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Short communication

Oral absorption of atorvastatin solid dispersion based on cellulose or pyrrolidone derivative polymers

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ABSTRACT

The objectives of this study were to investigate the effects of hydrophilic polymer on the supersaturation and oral absorption of amorphous atorvastatin calcium. Solid dispersions of atorvastatin calcium were prepared by a supercritical antisolvent (SAS) process. The solid dispersion with polyvinylpyrrolidone vinyl acetate (PVP VA64) achieved a higher degree and extent of supersaturation than the dispersions prepared with water-soluble polymers such as hydroxypropylmethyl cellulose (HPMC) and polyvinylpyrrolidone (PVP K30). The absorption of atorvastatin in rats was markedly increased when atorvastatin was orally administered in a PVP VA64 solid dispersion due to enhanced supersaturation and dissolution properties. Therefore, the oral absorption of atorvastatin calcium increased with the degree of supersaturation of solid dispersions prepared using an SAS process.

1. Introduction

Supersaturatable formulation approaches including solid dispersions have been shown to improve oral absorption of poorly soluble drugs; they are now being widely explored in the pharmaceutical industry [1]. In addition, it has been suggested that amorphous forms play an important role in solubility and dissolution rates. In general, amorphous forms result in higher solubility and a faster dissolution rates [2–4]. Previously, we reported the utility of amorphous nanoparticles in enhancing the supersaturation, dissolution, and absorption properties of atorvastatin [5,6]. In addition, we investigated the effect of a supercritical antisolvent (SAS) process parameters on the particle formation of atorvastatin calcium [5,7]. However, amorphous atorvastatin calcium nanoparticles recrystallized and grew crystals during dissolution due to their amorphous nature [5,6]. The inhibition of crystallization and crystal growth by hydrophilic polymers has been reported previously [8]. Here, we evaluated the use of hydrophilic polymer to inhibit recrystallization of amorphous atorvastatin calcium nanoparticles. In addition, solid dispersions of atorvastatin calcium were prepared using SAS process. The objectives of this study were to investigate the effects of hydrophilic polymer on the supersaturation and oral absorption of atorvastatin calcium. *In vitro* and *in vivo* correlations were also investigated in rats.

2. Materials and methods

2.1. Materials

Atorvastatin calcium trihydrate (Form I) was obtained from Zhejiang Jiangbei Pharmaceutical Co., Ltd (China). Carbon dioxide (CO_2) with 99.9% purity was supplied by Hanmi Gas Co. Ltd. (South Korea). The following excipients were evaluated as hydrophilic polymer: hydroxypropylmethyl cellulose (HPMC 2910, Shin-Etsu chemical Co., Ltd., Japan), polyvinylpyrrolidone (PVP K30, BASF Co. Ltd., Germany) and polyvinylpyrrolidone vinyl acetate (PVP VA64, BASF Co. Ltd., Germany). All organic solvents were of high performance liquid chromatography (HPLC) grade.

2.2. Preparation of solid dispersion

The atorvastatin calcium solid dispersions with HPMC 2910, PVP K30 or PVP VA64 were prepared using an SAS process with a 50:50 w/w% of drug/polymer ratio. The SAS process was performed as previously described [5–7]. First, PVP VA64 and drug were dissolved at 50 mg/mL in ethanol, and HPMC 2910 and drug were dissolved in a 1:1 solution of ethanol and dichloromethane (1:1). The drug solutions were sprayed into the particle precipitation vessel through

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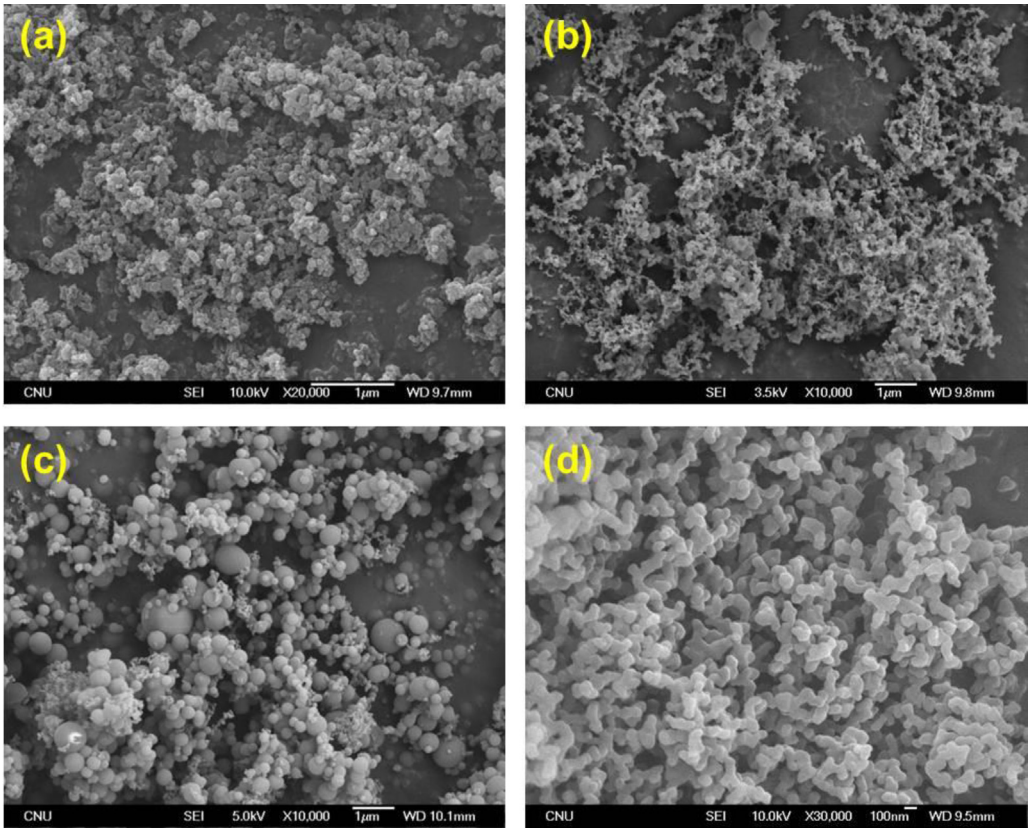

Fig. 1. SEM images of amorphous atorvastatin calcium nanoparticles (a) and solid dispersions prepared by the SAS process: HPMC (b), PVP K30 (c) and PVP VA 64 (d).

a spray nozzle with supercritical CO_2. During particle precipitation, the operating temperature and pressure were fixed at 40 °C and 12 MPa, respectively. The flow rate of the supercritical CO_2 and drug solutions were 45 g/min and 0.5 g/min, respectively.

2.3. Characterization of solid dispersion

The morphology of the particles was observed using scanning electron microscopy (SEM; JSM-7000F, JEOL Ltd., Japan). The particle size and size distribution were measured by dynamic light scattering (ELS-8000, Otsuka Electronics, Japan). The samples were dispersed in mineral oil (Marcol 52, Exxon Mobil Co., USA) and sonicated before measurement. Powder X-ray diffraction patterns were recorded on a Rigaku Powder X-ray diffraction system, Model D/MAX-2200 Ultima/PC (Japan). The specific surface area was determined using the gas adsorption method (ASAP 2010, Micromeritics Instrument Corporation, USA). Supersaturated dissolution tests were performed using a USP rotating paddle apparatus with a VK 7000 dissolution testing station and VK 750d heater/circulator (Vankel, USA). Tests were conducted at 37 °C and 50 rpm in 300 mL of water. Accurately weighed samples containing the equivalent of 300 mg atorvastatin were dispersed in the dissolution medium. Then, 2 mL aliquots were collected at different time intervals and filtered using 0.22-μm nylon syringe filter. The filtered samples were diluted with methanol, and the concentration of atorvastatin was analyzed by HPLC. Powder dissolution studies were performed using the USP paddle method (50 rpm and 37 ± 0.1 °C). Accurately weighted samples containing the equivalent of 10 mg atorvastatin were placed in 900 mL of distilled water. Then, 4 mL aliquots were withdrawn at certain time intervals and filtered using a 0.22 μm nylon syringe filter. Filtered samples were diluted with methanol, and the concentration of atorvastatin was analyzed by HPLC. HPLC analyses of *in vitro* samples of atorvastatin were performed on a Waters™ HPLC system consisting of a pump (Model 600), an auto-sampler (Model 717 plus) and UV detector (Model 486 Tunable Absorbance Detector). A C_{18} analytic column (Xterra, 5 μm, 4.6 mm × 250 mm, Waters) was used at room temperature. The mobile phase was composed of a 60:40 mixture of acetonitrile:50 mM sodium acetate in water, where the pH was adjusted to 4.0 with glacial acetic acid. The injection volume was 20 μL and the eluent flow rate was 1.0 mL/min. The signal was monitored at 245 nm.

2.4. Pharmacokinetics in rats

The bioavailability of the solid dispersions was evaluated in rats. The study was conducted in compliance with the Good Laboratory Practice Regulations, Korea Food and Drug Administration (KFDA2005-79). The study protocol was approved by the ethics committee of Chungnam National University. Male Sprague–Dawley rats weighing 240–260 g (Samtaco Bio Korea Inc., Korea) were divided into four groups of five animals each. After anesthesia with diethyl ether, the femoral artery was cannulated with a 23-gauge polyethylene cannula. After the rats recovered from the anesthesia, gelatin minicapsules (Size 9, Torpac, Fairfield, NJ, USA) filled with amorphous nanoparticles or solid dispersions equivalent to 10 mg/kg of atorvastatin were administered orally to rats using a minicapsule dosing syringe. After administration of the capsules, the rats were immediately given 1 mL of distilled water. Serial blood samples (approximately 350 μL each) were collected from the femoral artery at certain time intervals. The blood samples were placed in heparinized tubes, and the plasma was separated by centrifugation (10,000 rpm, 10 min). The atorvastatin concentrations in plasma samples were determined by LC–MS as reported previously [5,6]. The $AUC_{0\rightarrow 12\,h}$ was calculated using non-compartmental analysis (WinNonlin 2.1; Pharsight