Preparation and evaluation of fenofibrate loaded mesoporous silica

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ABSTRACT SUMMARY
The aim of this study was to enhance the bioavailability of a poorly water-soluble drug, fenofibrate, by melt-adsorption method using supercritical CO2.

Fenofibrate was loaded onto Neusilin® UFL2 by melt adsorption using supercritical CO2. For comparison, fenofibrate-loaded Neusilin® UFL2 was prepared by solvent evaporation and hot melt-adsorption methods. The pharmacokinetic profiles were obtained in Sprague Dawley(SD) rats.

Fenofibrate was distributed into the pores of Neusilin® UFL2 and exhibited reduction in crystal formation following adsorption. Compared to raw fenofibrate, fenofibrate from the prepared powders showed significantly increased dissolution rate and bioavailability.

INTRODUCTION
According to the Biopharmaceutics Classification System (BCS), fenofibrate is a Class II drug with low solubility and high permeability. Thus, the dissolution rate of fenofibrate may limit its absorption in the gastrointestinal tract.

Particle size reduction or amorphization of a drug promote rapid dissolution and effective absorption in the body.1,2 However, handling micronized drugs is problematic because extremely small particles tend to agglomerate. To avoid these difficulties, the drug is adsorbed onto a mesoporous carrier.3 The agglomeramation of drug particles is prevented by binding of the drug to the carrier. Neusilin® UFL2 is a fine amorphous powder of magnesium aluminometasilicate that exhibits the structure of a secondary agglomeration particle, which is approximately 5 µm in diameter with high porosity.

However, because of the presence of residual solvent, it is disadvantageous to use toxic solvents. To overcome this problem, supercritical CO2 technology was used in this study.

EXPERIMENTAL METHODS

Supercritical method: The amount of fenofibrate (10 g) was mixed with Neusilin® UFL2 (15 g) and the mixture was placed into a stainless pressure vessel containing a stirrer. After sealing the vessel, supercritical carbon dioxide was pumped inside. The rotation speed was 100 rpm for 1 h at 9MPa and 323.15K to adsorb a melted mixture onto the Neusilin® UFL2. This apparatus is schematized in Figure 1.

Solvent evaporation method: The mount of fenofibrate (400mg) was dissolved in ethanol, and 600 mg of Neusilin® UFL2 were then added to the fenofibrate solution. The suspension was brought to equilibrium while stirring for 12 h, following which ethanol was evaporated at 50°C.

Hot melt adsorption method: The mount of fenofibrate (400mg) was fully mixed with 600 mg of Neusilin® UFL2. The mixture was heated above 90°C to melt the fenofibrate, which was then allowed to cool to room temperature.

Figure 1. Schematic diagram of the experimental apparatus

The prepared fenofibrate formulations were characterized by differential scanning calorimetry(DSC), powder X-ray diffractometry(PXRD), scanning electron microscopy(SEM), and energy-dispersive X-ray spectrometry(EDS). In vitro dissolution and in vivo bioavailability were also investigated.

RESULTS AND DISCUSSION

In crystallinity evaluation, it was observed that when the fenofibrate loaded Neusilin® UFL2 by the supercritical method, both the endothermic peak of DSC and the diffraction peaks of PXRD patterns did not appear (Figure 2). This is attributed to the high diffusivity, low viscosity and noncohesiveness characteristic of the supercritical fluid. In case of solvent evaporation method, the introduction of fenofibrate into the pores was also obturated due to high diffusivity, high velocity and disturbance of the wettability, as well as the surface tension of the organic solvent. Similarly, with the hot melt adsorption method, the introduction of fenofibrate into the pores was also obturated due to high viscosity of molten fenofibrate.

As shown in Figure 3, the raw fenofibrate particles appear as irregular-shaped crystals with broad size distribution. In the EDS patterns of the raw fenofibrate, the chloride peak of fenofibrate can be identified. In the case of raw Neusilin® UFL2, the major elements identified were silicon, magnesium, and aluminum. The SEM photograph of the powders prepared by the
supercritical method revealed no distinct difference in the surface morphologies of the raw Neusilin® UFL2 and SC. In addition, no fenofibrate crystals were observed. However, the EDS patterns of SC revealed small chloride peaks in addition to the large silicon, magnesium, and aluminum peaks, which indicate that the fenofibrate was adsorbed onto the pores of Neusilin® UFL2.

![Figure 2. Powder X-ray diffraction patterns (a) DSC thermograms (b) of raw fenofibrate and prepared powders](image)

Figure 2. Powder X-ray diffraction patterns (a) DSC thermograms (b) of raw fenofibrate and prepared powders

![Figure 3. SEM image and EDS patterns of raw fenofibrate (a), raw Neusilin® UFL2 (b), and prepared powder (SC) (c)](image)

Figure 3. SEM image and EDS patterns of raw fenofibrate (a), raw Neusilin® UFL2 (b), and prepared powder (SC) (c)

The results in Figure 4 show higher dissolution rates from prepared powders. In particular, the SC prepared by using the supercritical method exhibited a faster dissolution rate than the raw fenofibrate and commercial product, with approximately 1.89- and 1.25-fold.

![Figure 4. Dissolution profiles of raw fenofibrate, commercial product (Lipidi Supra®) and prepared powders in 0.025 M SLS](image)

Figure 4. Dissolution profiles of raw fenofibrate, commercial product (Lipidi Supra®) and prepared powders in 0.025 M SLS

The pharmacokinetic profiles after oral administration of raw fenofibrate, commercial product and SC to male SD rats are presented in Figure 5. The prepared powder (SC) exhibited significantly increased AUC$_{0→12h}$ (4.62-fold) and C$_{max}$ (4.52-fold) compared with the raw fenofibrate (P < 0.05). Furthermore, the AUC$_{0→12h}$ and C$_{max}$ of SC were comparable to the commercial product (P > 0.05).

![Figure 5. Serum concentration time-profile of fenofibrate in rats after oral administration of the raw fenofibrate, commercial product (Lipidi Supra®) and prepared powder at a dose equivalent to 50 mg of fenofibrate/kg of body weight](image)

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**CONCLUSION**

In this study, an amorphous fenofibrate formulation was successfully prepared by melt adsorption using supercritical CO2. Fenofibrate adsorbed onto Neusilin® UFL2 exists in an amorphous form and exhibits an enhanced dissolution rate and bioavailability. The melt adsorption method using supercritical CO2 does not require organic solvents and can be applied to improve the bioavailability of other poorly water-soluble drugs that have low melting points.

**REFERENCES**


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