# Preparation and Characterization of Sealed Heated Mixture of Ethenzamide and Porous Calcium Silicate

Takehisa HANAWA,* Rieko IKOMA, Atsushi WATANABE, Masato HIDAKA, and Masayasu SUGIHARA

*Pharmaceutical Department, Tokyo Women's Medical College, Kawada-cho, Shinjuku-ku, Tokyo 162, Japan.*

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**A sealed heated mixture of ethenzamide (EZ) and porous calcium silicate (Florite®RE: FR) was prepared by heating the physical mixture in a sealed container. No diffraction peaks due to EZ crystals were observed in the powder X-ray diffraction pattern of the sealed heated mixture (FR : EZ = 9 : 1) nor was an endothermic peak observed on the differential scanning calorimetric measurement of the sealed heated mixture (FR : EZ = 9 : 1), indicating the amorphization of the EZ crystals caused by heating in a sealed container. The sealed heated mixture with FR showed a greater dissolution rate than EZ crystals or the sealed heated mixture with nonporous calcium silicate (CS). The sealed heating method using porous FR thus provides a promising way of amorphizing EZ crystals without using any solvents and of improving the dissolution rate of EZ.**

**Key words** porous calcium silicate; ethenzamide; sealed heating; amorphous; dissolution

The dissolution rate of poorly water soluble medicinals depends upon the effective surface area and the energy state of its crystals. The amorphous state of medicinals is known to exhibit a much higher dissolution rate than the crystalline state.[1] It has been reported that some adsorbents[2,3] and porous powders[4,5] can transform the medicinal crystals to the amorphous state during storage at moderate temperatures.

Florite® RE (FR) is a calcium silicate with interesting properties because of its porous structure[6-8]; it has been used as a support material for controlled drug release.[9,10] We reported earlier that the grinding of FR and acetaminophen crystals together brought about amorphization and an improvement in the dissolution rate of acetaminophen compared to the crystals.[11] The advantage of the co-grinding method was to prepare the amorphous state of medicinal crystals without using any solvents. However, in the ground mixture of FR and acetaminophen, though the crystallinity of the acetaminophen crystals completely disappeared, the specific surface area of FR also was significantly decreased by the grinding and the unique porous feature of FR was missing. Nakai *et al.* demonstrated that a sealed heating method was useful for obtaining the cyclodextrin inclusion complex without using any solvents. They showed that the cyclodextrin inclusion complex could be prepared by heating a physical mixture of sublimable compounds of benzoic acid, salicylic acid or *p*-hydroxybenzoic acid esters with cyclodextrins such as α-, β- or heptakis (2,6-di-*O*-methyl)-β-cyclodextrin in a sealed container.[12] The sealed heating, which is distinct from the co-grinding, retained the porous structure when FR and an organic compound were used as the materials.

In this study, we attempted the sealed heating of ethenzamide (EZ) with FR to obtain the amorphous state of EZ. The physicochemical properties of the sealed heated (SH) mixture were investigated using differential scanning calorimetry (DSC), Fourier transform infrared (FT-IR) spectroscopy, and X-ray diffractometry. Furthermore, the effects of porous and nonporous features of the surface were compared using a nonporous calcium silicate (CS) as a reference material.

## Experimental

**Materials** FR was generously supplied by Tokuyama Co., Ltd. (Yamaguchi, Japan). CS was purchased from Kanto Chemical Co. Inc. (Tokyo, Japan). FR and CS were sieved through screens (149 μm) and used after drying under a vacuum at 150 °C for 6 h. EZ was of reagent grade and used without further purification.

**Heating in a Sealed Container** A physical mixture of EZ with FR or CS was prepared at definite weight ratios (FR : EZ = 9 : 1, 7 : 3, 5 : 5) by simple blending with mortar and pestle. The physical mixture (300 mg) was sealed in a 2 ml glass ampule, and was then heated at 120 °C for 6 h in an oven (Shimadzu GC-7AG, Kyoto, Japan). We called this treatment the "SH treatment."

**X-Ray Diffractometry** X-Ray diffraction patterns for the powdered samples were determined using a Rigakudenki 2027 diffractometer (Tokyo, Japan) under the following conditions; target Cu, filter Ni,

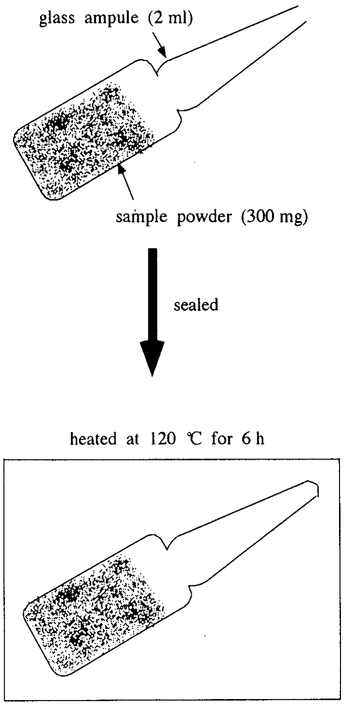

Fig. 1. Schematic View of the Procedure of Sealed Heating Method

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* To whom correspondence should be addressed.

voltage 30 kV, current 5 mA, count range 2000 cps and scanning speed 4°/min.

**IR Absorption Spectroscopy** IR absorption spectroscopy was completed with a Nicolet FT-IR spectrophotometer 5ZDX (WI, U.S.A.) using the Nujol method.

**Thermal Analysis** DSC measurements of the samples were taken with a Du Pont TA9900 thermal analysis system under a stream of nitrogen gas using a sample of about 2.0 mg at a heating rate of 10 °C/min. A liquid sample pan was used.

**Dissolution Study** The dissolution behaviors of the EZ from the mixtures were investigated with the JP12 paddle method (paddle rotating speed: 100 rpm) at 37.0 ± 0.5 °C. Five hundred milliliters of distilled water was used as the test fluid. Varied weight of the mixture which corresponded to 50 mg of EZ was added to each test fluid for the dissolution study. Aliquots (5.0 ml) of the solution were withdrawn and filtered through 0.45 μm membrane at appropriate time intervals. The concentration of EZ was measured spectrophotometrically (Shimadzu UV240, Kyoto, Japan) at 233 nm. The percent released was calculated on the basis of the theoretical value of EZ loaded.

**Microscopic Study** A microscope (Nikon S-ke II) equipped with a polarizing plate was used to evaluate the mixing state.

## Results and Discussion

**Physicochemical Properties of the SH Mixture of FR and EZ** Figure 2 shows the changes in the X-ray diffraction patterns for the physical or SH mixtures of FR and EZ containing 10, 30 and 50% EZ. The diffraction patterns of the physical mixtures show the diffraction peaks due to EZ crystals at $2\theta = 14.0$, 18.0 and 25.0°. After heating at 120 °C for 6 h, these X-ray diffraction peaks were still observed in the SH mixtures containing 30 and 50% EZ. In contrast, for the SH mixture containing 10% EZ, the peaks due to EZ crystals disappeared. (Fig. 2f) The microscopic observations are shown in Fig. 3. In the microphotograph of the physical mixture, EZ crystals were observed as polarized flakes, whereas in the SH mixture containing 10% EZ, EZ crystals were no longer detectable.

Figure 4 shows the DSC curves of the mixtures containing 10, 30 and 50% EZ before and after the SH

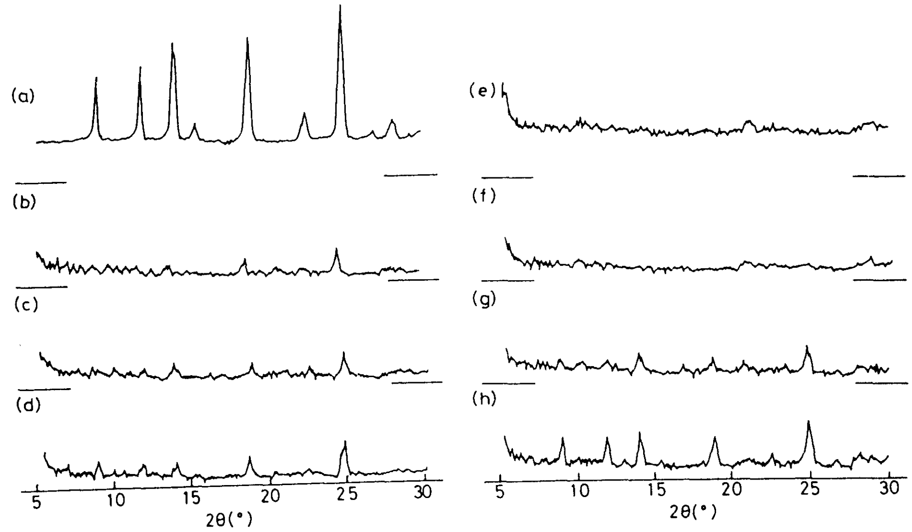

Fig. 2. X-Ray Diffraction Patterns of Physical and SH Mixtures of FR and EZ

(a) EZ crystals, (b) physical mixture of FR and EZ (FR : EZ = 9 : 1), (c) physical mixture of FR and EZ (FR : EZ = 7 : 3), (d) physical mixture of FR and EZ (FR : EZ = 5 : 5), (e) Florite® RE, (f) SH mixture of (b), (g) SH mixture of (c), (h) SH mixture of (d).

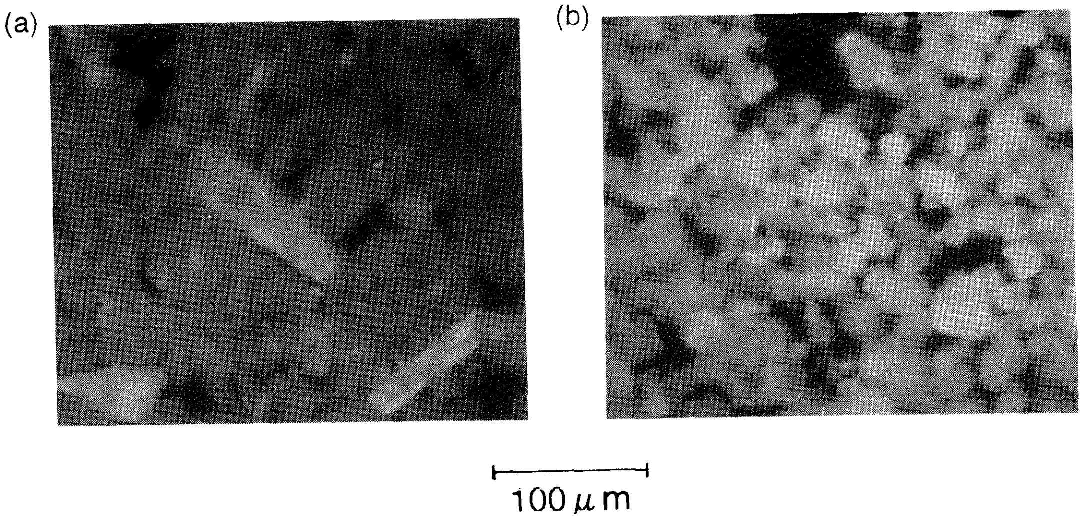

Fig. 3. Polarized Micrographs of Physical and SH Mixtures of FR and EZ

(a) Physical mixture of FR and EZ (FR : EZ = 9 : 1), (b) SH mixture of (a).

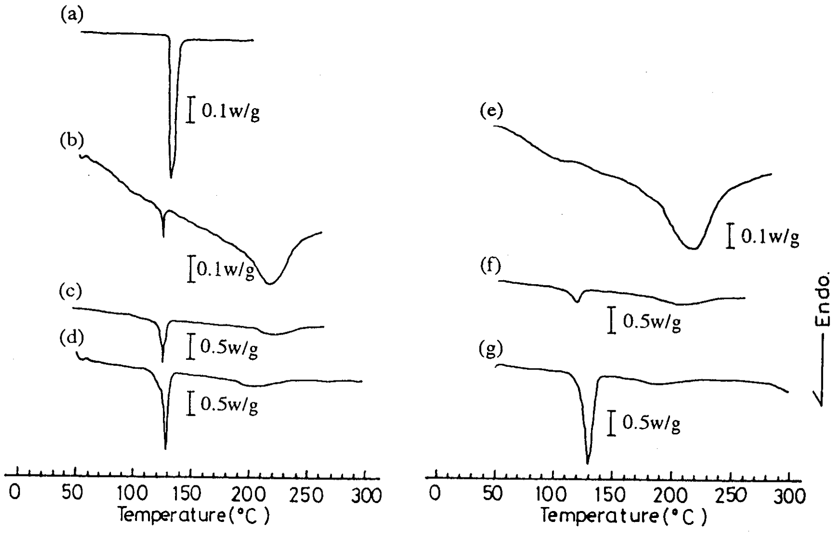

Fig. 4. DSC Curves of Physical and SH Mixtures of FR and EZ

(a) EZ crystals, (b) physical mixture of FR and EZ (FR : EZ = 9 : 1), (c) physical mixture of FR and EZ (FR : EZ = 7 : 3), (d) physical mixture of FR and EZ (FR : EZ = 5 : 5), (e) SH mixture of (b), (f) SH mixture of (c), (g) SH mixture of (d).

treatment. On the DSC curves of the physical mixtures, an endothermic peak due to the melting of EZ crystals was seen at 133.0 °C. (Fig. 4b, c, d) After SH treatment at 120 °C for 6 h, an endothermic peak was still observed in the SH mixtures of 30 and 50% EZ; however, in the SH mixture containing 10% EZ, the endothermic peak had disappeared. (Fig. 4e) From the X-ray diffraction, microscopic and DSC studies of the SH mixture containing 10% EZ, the EZ crystals are believed to be in an amorphous state in the mixture. Konno *et al.*[2,3] also demonstrated that the vapor pressure of the drug was an indication by which the propensity for a crystallinity change of a solid drug in a mixture with an adsorbent could be predicted. In this study, because EZ was sublimable at 105 °C,[13] the amorphization of EZ seems attributable to the adsorption of EZ molecules into the FR particles through a gaseous phase during heating.

To investigate the molecular states of EZ in the SH mixture, IR measurement was performed on the 10% EZ mixture. Figure 5a shows the IR spectrum of EZ crystals by Nujol method. The carbonyl stretching vibration band of EZ was observed at 1628 cm$^{-1}$. In the physical mixture with FR, this peak was shifted to a higher frequency of 1639 cm$^{-1}$ (Fig. 5b), although no further peak shift was observed in the SH mixture. Calcium oxide and silicon oxide, which are constituents of FR, were mixed with EZ and heated in a sealed container at 120 °C for 6 h. In the physical mixture of silicon oxide and EZ, the peak was shifted to higher frequency, while no further peak shift was observed after SH treatment. (Fig. 5d, e) In the mixture with calcium oxide, however, no peak shift was observed in either physical or SH mixture. From these results, the peak shift observed for the physical mixture of FR and EZ seems to be due to hydrogen bonding between the silanol groups which existed on the FR surface and the carbonyl groups of EZ molecules. In SH mixtures, EZ molecules would be adsorbed physically onto the surface of FR during SH treatment.

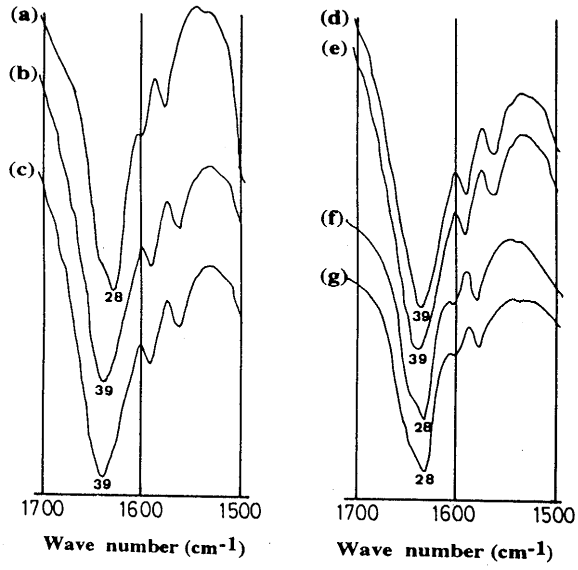

Fig. 5. IR Spectra of Physical and SH Mixtures of EZ and Various Supports

(a) EZ crystals, (b) physical mixture of FR and EZ (FR : EZ = 9 : 1), (c) SH mixture of FR and EZ, (d) physical mixture of silicone dioxide and EZ ($SiO_2$ : EZ = 9 : 1), (e) SH mixture of $SiO_2$ and EZ, (f) physical mixture of calcium oxide and EZ (CaO : EZ = 9 : 1), (g) SH mixture of CaO and EZ.

**Release Behavior of EZ from the SH Mixture with FR** Figure 6a shows the release profiles of EZ from the mixture of FR and EZ before and after the SH treatment. The data are the average of three measurements. No remarkable differences between the physical mixture containing 10% EZ and the EZ crystals in the EZ release profiles were observed, while the release rate from the SH mixture was significantly greater than the others, and the released amount of EZ during the initial 5 min was approximately twice that from the physical mixture. Figure 6b shows the release profiles of EZ from the SH mixtures containing various amounts of EZ. The release rate of EZ from the SH mixture was decreased with increase in the EZ content. This was explained by presuming the existence of an excess amount of EZ crystals, which were

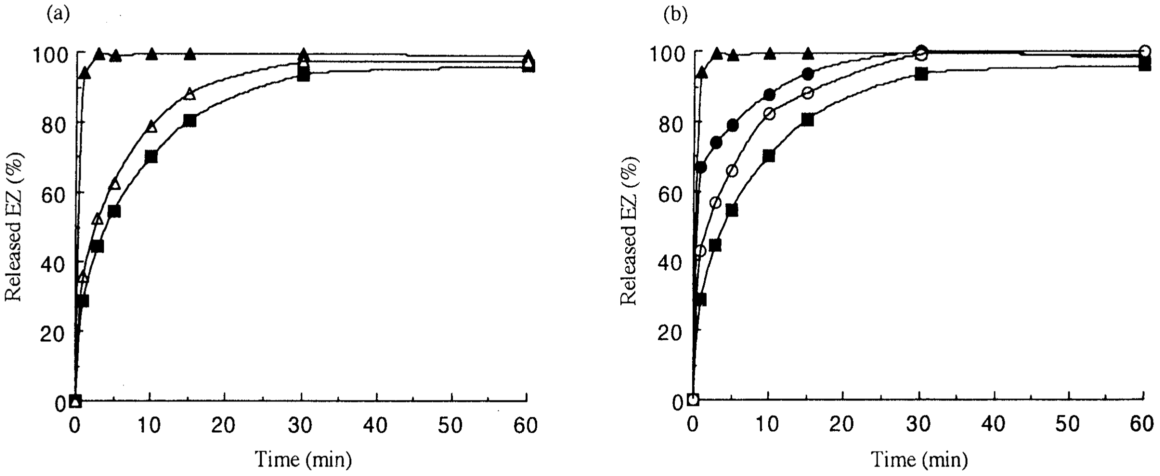

Fig. 6. Release Profiles of EZ from Mixtures of FR and EZ

(a) Release profiles of EZ from mixtures of FR and EZ before and after sealed heating. ■, EZ crystals; △, physical mixture of FR and EZ (FR : EZ=9 : 1); ▲, SH mixture (FR : EZ=9 : 1). (b) Release profiles of EZ from the SH mixtures of FR and EZ prepared with various mixing weight ratios. ■, EZ crystals; ▲, SH mixture (FR : EZ=9 : 1); ●, SH mixture (FR : EZ=7 : 3); ○, SH mixture (FR : EZ=5 : 5).

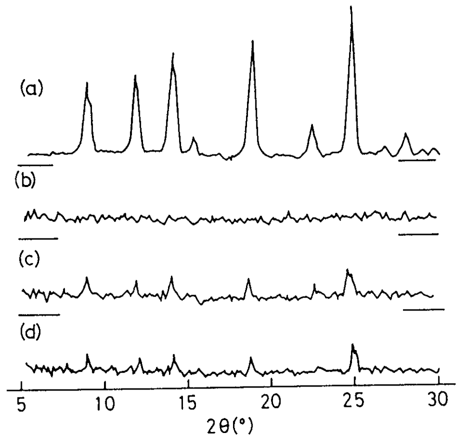

Fig. 7. X-Ray Diffraction Patterns of Physical and SH Mixtures of CS and EZ

(a) EZ crystals, (b) CS, (c) physical mixture of CS and EZ (CS : EZ=9 : 1), (d) SH mixture of CS and EZ.

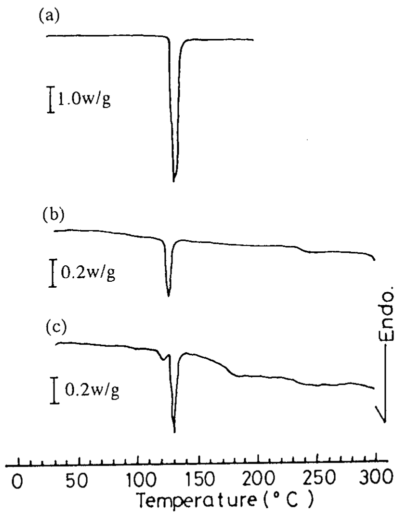

Fig. 8. DSC Curves of Physical and SH Mixtures of CS and EZ

(a) EZ crystals, (b) physical mixture of CS and EZ (CS : EZ=9 : 1, w/w), (c) SH mixture of CS and EZ.

not amorphized during the SH treatment.

**Physicochemical Properties of the SH Mixtures of CS and EZ** CS having nonporous features was used as a reference support. The specific surface area of CS was determined as 27 $m^2/g$ by $N_2$ gas adsorption method, which was about one-fourth of FR (120 $m^2/g$). Figure 7 shows the X-ray diffraction patterns of the mixtures of CS and EZ (CS : EZ=9 : 1). In that of the physical mixture, the diffraction peaks due to EZ crystals were observed at $2\theta=14.0$, 18.0 and 25.0°; after the SH treatment, these peaks were still observed. Furthermore, the microscopic study showed that the polarized light due to the EZ crystals could still be seen in the SH mixture (data not shown). Figure 8 shows the DSC curves of the mixture of CS and EZ (CS : EZ=9 : 1) before and after the SH treatment. The endothermic peak due to the fusion of EZ crystals was observed at 133 °C in both curves. However, on the DSC curve of the SH mixture, a small endothermic peak was also observed at 119 °C. Though this could not be confirmed in the X-ray diffraction pattern, vanishingly small part of EZ crystals seems to change during SH treatment, and another endothermic peak was seen at 119 °C which is below the melting point of EZ crystals.

X-Ray diffraction, microscopic and DSC studies showed that only a vanishingly small part of EZ crystals were amorphized on the surface of the CS during the SH treatment.

The effect of the porous structure of FR on the EZ release behavior was determined by preparing a SH mixture of nonporous CS and EZ, and a dissolution test was carried out. Figure 9 shows the release profiles of EZ from the SH mixture with FR or CS : EZ release rate from the mixture with FR was greater than that from the SH mixture with CS. As an amorphization of EZ in the SH mixture did not take place on the surface of the CS by SH treatment, release retardation of EZ can be attributed to the existence of crystalline EZ on the surface of the CS particles. The porous feature of FR seems to play an important role in the amorphization of EZ crystals during the SH treatment and to improve EZ dissolution.

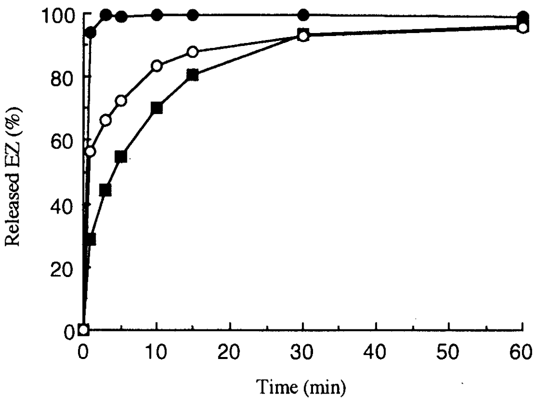

Fig. 9. Release Profiles of EZ from the SH Mixtures of FR–EZ System and CS–EZ System

■, EZ crystals; ●, SH mixture (FR : EZ = 9 : 1); ○, SH mixture (CS : EZ = 9 : 1).

In conclusion, EZ crystals could be amorphized by heating with FR in a sealed container. A comparison with CS, which has no porous feature, found that the porous surface feature of FR was one of the significant characteristics needed for the amorphization of these crystals. Furthermore, the SH method using FR should be able to support the EZ molecules in an amorphous state and to improve EZ dissolution. As another method to adsorb a drug into porous powder, we tried the evaporation method.[14] Though a drug can be adsorbed using some organic solvents, the technique does involve problems of environmental pollution and toxicity of residual organic solvent.[15,16] These are not encountered using the new and effective SH method described here to adsorb drugs on a porous powder, as it is very simple and does not involve a dissolution process.

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