A Combination of a Coaxial Electrospray Deposition and a Post-Heating Process as a Technique That Improves Oral Bioavailability of Poorly Water-Soluble Drugs

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ABSTRACT SUMMARY

A coaxial electrospray technique was applied to a poorly water-soluble drug, fenofibrate (FEN), to increase its oral bioavailability. Significant improvement of dissolution behaviors of FEN was observed for an electrosprayed formulation, presumably due to a decrease in particle size and an increase in dispersion efficiency. Further improvement was expected through a decrease in crystallinity; however, complete amorphization was not possible only by the electrospray technique. The electrosprayed formulation was successively heated at temperature above the melting point of FEN to transform FEN in particles completely into an amorphous form. This instantaneous post-heating process resulted in a 2-fold increase in oral bioavailability of FEN with statistical significance in rats.

INTRODUCTION

Amorphization is one of important formulation technologies that improve oral bioavailability of poorly water-soluble drugs. However, commercial products to which this technology is applied are limited, due to their low and unpredictable stability. Amorphous formulations often possess special requirements for manufacturing facilities. An increase in the investment for facilities also prevents pharmaceutical industries from employing this technology. Another problem of amorphous formulations is that drugs are usually exposed to high temperature that may cause their chemical degradation.

Electrospray deposition (ESD) is a versatile technique that has been applied to micro/nanofabrication of various materials including pharmaceutical products. In this technology, a high voltage is applied to solution that contains drugs and excipients and then fine droplets are obtained. Its driving force is the coulombic repulsion between ions near the solution surface. Solvent is quickly removed from the droplets and residual solutes accumulate on targets as nano-sized particles. Various benefits for drug dissolution, such as enhanced dissolution rate, are expected for resulting particles, depending on their morphologies and characteristics of excipients. In addition to its applicability to nanofabrication, the ESD is also regarded as an amorphization technique. Thus, this method is expected to improve dissolution behaviors of poorly water-soluble drugs through a couple of mechanism: nanosizing and amorphization.

The notable advantage of the ESD is that it can be operated under ambient temperature and pressure conditions. In our previous studies¹⁻², effects of various solution and processing parameters on particle morphologies were clarified, and it was revealed that oral bioavailability of griseofulvin, which is a typical drug with poor water solubility, was improved through core-shell type amorphous particulate formulations prepared using a coaxial nozzle-equipped ESD. This report describes the usefulness of a combination of the ESD system and a post-heating process as a technique for the improvement of oral bioavailability.

EXPERIMENTAL METHODS

Eudragit L-100 (L-100) was used as an excipient because this enteric coating agent was useful for preparing particles with high dispersion efficiency¹⁻². L-100 and FEN were separately dissolved in ethanol and supplied to the coaxial nozzle (outer solution: L-100, inner solution: FEN). Poly(vinyl pyrrolidone) (PVP) was dissolved in the inner solution as a dispersant, when necessary. Positive and negative voltages (±12.5 kV) were applied to the nozzle and an alumina target, respectively. Their distance was set to 15 cm. The electrospray was conducted at ambient temperature. The humidity was kept at <20%RH by flowing nitrogen gas. Resulting electrosprayed formulations were successively heated at 100°C for 30 sec, when necessary.

Samples obtained before and after the heating process were defined as intact and heated particles, respectively. Instrumental analysis was performed to evaluate the morphology of particles, the crystallinity and the melting point of FEN loaded in particles, and the drug loading. The USP dissolution procedure (paddle method, 100 rpm) was used to evaluate dissolution behaviors of FEN from particles. A simulated intestinal fluid of pH 6.8 was used as a medium and its volume was adjusted to 500 mL.

Each formulation was dispersed in an aqueous methylcellulose solution (0.1 w/v%) at a concentration of 1 mg/mL as a FEN equivalent. The dispersion was administered orally to rats at a volume of 2.0 mL/kg. Blood samples were collected at predetermined time intervals under ether anesthesia. Orally administered FEN is metabolized most completely in the liver during the first-pass metabolism. Since fenofibric acid, which is an active metabolite of FEN, emerges the systemic circulation, its concentration in plasma was analyzed by HPLC. The area under the plasma concentration-time curve (AUC) from 0 to infinity was calculated.

RESULTS AND DISCUSSION

Table 1 shows experimental conditions and characteristics of intact particles prepared through the electrospray technique without the post-heating process.
When concentrations of L-100 and FEN were set to 2% and 4%, respectively, the average crystallinity of particles was 62.5%. PVP addition resulted in a reduction of the crystallinity. The further reduction was observed when a decrease in the flow rate of the inner solution, which lowers FEN loading, was performed. However, the complete amorphization was not attained through optimization of experimental conditions. The volume-average diameter of particles was constantly around 1 μm, irrespective of the conditions.

FEN remained as a crystalline form possibly accelerates re-crystallization of the drug, which results in undesirable recovery of poor water solubility. The electrospray technique was followed by the heating process to attain complete amorphization. The melting point of FEN is 80°C and it is thermally stable during the heating process at temperature above the melting point. It is expected that FEN is obtained as an amorphous form through this melting procedure. The formulation no. 2 which possessed relatively high FEN loading was heated at 100°C for 30 sec. Scanning electron microscopy proved that the particle size was constant before and after the heating process. Complete transformation of FEN loaded in heated particles into the amorphous form was confirmed through analysis by X-ray powder diffraction and differential scanning calorimetry.

Fig. 2 shows dissolution profiles of FEN from its crystalline powders and formulations. FEN crystal was hardly ever dissolved in neutral solution because of its poor water solubility. Significant improvement of FEN dissolution was observed for the ESD formulation. It was presumably due to a decrease in particle size and an increase in dispersion efficiency. However, a part of FEN released from the intact particles appeared to be re-precipitated in the dissolution medium during a 1-hr experiment. The post-heating process allowed the re-precipitation to be completely circumvented. This preferable effect was concomitant with an increase in initial dissolution rate. These improvements of dissolution behaviors probably resulted from the complete amorphization of FEN loaded in the heated particles.

Data of rat experiments are shown in Fig. 3 AUC of fenofibric acid was estimated to be 9557 ± 1971 ng/hr/mL when FEN was administered as a crystalline powder. The ESD-improved dissolution behaviors of FEN probably resulted in an increase in AUC with statistical significance (14572 ± 2954 ng/hr/mL). The further increment in AUC was observed when FEN loaded in particles was completely transformed into the amorphous form through the post-heating process (18755 ± 1723 ng/hr/mL). Mogi et al. reported that average bioavailability of FEN after oral administration of its crystalline form in rats was 64%. Their data indicated that most of FEN was absorbed from the gastrointestinal tract after oral administration of FEN-containing heated particles.

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