International Journal of Pharmaceutics 475 (2014) 364–371

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

# Practical approach to prepare solid dispersion drug product using spherical silicate

Kentaro Nagane [a,b], Susumu Kimura [a], Koji Ukai [a], Noriko Ogawa [b], Hiromitsu Yamamoto [b,*]

[a] Pharmaceutical Science and Technologies, Eisai Co., Ltd., 1 Kawashimatakehaya-machi, Kakamigahara, Gifu 501-6195, Japan
[b] Department of Pharmaceutical Engineering, School of Pharmacy, Aichi Gakuin University, 1-100 Kusumoto, Chikusaku, Nagoya, Aichi 464-8650, Japan

ARTICLE INFO

*Article history:*
Received 10 June 2014
Received in revised form 27 July 2014
Accepted 12 August 2014
Available online 15 August 2014

*Keywords:*
Solid dispersion
Microbead silicate
Wurster-type fluidized bed granulator
Ibuprofen
Indomethacin
Phenytoin

ABSTRACT

The purpose of this study is to establish a novel approach for preparing a solid dispersion drug product using spherical silicate by a Wurster-type fluidized bed granulator. The spherical silicate used in this study has porous structure and ideal particle size for loading by a Wurster-type fluidized bed granulator. As model drugs, ibuprofen (IBU), indomethacin (IMC), and phenytoin (PNT) were used and the proposed approach was applied to prepare amorphous drug. All drugs could be loaded on the spherical silicate in an amorphous state. On the other hand, spray drying of spherical silicate suspended in IBU solution was conducted to prepare amorphous product of IBU as a reference; however, complete amorphization was not achieved. Dissolution profiles of each drug after loading on spherical silicate by a Wurster-type fluidized bed granulator were evaluated, and dramatic improvement of dissolution was observed compared with those of crystalline drug. In the proposed approach, specific surface area and particle size of spherical silicate were determined as a key factors to contribute to high yield of amorphous product.


## 1. Introduction

Currently, the development of combinatory chemistry and high throughput screening has contributed to the discovery of numerous poorly water-soluble drugs as candidates for new chemical entities (NCEs) (Lipinski et al., 2001). Some reports show that almost 70% of NCEs are categorized as water-insoluble (Ku and Dulin, 2012). Moreover, 40% of commercialized drugs with immediate release profiles have solubilities below 100 μg/mL and are defined as practically insoluble (Takagi et al., 2006). Furthermore, 12% of the drugs launched from 1995 to 2002 are classified as Class II according to the biopharmaceutical classification system (BCS) and 46% of them are classified as Class IV, which indicates that improving their dissolution profiles is one of the key factors for successful development (Stegemann et al., 2007).

To improve the dissolution of poorly water-soluble drugs, emulsification systems including the self-emulsifying drug delivery system (SEDDS) (Nanjwade et al., 2011), self-microemulsification drug delivery system (SMEDDS) (Spernath and Aserin, 2006), or self-nanoemulsifying drug delivery system (SNEDDS) (Khan et al., 2012) have all been thoroughly investigated, and nano-crystalline technologies such as nanocrystallization (Sinha et al., 2013) or nano-milling (Van Eerdenbrugh et al., 2008) have also been developed. Recently, solid dispersion technology with polymers by spray drying (Paudel et al., 2013) and hot-melt extrusion (Shah et al., 2013) have improved dramatically, resulting in the launch of a number of products (e.g., Kaletra®, a combination drug of lopinavir with ritonavir (Breitenbach, 2006), or Intelence® (Etravirine) (Weuts et al., 2011)). In addition to those technologies, Zelboraf® (Vemurafenib) (Shah et al., 2012) achieved enhanced solubility for a drug dispersed in a solid state using a novel technology utilizing a precipitation mechanism. Considering the examples described above, it can be concluded that technologies for preparing solid dispersions are currently unavoidable for the pharmaceutical development of NCEs (Smithey and Taylor, 2013).

Silica gel is a well-known material that can provide solid dispersion by immobilizing a drug in its mesopores (Takeuchi et al., 2005a). This immobilization is mediated by the interaction between the drug and silanol residue of the silicate via hydrogen bonding; however, most of the current technologies use micronized silica gel powder such as Sylysia® for spray drying (Takeuchi et al., 2005b) or hot-melt extrusion (Wang et al., 2006). While mesoporous silicate is already being used to prepare solid dispersions, it is manufactured using a classical solvent-evaporation method

*Abbreviations:* IBUI, buprofen; IMC, indomethacin; MBS, microbead silicate; PNT, phenytoin.

* Corresponding author. Tel.: +81 52 757 6770; fax: +81 52 757 6799.
*E-mail address:* hiromitu@dpc.agu.ac.jp (H. Yamamoto).

http://dx.doi.org/10.1016/j.ijpharm.2014.08.016
0378-5173/

**Table 1**
Physical properties of MBS provided by the suppliers.

| | Particle size | Mean particle size ($D_{50}$)[a] | Mesopore diameter | Specific surface area[a] |
|---|---|---|---|---|
| MBS | | | | |
| MB5D 100–200 | 75–150 μm | 92 μm | 10 nm | 349 $m^2/g$ |
| MB3A 100–200 | 75–150 μm | 99 μm | 2.5 nm | 772 $m^2/g$ |
| MB300 100–200 | 75–150 μm | 101 μm | 30 nm | 141 $m^2/g$ |
| MB5D 45–75 | 45–75 μm | 57 μm | 10 nm | 316 $m^2/g$ |
| MB5D 75–500 | 75–500 μm | 229 μm | 10 nm | N.D. |
| SYLOSPHERE® | | | | |
| C-1510 | N.D. | 9 μm | N.D. | 543 $m^2/g$ |

[a] The value determined by the authors.

(Mellaerts et al., 2008). Furthermore, while there are many reports in which silicate is used to produce solid dispersion, only a few reports regarding the methodology are available.

In this study, a novel approach for preparing a solid dispersion drug product using spherical silicate was established. In this approach, a Wurster-type fluidized bed granulator was used, originally applied for the layering, coating, or granulation process. One of the biggest advantages of this combination, i.e., the spherical silicate and Wurster-type fluidized bed granulator, is that it has the potential to prepare a drug product with a spherical flowable shape that is easy to handle in the subsequent processes like encapsulation or compaction into tablets. The other advantage is that the proposed method can easily adjust the amount of loaded drug by changing the amount of sprayed solution, and this can contribute to a rapid supply of drug products with different strength to markets. In addition, this study proved that the method can be applied to many types of drugs, implying its potential to be used widely in pharmaceutical development.

## 2. Materials and methods

### 2.1. Materials

Spherical microbead silicate (MBS) was obtained from Fuji Silysia Chemical Ltd. (Aichi, Japan), and the grade mainly used in this report is MB5D 100–200. Ibuprofen (IBU), phenytoin (PNT), and indomethacin (IMC) were purchased from Yonezawa Hamari Chemicals Co., Ltd. (Yamagata, Japan), Katwijk Chemie B.V. (Katwijk, Netherlands), and Kongo Yakuhin Co., Ltd. (Toyama, Japan), respectively. Ethanol dehydrate was purchased from Kanto Chemical Co., Ltd. (Tokyo, Japan).

### 2.2. Preparation of IBU loaded MBS by Wurster-type fluidized bed granulator

MBS of the grade MB5D 100–200 was placed in a Wurster-type fluidized bed granulator (MP-01, Powrex Co., Ltd., Hyogo, Japan). 40 g of IBU was dissolved in 800 g of ethanol dehydrate at a concentration of 4.8 wt% and then sprayed onto 200 g of fluidized MBS. IBU loading was carried out under the following conditions: inlet temperature, 25 °C; air rate, 0.5 $m^3$/min; feed rate, 5 g/min; sprayed air rate, 50 L/min.

After the solution was sprayed completely, MBS loaded with IBU was collected and vacuum dried at 40 °C for at least 12 h to remove residual ethanol from the beads.

### 2.3. Preparation of other drug-loaded MBS by Wurster-type fluidized bed granulator

IMC or PNT was loaded on MBS of the grade MB5D 100–200 under the same conditions used for IBU loading, except for the amount of the drug dissolved in ethanol (i.e., IMC: 2.4 wt% and PNT: 1.2 wt%).

### 2.4. Preparation of IBU-loaded MBS by spray drying

To compare the proposed method with a conventional method generally applied, IBU was also loaded onto MBS of the grade MB5D 100–200 by spray drying. In a method similar to the Wurster method, 4 g of IBU was dissolved and 20 g of MBS was suspended in 80 g of ethanol dehydrate. Then, the suspension was sprayed and dried in a spray drier (B-290, BÜCHI Labortechnik AG, Flawil, Switzerland). The operating conditions are as follows: the inlet air temperature was adjusted to 65 °C, the outlet air temperature was maintained at around 40 °C, and the sprayed solution was supplied at a rate of 5 g/min. The spray-dried powder was collected and vacuum dried overnight at 40 °C to remove the residual solvent in the beads.

### 2.5. Morphology and particle size distribution

The morphologies of the intact MBS and drug-loaded MBS were observed using a scanning electron microscope (SEM, VE-7800, Keyence Co., Ltd., Osaka, Japan).

Particle size distribution (PSD) of intact MBS dispersed in dried air at 0.1 MPa was measured by a diffractometer equipped with a pressurized dispersing unit (Aerotrac SPR model 7140, NIKKISO Co., Ltd., Tokyo, Japan).

### 2.6. Specific surface area calculated by nitrogen absorption

Nitrogen adsorption isotherms were obtained using the surface area and pore size analyzer (SA 3100, Beckman Coulter Inc., CA, US).

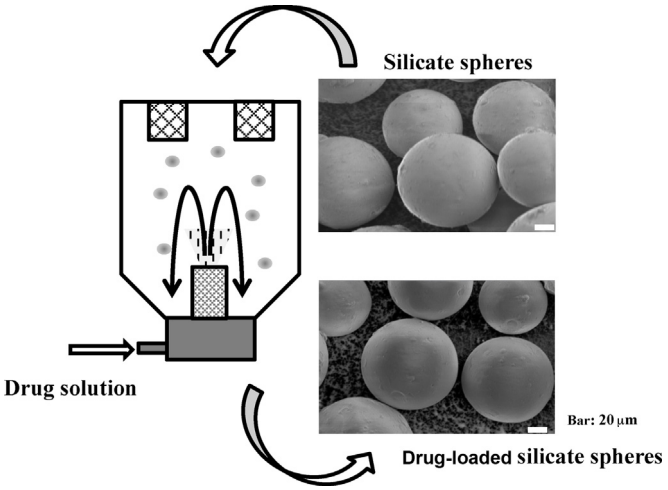


**Fig. 1.** Schematic diagram for the proposed method to prepare amorphous drug-loaded MBS.