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Original Research Paper

Dissolution improvement of fenofibrate by melting inclusion in mesoporous silica

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ABSTRACT

In this study, using mesoporous silica for the solubility enhancement of poorly water-soluble drug was investigated. Although the incorporating drug into mesoporous silica is generally performed through the solvent method, the new melting method was proposed in the present study. Fenofibrate, a poorly water-soluble drug, was incorporated into mesoporous silica by solvent method and melting method. The obtained samples were observed by SEM and their physicochemical properties were evaluated by PXRD and DSC measurement. The dissolution and supersaturated property were also investigated.

The results from SEM, PXRD and DSC measurement showed that drug could be loaded into pore via the melting method as well as by the solvent method. The drug loaded quantity depended on the pore volume. Drug up to 33% could be incorporated into mesoporous silica and existed in amorphous state. When drug was overloaded or difficulty in incorporation into pore was found, recrystallization of drug occurred at the outer surface of mesoporous silica. From the dissolution test, samples prepared by solvent method and melting method gave the supersaturated drug concentration which sample from melting method showed superior dissolution to the one from solvent method. From this study, drug was efficiently incorporated into mesoporous silica by the melting method which is a simple and solvent-free process, and the aqueous solubility enhancement of poorly water-soluble drug was achieved.

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1. Introduction

Using mesoporous silica has recently gained attention as one of alternative methods to improve the drug solubility. Mesoporous silica is a surfactant template with synthesized meso pore sizes approximately 2–50 nm. Due to its unique structural characteristics, i.e. uniform pore diameter and vast surface area [1,2], mesoporous silica has been applied to various fields such as separation, catalysis, and synthesis [3–5]. Size and molecular arrangement of drug in the pore of mesoporous silica can be controlled simultaneously with the drug amorphization and size reduction to nano level [6–9]. This will lead to the significant difference in dissolution property compared to the formulation containing bulk crystalline drug.

However, to date the method used to incorporate drug into mesoporous silica is the solvent method where solvent is used and the drying step is required to remove solvent in the final step. This results in the more complicated inclusion process and problems when applied to pharmaceutical production.

The purpose of this study was to establish the simple and effective method for incorporating drug into mesoporous silica. In addition to a conventional solvent method, drug in molten state was included in mesoporous silica by melting method. Fenofibrate was used as a model of poorly water-soluble drug. Several methods have been studied to enhance its poor aqueous solubility such as micronization and solid dispersion [10,11]. Fenofibrate loading into mesoporous silica by solvent method and melting method were investigated at various ratios. Moreover, inclusion drug into the macromolecule used as precursor for mesoporous silica was performed. Molecular state of drug in the prepared samples was evaluated using differential scanning calorimetry and powder X-ray diffractometry. Dissolution of fenofibrate loaded in the mesoporous silica by different methods and their supersaturated condition were studied.

2. Materials and methods

2.1. Materials

Fenofibrate was purchased from Sigma–Aldrich. Its chemical structure is shown in Fig. 1. Mesoporous silica samples were prepared by using Pluronic 123 [$(EO)_{20}(PO)_{70}(EO)_{20}$ triblock copolymer] and sodium silicate solution purchased from Sigma–Aldrich. All other chemicals and solvents were of reagent or HPLC grade and purchased from Kanto Chemicals (Japan).

2.2. Methods

2.2.1. Preparation of mesoporous silica

Mesoporous silica was synthesized by the previous reported method [7–12] using Pluronic 123 as a template. An amount of 4.00 g of Pluronic 123 was added to 120 g of 2.00 N HCl solution and stirred until fully dissolved. Sodium silicate solution (10.2 g) was diluted with 30 g of deionized water. The latter solution was poured into the Pluronic 123 solution while stirring at 35 °C. Then, the solution was kept under static condition at 35 °C for 24 h. The mixture was transferred to a Teflon-lined autoclave and aged at 90 °C for 48 h. The mixture was cooled to room temperature and filtered through a 0.45 μm membrane filter. Subsequently, obtained white powder was washed with deionized water and dried at 45 °C for 60 h. The silica–Pluronic 123 composite sample was referred to as "Pre MPS". The Pre MPS solid was calcined at 550 °C for 8 h to remove the Pluronic 123 template. This synthesized mesoporous silica was called "MPS".

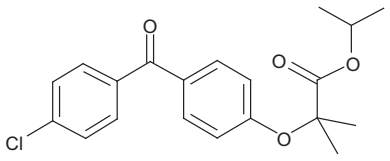

Fig. 1 – Chemical structure of fenofibrate.

2.2.2. Drug loading by solvent method

MPS or Pre MPS sample was soaked into 50 mg/ml of fenofibrate in dichloromethane. The moist powder was stirred using a spatula for pre-drying. Then, dichloromethane was completely evaporated in a water bath at 50 °C. The samples obtained by the solvent method were named as "Solv-MPS (FF: X%)" or "Solv-Pre MPS (FF: X%)". X% represented the weight percent of loaded fenofibrate (FF) in fenofibrate–MPS or fenofibrate–Pre MPS composite.

2.2.3. Drug loading by melting method

MPS or Pre MPS sample was mixed with fenofibrate in a mortar to obtain a physical mixture, PM. PM was transferred to a stainless steel container and heated at 100 °C for 1 h to melt fenofibrate. The samples obtained by the melting method were named as "Melt-MPS (FF: X%)" or "Melt-Pre MPS (FF: X%)". X% represented the weight percent of loaded fenofibrate (FF) in fenofibrate–MPS or fenofibrate–Pre MPS composite.

2.2.4. Scanning electron microscopy (SEM)

The morphology of prepared samples was observed using field emission scanning electron microscopy (JSM-6700F, JEOL Inc.). The samples were fixed on aluminum stabs using double-sided adhesive tape and coated with Au through a sputter-coater. SEM micrographs were obtained at an accelerated voltage of 3 kV.

2.2.5. Powder X-ray diffractometry (PXRD)

Crystallinity of the sample was analyzed using powder X-ray diffractometer (RINT-TTRIII, Rigaku) with Cu Kα radiation source. The sample was applied on a glass plate. The measurement was performed at a voltage of 50 kV and a current of 300 mA. The observed range was from 3° to 40° (2θ) with a step size of 0.02°.

2.2.6. Differential scanning calorimetry (DSC)

Thermal analysis was performed using differential scanning calorimetry (DSC Q1000, TA instrument). Approximately 2 mg of sample was weighed in a crimped aluminum pan and measured under nitrogen purge with a heating rate of 10 °C/min over the temperature range of −50 °C–200 °C.

2.2.7. Dissolution test

Dissolution test was carried out by using a USP apparatus II (DT-810, JASCO) with a paddle speed of 75 rpm at 37 °C. A