble drugs.

1. Introduction

Due to the poor water solubility, many pharmaceuticals lack a formulation strategy capable of producing high loads, fast dissolution rate, thus possess great challenge for their clinical application [1,2]. Many methods have been developed to find alternative excipient for hydrophobic drugs that would increase their therapeutic efficacy [3,4]. Actually, the absorption and bioavailability of poorly soluble drugs would be increased if the problem of poor solubility could be solved [5]. In recent past decades, many studies have been carried out to solve this problem [6–8]. A well-established method for improving the drug efficacy is to improve the dissolution rate of drug, which could be achieved by increasing drug surface area in contact with the dissolution media [9]. Some researchers used a solid dispersion to increase the solubility of water-insoluble drugs [10,11]. In recent years, an increasing number of researchers have focused on using nanomaterials to improve the dissolution rate of insoluble drugs [12–14]. The emergence of inorganic porous materials as drug carriers had opened up a new path for improving the solubility of hydrophobic drugs [1,15–17]. The solubility of hydrophobic drug was highly improved by loading drug onto a high surface area carrier [18–20]. Mesoporous silica nanoparticles (MSN) were great promising drug carriers because of their good biocompatibility, feasibility of surface modification, tunable pore size, high pore volume and large surface area [21–23]. MSN had been shown to overcome the poor water solubility of many hydrophobic drugs and enhance their bioavailability [24–26]. It had been reported that drug dissolution rate reduced as the pore size of MSN decreased [27].

Paclitaxel (PTX), a broad-spectrum anticancer drug, was effective in treating various types of solid tumors [28–30]. However, the hydrophobic nature of PTX confined its use as a suitable anticancer drug [31]. In this study, to overcome the poor water solubility of PTX and improve its bioavailability, MSN were synthesized as hydrophobic drug vehicles for PTX. Drug loading was carried out in different solvents including dichloromethane, ethanol and dimethyl sulfoxide (DMSO) by a solvent evaporation method, and their effects on drug loading were investigated. Additionally, the effects of drug loading period and mass ratio of drug to MSN on drug loading were also studied. Furthermore, the in vitro drug release of PTX loaded MSN was examined, and the results were compared with free PTX. The in vitro cytotoxicity of MSN, free PTX and PTX loaded MSN on

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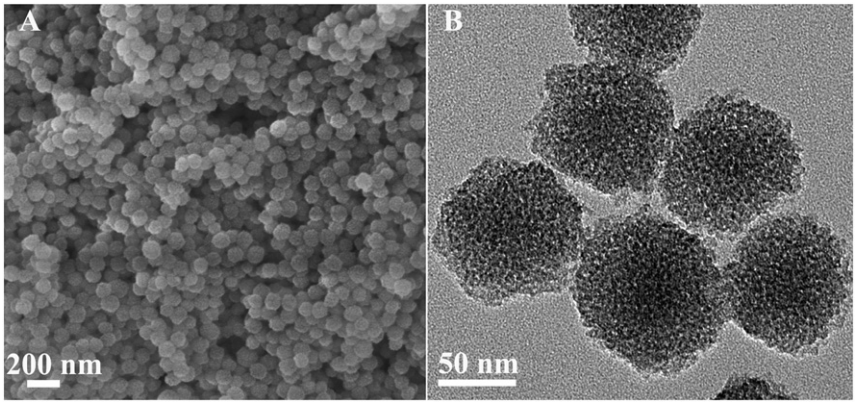

Fig. 1. The SEM image (A) and TEM image (B) of mesoporous silica nanoparticles.

HepG2 cells were evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.

2. Materials and methods

2.1. Materials

Tetraethylorthosilicate (TEOS, 98%), ammonia ($NH_3 \cdot H_2O$, 25–28%) and ethanol (EtOH, 99.7%) were purchased from Changsha Fuke Chemical Reagent Company. N-octadecyltrimethoxysilane (C_{18}TMS, 95%) was purchased from Changsha Baxi Chemical Reagent Company. Dichloromethane and dimethyl sulfoxide (DMSO) were purchased from Sinopharm Chemical Reagent Co., Ltd. Paclitaxel (PTX, 98%) was purchased from Shanghai Sigma-Aldrich Co., Ltd. RPMI-1640 medium (1640, Hyclone®), fetal bovine serum (FBS, Hyclone®), penicillin-streptomycin solution (Hyclone®), phosphate buffered saline (PBS, Hyclone®) and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazo-lium bromide (MTT) were provided by Sunshine Biotechnology Co., Ltd. (Nanjing, China). All chemicals except deionized water which was prepared with an ion exchange system were used as-received.

2.2. Preparation of MSN

MSN were synthesized according to our previous study [32]. C_{18}TMS (2 g) and TEOS (5 g) were dissolved in a solution composed of deionized water, ethanol and ammonia with a molar ratio of 5:13:1 at 30 °C. After reaction for 2 h under vigorous stirring, the mixture was filtered, washed and dried at room temperature. MSN were obtained after calcination at 550 °C for 6 h to remove surfactant template.

2.3. Drug loading study

For PTX loading, a solvent evaporation method was utilized. To determine the effects of solvents on drug loading, dichloromethane, ethanol and DMSO were chosen. Furthermore, the mass ratio of drug to carrier (1:2, 1:3, 1:4, 1:5) and the drug loading period (4 h, 8 h, 12 h, 24 h, 36 h) were also examined to determine their effects on drug loading. Briefly, 30 mg MSN were separately taken and mixed with PTX in a closed container containing 4 mL of dichloromethane, ethanol or DMSO for hours at 37 °C with stirring at 100 rpm. Then, the solvents were allowed to evaporate to 1 mL to produce a gradually increasing concentration of PTX, which may lead to a further concentration gradient of drug between the mesopores of MSN and the external solution, and enhance the uptake of drug into mesopores. Finally, The PTX loaded MSN samples were collected by centrifugation, washed with their loading solvent, dried in a vacuum oven. The obtained samples were denoted as MSN@PTX_{dic}, MSN@PTX_{eth} and MSN@PTX_{dim} respectively. HPLC was employed to determine the drug concentration in silica samples. Drug loading content was calculated according to the following equation:

$$\text{Drug loading content} = \frac{\text{Weight of PTX in MSN}}{\text{Weight of PTX loaded MSN}} \times 100\%$$

2.4. Drug release study

MSN@PTX_{dic} were selected to study the drug release behavior. Briefly, a certain amount of MSN@PTX_{dic} was dispersed into deionized water, then 0.5 mL of the dispersion was transferred into a dialysis bag and subsequently immersed into 25 mL of phosphate buffer solution (PBS, pH 7.4) containing 0.1% (v/v) Tween 80 at 37 °C with stirring of 100 rpm. At determined time intervals, 0.5 mL of release sample was withdrawn, followed by supplying the same volume of fresh PBS solution. The amount of the release drug was measured by HPLC method. For comparison, the release of PTX from free PTX was investigated under the same conditions.

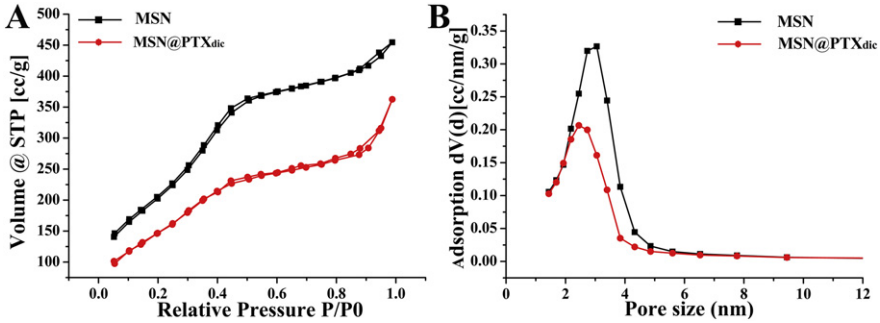

Fig. 2. The adsorption-desorption isotherms (A) and pore size distributions (B) of MSN and MSN@PTX_{dic}.