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Formulation of porous poly(lactic-co-glycolic acid) microparticles by electrospray deposition method for controlled drug release

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ABSTRACT

In the present study, the electrospray deposition was successfully applied to prepare the porous poly(lactic-co-glycolic acid) (PLGA) microparticles by one-step processing. Metronidazole was selected as the model drug. The porous PLGA microparticles had high drug loading and low density, and the porous structure can be observed by scanning electron microscope (SEM) and transmission electron microscopy (TEM). The production time has been shortened considerably compared with that of the traditional multi-emulsion method. In addition, no chemical reaction occurred between the drug and polymer in the preparation of porous microparticles, and the crystal structure of drug did not change after entrapment into the porous microparticles. The porous microparticles showed a sustained release in the simulated gastric fluid, and the release followed non-Fickian or case II transport. Furthermore, porous microparticles showed a slight cytotoxicity in vitro. The results indicated that electrospray deposition is a good technique for preparation of porous microparticles, and the low-density porous PLGA microparticles has a potential for the development of gastroretentive systems or for pulmonary drug delivery.

1. Introduction

Many drug delivery systems have been developed to regulate the release behavior and duration time of therapeutic agents at specific disease or injury sites. Biodegradable polymeric drug carriers have been paid more and more attention, which could offer several advantages over traditional systems, such as releasing the drug at controlled rate, targeting the agent to specific site, controlling the degradation and improving the bioavailability of drug [1,2]. Among them, porous microparticles have been widely used for the pulmonary and stomach-specific drug delivery because of their low density and high specific surface [3–5].

The traditional methods of the porous microparticle preparation are salt leaching, gas foaming and phase separation. And the porous structure can be formed by osmosis between internal and external phases in the multi-emulsion method [2,6,7]. However, the preparation process is tedious and time-consuming [2,6–8], and the drug loading and entrapment efficiency of multi-emulsion method are usually unsatisfactory. High drug loading is an important property for the ideal drug delivery system, especially for the sustained-release drug delivery systems [9]. In addition, long production time would reduce production efficiency, which can't satisfy the development of the modern pharmaceutics.

Electrospray deposition (ESD) is a novel versatile technique and has been applied to prepare the polymeric micro/nanofibers and micro/nanoparticles [10–14], and the porous fiber could also be prepared via the ESD method [15]. The electrospray process depends on coulomb repulsion to break the bulk liquid into fine charged droplets randomly, which can be described by an electrochemical model [16,17]. The solvent of the charged droplets will evaporate before reaching the receiver, so ESD could prepare the solid particles directly. At the same time, the porous morphology would be produced on the particle surface via the solvent evaporation. Moreover, the entrapment efficiency of ESD could approach 100% in theory, so the prepared particles have high drug loading. We have prepared the high drug loading nanoparticles by the ESD method in the previous study [18].

In the present study, we prepared the porous poly(lactic-co-glycolic acid) (PLGA) microparticles via the ESD method as a controlled-release drug delivery system. PLGA, a good biodegradable polymer, was selected as carrier material. And metronidazole (MTZ) was selected as the model drug, which has been widely used as a critical component of combination therapies for *Helicobacter pylori* infection [19]. The porous PLGA microparticles were characterized by the scanning electron microscope (SEM), transmission electron microscopy (TEM), Fourier transforms infrared spectroscopy (FT-IR) and X-ray diffraction (XRD). Meanwhile, the density, cytotoxicity and the in vitro release profile of MTZ-loaded PLGA porous microparticles were also investigated.

2. Material and methods

2.1. Materials

Poly(lactic-co-glycolic acid) (PLGA, molecular weight — 10 kDa) was purchased from Dai-gang Biology Co. Ltd. (Shandong, China). Metronidazole (MTZ) was kindly supplied by Southwest Pharmaceutics Co.

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Ltd. (Chongqing, China). Dichloromethane was purchased from Chuandong Chemical Reagent Factory (Chongqing, China). Human gastric epithelial cell line (GES-1) was supplied by the Institute of Pathology, Southwest Hospital, (Chongqing, China). RPMI 1640 medium and fetal bovine serum (FBS) were purchased from HyClone (Utah, USA). MTT was supplied by Amresco (Solon, USA). All other materials and reagents used in the study were analytically graded.

2.2. Preparation of the porous microparticles

The porous PLGA microparticles were prepared using ESD in this study; PLGA was dissolved in dichloromethane with different concentrations ranging from 1% to 4% (w/v), and MTZ was dissolved in the PLGA solutions at a concentration of 3.0 mg/mL. The spray solution was supplied by the syringe pump (Longer, China) for spraying from the grounded nozzle (inner diameter 0.88 mm, outer diameter 1.27 mm). The nozzle was connected to the positive electrode of a high-voltage power supply (Dongwen, China). Aluminum foil was used as collector and placed perpendicularly to the nozzle. The schematic representation of the ESD system for the preparation of 1the porous PLGA microparticles was shown in Fig. 1.

The preparation of the porous PLGA microparticles was carried out at room temperature, and processing parameters were as follows: applied voltage: +15 kV; flow rate of spray solution: 900 μL/h; and distance between nozzle and aluminum foil: 100 mm. And the porous PLGA microparticles were collected from the aluminum foil by a brush.

2.3. Particle size and zeta potential measurements

Particle size distribution and polydispersity index (PDI) of PLGA porous microparticles were measured by laser light scattering particle size analyser (3500S, Microtrac Inc., USA). And the zeta potential of PLGA porous microparticles was also analyzed using a Zetasizer (Nano ZS90, Malvern, UK). Samples were diluted to appropriate concentrations with deionized water for the determination of size distribution and zeta potential. All experiments in this study were performed at least three times.

2.4. Morphology of porous microparticles

Morphologies of the porous PLGA microparticles were investigated by SEM and TEM. The porous microparticles were sprayed on the aluminum foil, and a piece of foil was putter-coated using a platinum coater for SEM examination (Nova400, FEI, USA). And the porous microparticle suspensions were dropped on copper grids, natively stained by phosphotungstic acid and dried at room temperature for TEM observation (Tecnai G2 20, FEI, USA). In addition, we also took the optical photos of the porous PLGA microparticles floating in the SGF under and without the magnetic stirring.

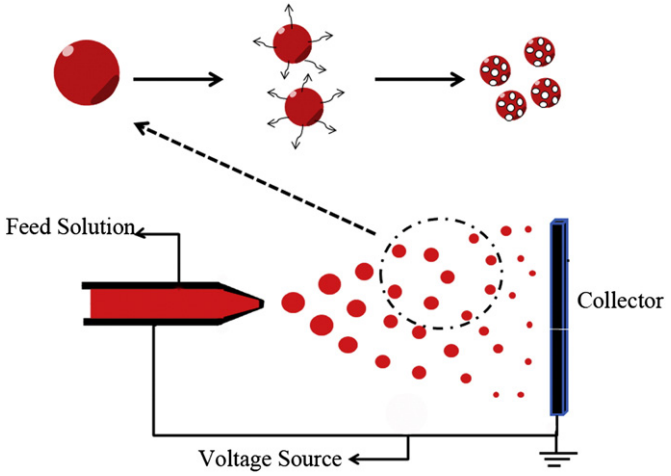

Fig. 1. The schematic representation of ESD system for the synthesis of PLGA porous microparticles.

2.5. Loading capacity of porous microparticles

The loading capacity (LC) and entrapment efficiency (EE) of the MTZ-loaded porous PLGA microparticles were measured by the following method. 5 mg MTZ-loaded porous PLGA microparticles were taken into 1 mL dichloromethane to break the microparticles for 1 min, and then 4 mL phosphate buffered solution (PBS, pH 7.4) was put into the solution; the mixed solution was stirring for 6 h until dichloromethane was volatilized completely. The content of MTZ in the solution was analyzed by UV spectrophotometer at 300 nm (PerkinElmer, Lambda 900, USA). All samples were measured in triplicate. The LC and EE were calculated by Eqs. (1) and (2):

$$\mathrm{LC} = \frac{\text{Weight of MTZ in microparticles}}{\text{Weight of microparticles}} \times 100\% \quad (1)$$

$$\mathrm{EE} = \frac{\text{Loading capacity of microparticles}}{\text{Loading capacity of microparticles in theory}} \times 100\%. \quad (2)$$

2.6. Density of porous microparticles

The bulk density, tap density and true density of the MTZ-loaded porous PLGA microparticles prepared with different PLGA concentrations (from 1% to 4%) were measured as described previously [20]. Briefly, the bulk density was measured by filling the MTZ-loaded porous PLGA microparticles in a bottom-sealed 1 mL graduated syringe with a funnel. The weight of the porous microparticles required to fill the 1 mL graduated syringe was recorded to calculate the bulk density. The tap density of the porous PLGA microparticles was evaluated by tapping on a hard bench until no change in the volume of the microparticles was observed. The resultant volume was recorded to calculate the tap density. In addition, the true density of drug-loaded porous PLGA microparticles prepared with different PLGA concentrations was measured by gas pycnometer helium true density analyzer (G-DenPyc2900, Gold APP Instruments, China). Each measurement was performed at least ten times.

2.7. FTIR studies

FT-IR spectra (ranging 400–4000 cm^{-1}) of MTZ, PLGA, physical mixture of MTZ and PLGA (mass ratio of MTZ to PLGA: 3/10), and drug-loaded porous microparticles (1% PLGA) were determined by FT-IR spectrophotometer (Nicolet, 5DX/550II, 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.

2.8. XRD studies

The XRD experiments were carried out using an X-ray diffractometer (Shimadzu, 6000 X-ray diffractometer, Japan). MTZ, PLGA, physical mixture of MTZ and PLGA (mass ratio of MTZ to PLGA: 3/10), and drug-loaded porous microparticles (1% PLGA) were analyzed in the 2θ ranging from 5 to 45° with a step width of 0.04° and a count time of 2 s.

2.9. In vitro release study

An adequate amount of PLGA porous microparticles has been prepared by ESD for about 24 h, and the in vitro release studies were carried out as follows: 20 mg MTZ-loaded porous PLGA microparticles and 3 mL simulated gastric fluid (SGF, pH 1.2) were put into a dialysis tube