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Porous hydrophilic core/hydrophobic shell nanoparticles for particle size and drug release control

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A B S T R A C T

Polymeric nanoparticle has been developed for drug delivery during the past decades. However, the size of hydrophilic nanoparticles would increase in the aqueous environment due to water absorption, and then influence the in vivo biodistribution and drug release behavior. In the present study, the metronidazole-loaded porous Eudragit® RS (ERS)/poly(methyl methacrylate) (PMMA) core/shell nanoparticles were prepared by coaxial electrospray. Compared to the hydrophilic ERS nanoparticles, the porous hydrophilic core/hydrophobic shell nanoparticles displayed a slower drug release, and the release rate can be adjusted to change the surface area and particle size. In addition, the porous core/shell nanoparticles could maintain a stable particle size distribution in simulated body fluid for 8 h, which can be attributed to the bioinert nature of PMMA coating. And porous core/shell nanoparticles showed slight in vitro cytotoxicity and good cellular internalization property. The results demonstrated that the prepared porous hydrophilic core/hydrophobic shell nanoparticles is a potential candidate for delivering drugs, which can also be used as a platform and further modified into targeted drug delivery systems for clinical application.

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1. Introduction

Polymeric nanoparticles have been extensively applied for delivering drugs during the past decades due to the high surface to volume ratio, modifiable platform, controlled drug release property, tunable size and shape, and good biodegradability [1,2]. And various therapeutic agents such as anti-cancer drugs [3], vaccines [4], proteins, nucleic acid [5] and other drugs have been incorporated into polymeric nanoparticles to improve their bioavailability [6]. In addition, a number of polymers have been explored to synthesize the polymeric nanoparticles, including poly(lactic acid) [7], poly(lactide-co-glycolide) [8], poly(methylmethacrylate) [9], chitosan [10,11], cyclodextrin [12], gelatin [13], and other polymers [14].

The size of polymeric nanoparticles significantly affects their in vivo absorption and biodistribution after oral administration, and small nanoparticle showed increased GI uptake [15]. Meanwhile, polymeric nanoparticles have been widely used for intravenous application, and the particle size also influences their circulation time, biodistribution and the extent of cellular uptake by phagocytosis and endocytosis [16, 17]. In addition, the size of nanoparticles has a pronounced influence on the release kinetics due to the different surface area/volume ratios [18]. However, the size of swellable polymeric nanoparticles would change in aqueous environment due to the water absorption [19], which would affect the in vivo biodistribution of polymeric nanoparticles and drug release profiles.

The aim of present study was to prepare a porous hydrophilic core/hydrophobic shell nanoparticles by coaxial electrospray to control the particle size distribution and drug release behavior. The size of polymeric nanoparticles can remain stable because of the hydrophobic shell, and the drug release rate can be controlled by changing the surface area and the particles size. Eudragit® RS (ERS), a pH-independent swellable polymer, was chosen as the core material [20], and the hydrophilic ERS nanoparticles were entrapped into the porous hydrophobic poly(methyl methacrylate) (PMMA) shell [21]. Furthermore, coaxial electrospray has been applied to prepare the core/shell polymeric micro/nanoparticles [22,23], and the most outstanding features of electrospray are rapid and efficient, i.e. preparation of the solid nanoparticle by one step and entrapment of the drug into nanoparticles without loss (100% entrapment efficiency) [24]. We have prepared the high drug loaded pH-sensitive nanoparticles and core/shell nanoparticles using single-axial electrospray and coaxial electrospray, respectively [24,25]. In addition, the structure of porous hydrophilic core/hydrophobic shell nanoparticles was observed by the scanning electron microscope

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(SEM) and transmission electron microscopy (TEM), and the cytotoxicity assay, cellular uptake and the in vitro release profile were also investigated.

2. Materials and methods

2.1. Materials

Eudragit ® RS (MW = 320 kDa, ERS) was a kind gift from Evonik Industries (Essen, Germany). Poly(methyl methacrylate) (MW = 98 kDa, PMMA) was supplied by the LG Chem. Ltd. (Taejon, Korea). Metronidazole (MTZ) was kindly gifted by the Southwest Pharmaceutics Co. Ltd. (Chongqing, China). Caco-2 cells were supplied by the Institute of Pathology, Southwest Hospital (Chongqing, China). MTT was supplied by the Amresco (Solon, USA). Fluorescein isothiocyanate (FITC) was purchased from the Sigma (Missouri, USA). Rhodamine B (RhB) was purchased from the Sangon Biotech Co. Ltd. (Shanghai, China). All other materials and reagents used in the study were analytical grade.

2.2. Preparation of porous core/shell nanoparticle

The porous ERS/PMMA nanoparticles with core/shell structure were prepared using coaxial electrospray method. ERS (100 mg) and MTZ (35 mg) were dissolved in 10 mL of dichloromethane as the inner fluid, and PMMA was dissolved in dichloromethane at different concentrations (from 1% to 4%, w/v) as the outer fluid. The inner and outer diameters of inner nozzle are 0.3 mm and 0.5 mm respectively, and the inner diameter of outer nozzle is 1.0 mm. The polymer solutions were loaded in plastic syringes and supplied by separate syringe pump (Langer, China). The flow rates of inner fluid and outer fluid were 200 μL/h and 400 μL/h, respectively. While, the nozzle was connected to the positive electrode (+15 kV) of a high-voltage power supply (Dongwen, China), aluminum foil was placed vertically to the coaxial nozzle as a collector, and the needle-to-collector distance was kept at 90 mm.

The core/shell structure of porous ERS/PMMA nanoparticles was observed by fluorescence microscopy. The green (FITC) and red (RhB) dye were added into the inner fluid and outer fluid, respectively, and the FITC-loaded porous core/shell nanoparticles were also prepared for the cellular uptake study. In addition, the ERS nanoparticles were also prepared using single-axial electrospray. The inner diameter of nozzle is 1.0 mm, and the flow rate of fluid was 400 μL/h. Other fabrication parameters were the same as those in the preparation of core/shell nanoparticles.

2.3. Measurement of the particle size and zeta potential

Particle size distribution, polydispersity index (PDI) and zeta potential of porous ERS/PMMA core/shell nanoparticles were measured by photon correlation spectroscopy and electrophoretic laser Doppler anemometry respectively using a Zetasizer (Nano ZS90, Malvern, UK).

2.4. Observation of the morphology

The surface morphology of porous ERS/PMMA core/shell nanoparticles was observed by SEM and TEM. A piece aluminum foil loaded with nanoparticle was coated with gold metal under vacuum for SEM observation (EVOLS25, Zeiss, Germany). The nanoparticle solution were dropped on copper grids, natively stained by phosphotungstic acid and dried at room temperature for TEM observation (Tecnai G2 20, FEI, USA). And the core/shell structure of ERS/PMMA nanoparticles was also characterized by fluorescence microscopy (DMI 4000B, Leica, Germany). The green dye (FITC) and red dye (RhB) were excited at 488 and 543 nm, respectively. In addition, the morphology of drug-loaded porous ERS/PMMA core/shell nanoparticles (2% of PMMA) after incubation in simulated body fluid (SBF, pH 7.4) for different times (2, 4, 6 and 8 h) was also observed by SEM.

2.5. Determination of the entrapment efficiency and loading capacity

The encapsulation efficiency (EE) and loading capacity (LC) of porous ERS/PMMA core/shell nanoparticles were determined as follows: MTZ-loaded nanoparticles were incubated in dichloromethane to dissolve the nanoparticles with stirring for 1 min at 100 rpm, and then PBS solution (pH 7.4) was added into the solution. The mixture solution was stirring at 300 rpm for 4 h to evaporate the organic solvent completely. Finally, the solution was separated by a centrifuge (5417R, Eppendorf, Germany) at 12,000 rpm for 30 min and analyzed using a spectrophotometer at 300 nm (Lambda 900UV, PerkinElmer, USA). The EE and LC were calculated by the following equations:

$$LC = \frac{\text{Amount of Drug in Nanoparticles}}{\text{Amount of Nanoparticles}} \times 100\% \tag{1}$$

$$EE = \frac{\text{LC of Nanoparticles}}{\text{LC of Nanoparticles in Theory}} \times 100\%. \tag{2}$$

2.6. Fourier transform infrared spectroscopy analysis

The chemical structure and complex formation of PMMA, ERS, MTZ, and MTZ-loaded porous ERS/PMMA nanoparticles were analyzed by a FT-IR spectroscopy (5DX/550II, Nicolet, USA), the samples used for the FT-IR spectroscopic characterization were prepared by grinding the dry specimens with KBr and pressing them to form disks.

2.7. X-ray diffraction analysis

The XRD experiments were carried out using an X-ray diffractometer (6000X, Shimadzu, Japan). PMMA, ERS, MTZ, and MTZ-loaded porous ERS/PMMA nanoparticles, and physical mixture of drug and polymers were analyzed in the 2θ ranging from 5° to 45° with a step width of 0.04° and a count time of 2 s.

2.8. Differential scanning calorimetry

The thermal properties of PMMA, ERS, MTZ, and drug-loaded porous ERS/PMMA nanoparticles, and physical mixture of drug and polymers were measured by differential scanning calorimetry (DSC, 204F1, Netzsch). The temperature scanning rate was 10 °C/min and scanned up to 200 °C.

2.9. Specific surface area analysis

BET specific surface area of nanoparticles with different PMMA concentrations were calculated from nitrogen adsorption–desorption isotherms determined at 77 K using a surface area analyzer (Micromeritics ASAP2020M, USA), and the sample was outgassed under a vacuum at 298 K for at least 8 h.

2.10. In vitro release studies

The release studies of MTZ from porous ERS/PMMA core/shell nanoparticles prepared with different PMMA concentrations and ERS nanoparticles were investigated and conducted as follows: 20 mg of MTZ-loaded nanoparticles and 3 mL of SBF were put into a dialysis tube (MWCO: 12,000) and then the dialysis tube was placed in 30 mL of SBF at 37 °C and kept under shaking at 100 rpm. At specific time intervals, the medium (1 mL) was taken and replaced with fresh SBF. The concentration of the released drug was determined by UV spectrophotometry.

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