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Preparation of drug nanoparticle-containing microparticles using a 4-fluid nozzle spray drier for oral, pulmonary, and injection dosage forms

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Abstract

We prepared microparticles containing nanoparticles of water-insoluble pranlukast hemihydrate (PLH) using a 4-fluid nozzle spray drier. These particles were designed to improve the absorption of PLH and to allow delivery by oral, pulmonary, and injection routes. Mannitol (MAN) was used as a water-soluble carrier for the microparticles. We orally administered suspensions of PLH powder and PLH-MAN microparticles to rats. We also compared the *in vitro* aerosol performance of the PLH powder and PLH-MAN microparticles using a cascade impactor, and we compared the delivery of PLH by oral administration of PLH powder and pulmonary delivery of PLH-MAN microparticles at PLH/MAN ratios of 1:4 and 1:10. The absorption of PLH was markedly enhanced by pulmonary deliver of PLH-MAN composite microparticles. The area under the plasma concentration–time curve per dose for pulmonary administration of the 1:4 and 1:10 PLH-MAN microparticles was approximately 85- and 100-fold higher, respectively, than for oral administration of PLH powder. Also, we found that PLH rapidly disappeared from the plasma following injection of PLH aqueous solution or PLH-MAN microparticles dissolved in water. The PLH particles remaining after dissolution of MAN from the 1:10 PLH-MAN microparticles were 200 nm in diameter. Therefore, PLH particles may be captured immediately after injection by reticuloendothelial tissues such as the liver and spleen. This study demonstrated that it is possible to use the 4-fluid spray drier to prepare microparticles containing PLH nanoparticles that that improve drug absorption and can be administered by oral, pulmonary, and injection routes.

Keywords: 4-fluid nozzle; Nanoparticle; Microparticle; Spray dry; Insoluble drug

1. Introduction

Many recent drug candidates are poorly water-soluble and have an inherently low mucosal permeability. This complicates the development of pharmaceutical formulations. For example, pranlukast hemihydrate (PLH) is a leukotriene antagonist used for the treatment of bronchial asthma. This drug has an extremely low aqueous solubility of 1.2 μg/mL at 25 °C, which results in very poor oral absorption.

There are various techniques for improving the solubility of water-insoluble drugs. Traditional methods for producing particles with enhanced solubility include the pulverization of large drug particles using a ball or jet mill [1–3]. Spray freezing and drying methods have been recently explored for preparing polymer-containing solid dispersion particles to enhance the dissolution rate of drugs [4–13]. However, the solid dispersion method requires a common solvent for the water-insoluble drug and the water-soluble polymer.

The 4-fluid nozzle spray drier has a unique nozzle with two liquid and two gas passages, which allows drug and carrier to be dissolved in separate solvents, thereby avoiding the need for a common solvent. We have previously used this technique to prepare particles of pharmaceutical drugs for inhalation as a dry powder [14] and to generate two-drug composite microparticles [15] and microspheres containing polymeric nanoparticles [16].

The lung is an attractive route for drug delivery because it has a large surface area (~75–140 m^2) and because the thickness of the air–blood barrier in the alveolar epithelium is less than 1 μm [17,18]. Therefore, delivery through the lung is expected to improve drug absorption.

In this study, we used mannitol (MAN) as a water-soluble carrier for microparticles. An organic solution of PLH and an aqueous solution of MAN were simultaneously introduced

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through different liquid passage of the 4-fluid nozzle. In this way, we prepared PLH nanoparticle-containing microparticles, and we investigated their ability to enhance the oral and pulmonary absorption of PLH and their use for intravenous injection.

2. Materials and methods

2.1. Materials

2.1.1. Plh

(4-oxo-8-[4-(4-phenylbutoxy)benzoylamino]-2-(tetrazol-5-yl)-4H-1-benzopyran 1/2H_2O) was kindly supplied by Ono Pharmaceutical Co. Ltd. (Tokyo, Japan). MAN was purchased from Wako Pure Chemical Industries (Osaka, Japan). Carboxymethylcellulose sodium ($[C_6H_7O_2(OH)x(OCH_2COONa)y]n$, where $x+y=3$ and $n=1050$) was purchased from Tokyo Chemical Industry (Tokyo, Japan). Lactose (Pharmatose 325 M) was kindly supplied by DMV Japan (Tokyo, Japan). All solvents were regent grade.

2.2. Preparation of PLH-containing microparticles using a 4-fluid nozzle spray drier

Spray-dried particles were prepared using a model MDL-050 4-fluid nozzle spray drier (Fujisaki Electric, Tokushima, Japan). The 4-fluid nozzle has two chisel-shaped nozzles through which compressed air passes and two additional nozzles through which sample solutions pass [15,16]. Different liquids and gases can be supplied to each passage individually. The edge of the nozzle, which is a slit, functions as the liquid flow side at the time of operation. At the liquid flow sides, the sample solutions are withdrawn by high-speed compressed air in the acceleration zone. Air collides at the tip of the edge, and a powerful shock wave is generated at the collision focal spot. As a result, the drawn solutions are atomized into droplets. The droplets are then dried by heated air, and the dried particles are collected.

PLH was dissolved at 0.83% (w/v) in a 1:1 solution of 50 mM aqueous sodium bicarbonate/ethanol, and MAN was dissolved in water at 3.33% and 8.83% (w/v). This gave PLH/MAN composition ratios of 1:4 and 1:10 (w/w). The PLH solution and the aqueous solution of MAN were supplied through different liquid passages of the 4-fluid nozzle. Spray drying was performed under the following conditions: inlet temperature, 90 °C; outlet temperature, 40 °C to 45 °C; supply rate for PLH or MAN solutions, 5 mL/min; spray rate for air, 30 L/min; spray air pressure, 8 kgf/cm^2.

2.3. Scanning electron microscopy (SEM)

Particles were observed with an S-2250 N scanning electron microscope (Hitachi, Tokyo, Japan). The samples were coated with 25-nm thick gold using a model SC-701 quick carbon coater (Sanyu Electronics, Tokyo, Japan).

2.4. Measurement of mean particle diameter

The diameters of the microparticles (horizontal feret diameters) were determined by image analysis from approximately 500–800 particles using WinROOF image analysis software (Mitani, Fukui, Japan). The mean particle diameter was defined as the median diameter of the cumulative curve of the number-basis particle size distribution.

PLH powder were dispersed in ultrapure water. The PLH dispersion was agitated for 72 h at 37 °C and then cooled to room temperature. This dispersion was filtered through a 0.1-μm membrane filter (DuraporeR, Nihon Millipore, Tokyo, Japan) to obtain a saturated aqueous solution of PLH. PLH-MAN microparticles were placed in this solution to dissolve the MAN. The particle size distribution of PLH (0.05 mg/mL) was determined using a model DLS-7000 super dynamic light scattering spectrophotometer (Otsuka Electronics, Osaka, Japan) with excitation using an Ar laser at 5 A and 90°.

2.5. Powder X-ray diffraction measurements

A Geigerflex RAD-IB powder X-ray diffractometer (Rigaku, Tokyo, Japan) was used to analyze the crystallinity of the samples. The conditions were as follows: target, Cu; filter, Ni; voltage, 40 kV; current, 20 mA; scan rate, $2\theta=3°$/min.

2.6. In vivo oral absorption study

Sprague–Dawley male rats (8 weeks old; 250–300 g, Japan SLC Inc., Shizuoka, Japan) were used. The rats were fasted for 1 day before the experiments. Rats were anesthetized by intraperitoneal injection of sodium pentobarbital, and the experiments were performed under incandescent lighting to maintain the body temperature of the rats.

Carotid arterial cannulation was performed using a polyethylene tube (0.965 mm outside diameter). A syringe (1 mL) filled with heparin was placed at one end of the polyethylene tube through a 23-gauge needle. PLH powder or PLH-MAN (1:4) microparticles were suspended in an aqueous 0.5 w/v% carboxymethylcellulose sodium solution. One mL of the suspension was orally administrated to rats (150 mg/kg PLH). Blood samples (400 μL) were taken from a carotid artery through the cannula. Plasma was obtained from the blood samples by centrifugation at 9730 ×g for 15 min at 4 °C. Two hundred μL of ethanol was added to 50 μL of plasma. After vortex mixing, the solution was centrifuged at 9730 ×g for 5 min at 4 °C to separate the plasma proteins. The supernatant was evaporated to dryness using a HVC-500 mini-centrifugal concentrator (Asahi Techno-glass, Chiba, Japan). The residue was dissolved in 200 μL of HPLC. Mobile phase (5:5:1 acetonitrile/20 mM monobasic potassium phosphate solution/methanol). Sixty-five μL of the solution was analyzed by HPLC to determine the plasma concentration of PLH. The HPLC conditions were as follows: pump; Jasco-880-PU, detector; Jasco-875, integrator; Jasco-807-IT, column; Mightysil RP-18 (4.6 mm $\phi\times$150 mm; Kanto Chemical, Tokyo, Japan); column temperature, 25 °C; detection wavelength, 260 nm; flow rate, 1.0 mL/min. The area under the plasma concentration–time curve (AUC) was determined by the trapezoidal method.