International Journal of Pharmaceutics 519 (2017) 213–219

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Amorphous solid dispersion of cyclosporine A prepared with fine droplet drying process: Physicochemical and pharmacokinetic characterization

Hiroki Suzuki[a], Tatsuru Moritani[b], Tadahiko Morinaga[b], Yoshiki Seto[a], Hideyuki Sato[a], Satomi Onoue[a,*]

[a] Department of Pharmacokinetics and Pharmacodynamics, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan
[b] Functional Material Development Center, Imaging Engine Development Division, RICOH Company, Ltd., 16-1 Honda-machi, Numazu-shi, Shizuoka 410-1458, Japan

ARTICLE INFO

Article history:
Received 8 September 2016
Received in revised form 9 December 2016
Accepted 10 January 2017
Available online 16 January 2017

Keywords:
Amorphous solid dispersion
Cyclosporine A
Dissolution
Fine droplet drying process
Oral absorption

ABSTRACT

The present study aimed to develop an amorphous solid dispersion (ASD) of cyclosporine A (CsA) by a fine droplet drying (FDD) process for improvement in oral absorption of CsA. CsA and hydroxypropyl cellulose-SSL were dissolved in 1,4-dioxane, and the solution was powdered by the FDD process to obtain the ASD formulation of CsA (ASD/CsA). The ASD/CsA was characterized in terms of morphology, particle size distribution, crystallinity, dissolution behavior, physicochemical stability, and pharmacokinetic behavior in rats. The ASD/CsA was obtained in the form of uniform spherical particles, and the span factor was calculated to be ca. 0.4. CsA in the formulation existed in an amorphous state. The ASD/CsA exhibited a higher dissolution behavior of CsA than amorphous CsA, whereas storage of the ASD/CsA under accelerated conditions led to impairment in the dissolution behavior. The constant release of CsA from non-aged ASD/CsA was observed during dissolution testing. After oral administration of CsA samples (10 mg-CsA/kg) in rats, the ASD/CsA showed a high and sustained plasma concentration of CsA as evidenced by a 18-fold increase in the oral bioavailability of CsA compared with amorphous CsA. From these findings, the FDD process might be an efficacious option for the ASD formulation of CsA with enhanced biopharmaceutics properties.

1. Introduction

Advanced high-throughput screening methods have created many biopharmaceutics classification system (BCS) class II drugs with low solubility and high permeability, leading to insufficient oral bioavailability (BA) (Horter and Dressman, 2001; Ku and Dulin, 2012; Takagi et al., 2006). The oral BA of BCS class II drugs can be increased even by a small increase in their dissolution rate (Lobenberg and Amidon, 2000). The dissolution rate of drugs proportionally accelerates with an increase in their surface areas (Horter and Dressman, 2001; Mosharraf and Nystrom, 1995), so the particle size and size distribution of drugs are critical factors determining dissolution behavior (Kawabata et al., 2011; Scholz et al., 2002). Spray drying is a useful technology to obtain fine powders with a high dissolution behavior (Patel et al., 2014; Vandenheuvel et al., 2013). For spray drying, a rotary atomizer, a pressure nozzle, and an ultrasonic nozzle are employed and atomize a fluid material through centrifugal, pressure, and vibration energy, respectively (Sosnik and Seremeta, 2015). When using the rotary atomizer and pressure nozzle, detailed optimization of the process would be needed for strict control of the droplet size (Bittner and Kissel, 1999). The variability of droplet size would cause a relatively wide distribution of the resultant spray-dried powders, resulting in inconsistent dissolution behavior. In contrast, the ultrasonic nozzle produces droplets with a narrow size distribution (Cal and Sollohub, 2010; Gaspar et al., 2014). This

Abbreviations: ASD, amorphous solid dispersion; ASD/CsA, amorphous solid dispersion of cyclosporine A; AUC, area under the curve of blood concentration versus time curve; BA, bioavailability; C_{max}, maximum concentration; CsA, cyclosporine A; CV, coefficient of variation; FDD, fine droplet drying; HPC, hydroxypropyl cellulose; PLM, polarized light microscopy; RH, relative humidity; SEM, scanning electron microscopy; XRPD, X-ray powder diffraction; $T_{1/2}$, half-life; T_{max}, time to maximum concentration.

* Corresponding author.
E-mail address: onoue@u-shizuoka-ken.ac.jp (S. Onoue).

http://dx.doi.org/10.1016/j.ijpharm.2017.01.018
0378-5173/

nozzle uses piezoelectric transducers to generate droplets by vibration of the nozzle tip at a frequency of 20–130 kHz (Dhumal et al., 2009; Klaypradit and Huang, 2008; Legako and Dunford, 2010b; Rodriguez et al., 1999), and variations in the operating conditions lead to precise control of the particle size and density (Singh and Van den Mooter, 2016). However, some problems still remain such as the low throughput and less control of the particle shape (Gaspar et al., 2014; Legako and Dunford, 2010a).

An inkjet technology for printers also utilizes a piezo element as an actuator to generate ink droplets. For the technical development of an inkjet head using a piezo element, a resonance phenomenon of sonic wave has been proposed as a driving force to produce droplets (Norikane et al., 2011). This phenomenon can contribute to a high resonant frequency (>300 kHz). Since the size of atomized droplets is inversely proportional to the vibration energy, the inkjet head enables production of fine droplets with a narrow size distribution compared with conventional ultrasonic nozzles (Broniarz-Press et al., 2015; Taylor and McCallion, 1997). The powderization of droplets generated with an inkjet head may contribute to the preparation of particles with desirable characteristics, such as large effective surface areas, narrow size distribution, and uniform particle shape, possibly producing high and reproducible dissolution behavior of poorly-soluble drugs. Moreover, the inkjet head is a scalable atomizer, leading to high throughput. On the basis of these characteristics, the inkjet head may be capable of overcoming the remaining challenges of the conventional ultrasonic nozzle. In the present study, a new powderization technology employing the inkjet head, defined as the fine droplet drying (FDD) process, was first applied in the formulation development to obtain powder formulations of poorly soluble drugs with favorable dissolution behavior.

The first foray of the FDD process into the pharmaceutical field was to produce amorphous solid dispersion (ASD) of cyclosporine A, a typical model of a BCS class II drug, for improvement in the oral absorption. CsA and hydroxypropyl cellulose (HPC)-SSL were dissolved in an organic solvent, followed by powderization with the FDD process to prepare ASD formulation of CsA (ASD/CsA). The physicochemical properties of ASD/CsA were characterized in terms of morphology, particle size distribution, crystallinity, dissolution behavior, and physicochemical stability. Oral absorption of CsA was also evaluated after administration of ASD/CsA in rats.

2. Materials and methods

2.1. Chemicals

Amorphous CsA was kindly supplied by ILS Inc. (Ibaraki, Japan). In accordance with a previous report, a saturated solution of CsA in acetone was stored at −20 °C, followed by isolation of precipitates from the cold acetone solution to obtain crystalline CsA (Onoue et al., 2010). HPC-SSL, 1,4-dioxane, and ammonium acetate were purchased from Wako Pure Chemical Industries (Osaka, Japan). Acetonitrile (HPLC grade) was bought from Kanto Chemical (Tokyo, Japan). All other reagents were purchased from commercial sources.

2.2. ASD formulation of CsA

In the present study, HPC-SSL was used for an ASD/CsA, and the FDD process using RICOH MH2420 (RICOH, Tokyo, Japan), an inkjet head, was conducted for preparation of the ASD/CsA (Fig. 1). Briefly, CsA (100 mg) and HPC-SSL (1900 mg) were dissolved in 1,4-dioxane. The 1,4-dioxane is a volatile solvent and can completely dissolve both CsA and HPC-SSL, and therefore was employed as a solvent in the present study. The solute concentration was 2% (w/v)

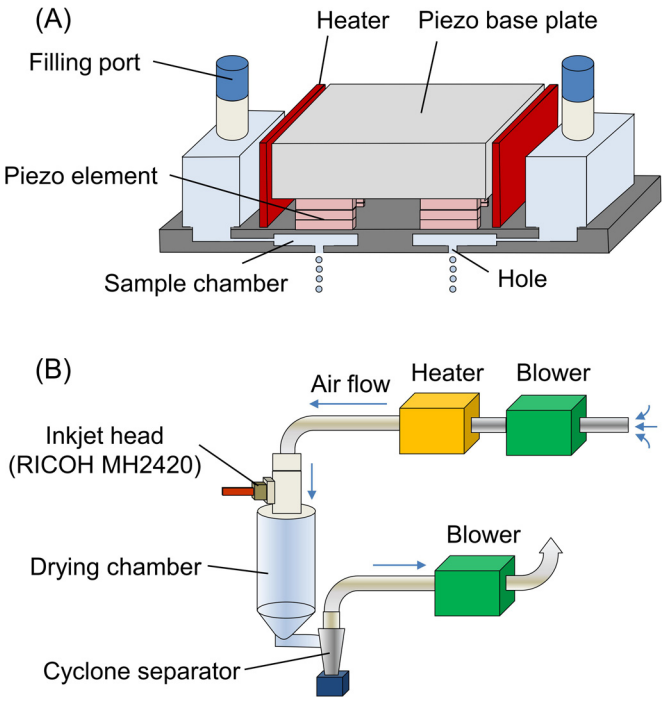

Fig. 1. Schematic illustrations. (A) Structural configuration of RICOH MH2420 and (B) scheme of FDD process.

to stably generate uniform droplets by atomization, and the solution was mixed for 1 h under constant stirring of 1000 rpm using a magnetic stirrer (AS ONE, Osaka, Japan), followed by filtration through a 1-μm filter. The filtered solution was fed at feed rate of 3 g/min into drying chamber using RICOH MH2420 with nozzle hole diameter of 8 μm. The atomized solution was dried with dry air. The dried particles were collected by cyclone separator into collection device. For the FDD process, the typical process parameters were frequency of piezo element, air flow temperature, and air flow rate, and these parameters were 310 kHz, 24 °C, and 50 m^3/h, respectively. Spray-dried ASD formulation of CsA was also prepared as a reference formulation. Spray drying was performed using 2-fluid nozzle as an atomizer and Pulvis Mini Spray GS310 (Yamato Scientific Co., Ltd, Tokyo, Japan) under the following conditions: spray pressure of 0.09 MPa; feeding rate of 3 mL/min; air flow temperature of 45 °C; and air flow rate of 40 m^3/h.

The amount of CsA in the obtained formulation was determined with a Waters Acquity UPLC system (Waters, Milford, Massachusetts), including a binary solvent manager, sample manager, column compartment, and SQD connected with the MassLynx software. Acquity UPLC BEH C 18 column (particle size: 1.7 μm, column size: 2.1 mm × 50 mm; Waters) was used at 65 °C. Acetonitrile (A) and 5 mM ammonium acetate (B) were selected as a mobile phase for the separation of CsA. The flow rate of mobile phase was 0.25 mL/min, and the gradient condition was set as follows; 0–1.0 min, 50% A; 1.0–2.5 min, 80–95% A; 2.5–3.0 min, 95% A; and 3.0-3.5 min, 50% A. Specific m/z 1203 was detected for CsA $[M+H]^+$.

2.3. Surface morphology

The surface morphology of amorphous CsA and ASD/CsA was visualized with scanning electron microscopy (SEM), Miniscope® TM3030 (Hitachi, Tokyo, Japan). CsA samples were fixed on an aluminum sample holder with double-sided carbon tape, and