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Solid dispersion of spironolactone with porous silica prepared by the solvent method

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Solid dispersions of spironolactone (SPI) with porous silica (Sylysia 730 and Sylysia 350) were prepared by the solvent method. The physicochemical properties of the prepared solid dispersions were evaluated by powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and atomic force microscopy (AFM). In the SEM study, no differences in the surface condition between Sylysia 350 and the solid dispersion of a Sylysia 350 : SPI system in a weight ratio of 1 : 1 were observed. However, AFM phase images showed that the surface of the solid dispersion of the Sylysia 350 : SPI system (weight ratio of 1 : 1) was rather smooth due to the adsorption of SPI as compared with that of a Sylysia 350 intact. The results of PXRD and DSC data in the solid dispersion of the Sylysia 350 : SPI system (weight ratio of 1 : 1) indicated that the molecular state of the adsorbed SPI changed from crystalline to amorphous. Although the decrease in the SPI concentration increased with the amorphous fraction in the solid dispersion, the diffraction peaks due to SPI crystals still remained in the solid dispersion of a Sylysia 730 : SPI system (weight ratio of 1 : 1), indicating that the mean pore diameter and specific surface area of an additive are some of the important factors for the amorphization of SPI crystals. The dissolution property of the SPI from the solid dispersions was remarkably improved in comparison with that of SPI crystals. The dissolution rate of the SPI from the solid dispersions with Sylysia 350 was faster than that of the SPI from the solid dispersions with Sylysia 730. The difference in the dissolution properties of SPI from both the solid dispersions was attributed to the difference in the molecular state of the SPI in both the solid dispersions. In the stability test, the amorphous state of the SPI in the solid dispersion of the Sylysia 350 : SPI system (weight ratio of 1 : 1) was maintained for 2 weeks at 25 °C and 0% RH, while the amorphous SPI without Sylysia 350 crystallized under the same conditions.

1. Introduction

Spironolactone (SPI), a synthetic steroid lactone that shows specific competitive antagonism to the action of aldosterone and other mineralocorticoids, is used for the treatment of congestive heart failure, hepatic ascites, primary aldosteronism, and essential hypertension. SPI has low bioavailability due to its slow-dissolution property.

The improvement in the dissolution of poorly water soluble drugs is important to enhance their bioavailability for oral dosage forms. Several pharmaceutical technologies were used to improve the dissolution of drugs. Amorphization is one of the useful techniques that have been commonly used for the enhancement of solubility. The amorphous state of drugs can be obtained by several methods such as simple grinding (Ohta et al. 2000), grinding with additives (Yamamoto et al. 1976), spray-drying (Ueno et al. 1998), complexation with cyclodextrins (Yamamoto et al. 1994), and mixing with porous materials (Okonogi et al. 1999).

Porous materials have a great capacity to adsorb organic compounds due to their huge specific surface area and porous structure. Controlled pore glass, porous crystalline cellulose (Oguchi et al. 1997), and zeolite (Ali et al. 1992) are examples of porous materials and have been utilized for pharmaceuticals. It has been reported that the physicochemical properties of crystalline drugs formed by mixing with porous materials changed by entrapping on the porous materials (Tozuka et al. 2005a; Tozuka et al. 2005b).

Porous silica is one of the porous materials that have many silanol groups on their surfaces and is used as a pharmaceutical excipient. Several grades of porous silica having different properties such as particle size, pore volume, pore size, and specific surface area are commercialized. Therefore, porous silica is expected to be applied to the carrier material for the preparation of solid dispersions. Takeuchi et al. (2005a, b) reported that the solid dispersion of silica could improve the dissolution properties of indomethacin and tolbutamide.

Atomic force microscopy (AFM) has become well established in pharmaceutical fields. In recent years, AFM measurements were used for the estimation of the difference in

the microstructure of pharmaceutical crystals (Moribe et al. 2005), analysis of the adhesive properties of drug particles in aerosol or dry powder inhalers (Paulus et al. 2003), and tablet surface characterization (Eve et al. 2002). However, there is no report that the surface microstructures of the solid dispersion of porous additives with pharmaceutical drugs were estimated by AFM.

In this study, we prepared solid dispersions of SPI with porous silica and investigated the physicochemical properties of SPI and the dissolution behavior of SPI from the solid dispersions. Changes in the molecular state of SPI were investigated by powder X-ray diffractometry (PXRD) and differential scanning calorimetry (DSC). Scanning electron microscopy (SEM) and AFM were used to investigate the surface properties of Sylysia 350 and the solid dispersion of Sylysia with SPI.

2. Investigation, results and discussion

2.1. Formation of solid dispersion of Sylysia 350 and SPI by solvent method

To observe the difference between the surface condition of Sylysia 350 and the solid dispersion of Sylysia with SPI, SEM and AFM measurements were performed. The SEM and AFM phase images of a Sylysia 350 intact and the solid dispersion of the Sylysia 350 : SPI system in a weight ratio of 1 : 1 are shown in Fig. 1.

The SEM images of both samples showed a rough surface due to the porous structure. However, no differences in the surface condition of each sample were observed. In the AFM phase image of the Sylysia 350 intact, many asperities of the surface due to the porous structure were observed. On the other hand, the surface of the solid dispersion of the Sylysia 350 : SPI system in the weight ratio of 1 : 1 was rather smooth. The differences in the AFM phase images between these samples are attributed to the adsorption of SPI molecules onto the pores of Sylysia 350 by the solvent method.

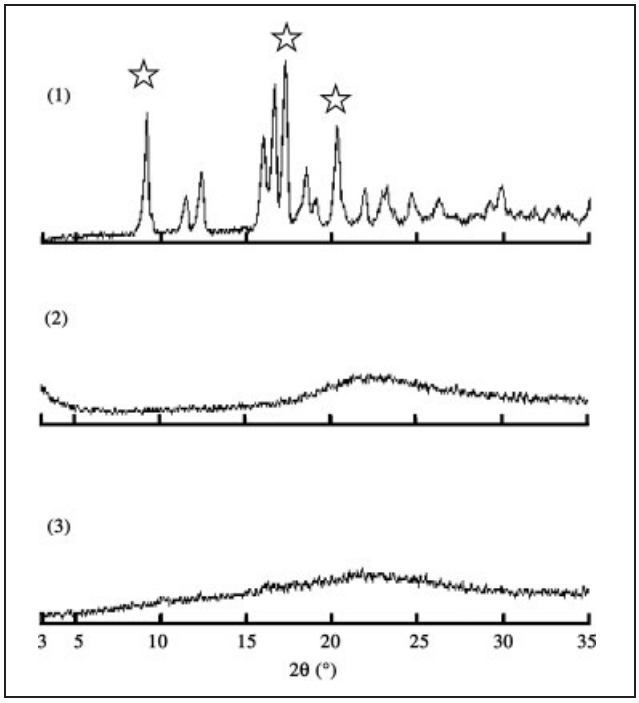

Fig. 2: Powder X-ray diffraction (PXRD) patterns of Sylysia 350 : SPI systems:
(1) SPI crystal; (2) Sylysia 350 intact; (3) Solid dispersion of Sylysia 350 : SPI (weight ratio of 1 : 1)

To investigate the molecular state of the SPI adsorbed on Sylysia 350 by the solvent method, PXRD patterns were determined. Fig. 2 shows the PXRD patterns of the Sylysia

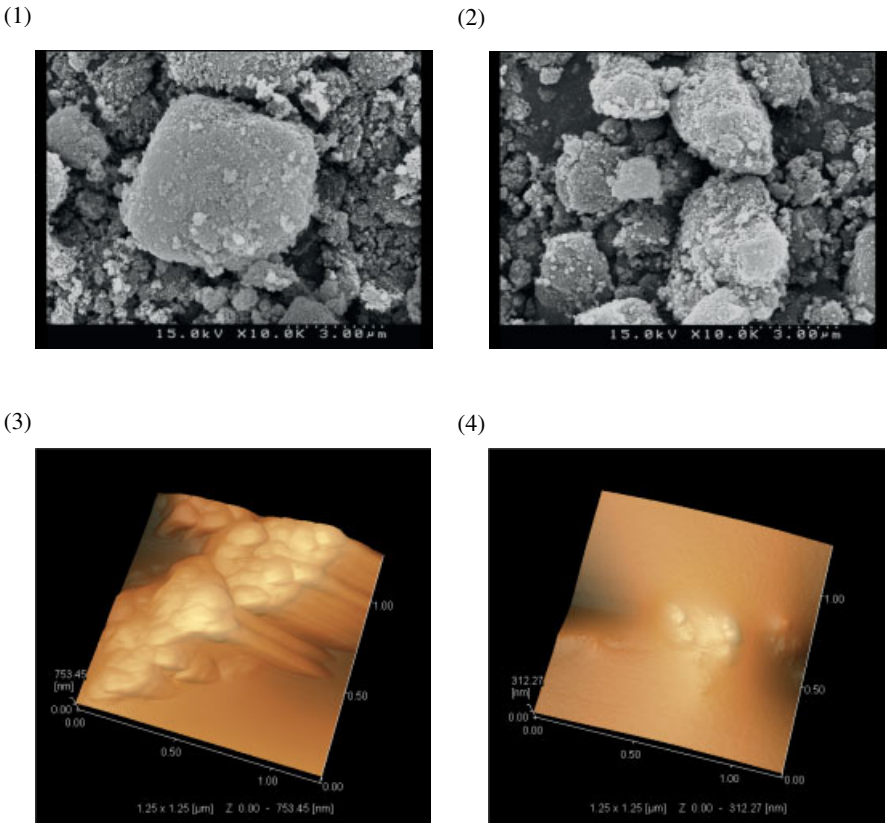

Fig. 1:
SEM images and AFM images of Sylysia 350 : SPI systems:
(1) SEM of Sylysia 350 intact; (2) SEM of solid dispersion of Sylysia 350 : SPI (weight ratio of 1 : 1); (3) AFM of Sylysia 350 intact; (4) AFM of solid dispersion of Sylysia 350 : SPI (weight ratio of 1 : 1)

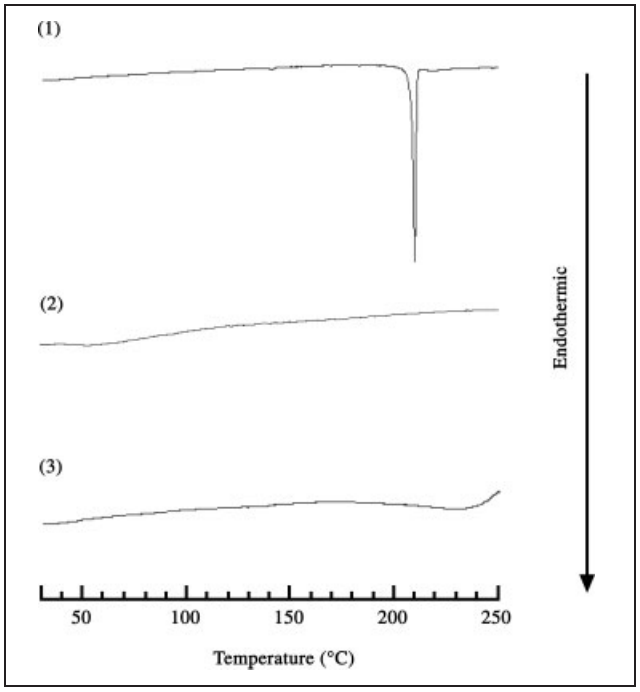

Fig. 3: DSC curves of Sylysia 350 : SPI systems: (1) SPI crystal; (2) Sylysia 350 intact; (3) Solid dispersion of Sylysia 350 : SPI (weight ratio of 1 : 1)

350 : SPI system. SPI shows crystalline diffraction peaks at $2\theta = 9.2°$, 17.3°, and 20.3° (as indicated by the open stars). On the other hand, the Sylysia 350 intact showed a halo pattern. The diffraction peaks due to SPI crystals disappeared in the solid dispersion. The DSC curves of the Sylysia 350 : SPI system are shown in Fig. 3. The SPI crystals showed an endothermic peak at 207.7 °C due to fusion. The melting peak of SPI disappeared in the solid dispersion. As reported by Yonemochi et al. (1995) and Okonogi et al. (1999) on a system of controlled pored glass, no glass transition was observed in the solid dispersion. The results of PXRD and DSC data indicated that SPI molecules adsorbed onto the pores of Sylysia 350 and the molecular state of the adsorbed SPI changed from crystalline to amorphous.

2.2. Effect of pore size, pore volume of Sylysia, and SPI concentration on SPI crystalline characteristics

It has been widely reported that the physicochemical properties of porous additives affects the molecular state of adsorbed molecules (Takeuchi et al. 2005b; Tozuka et al. 2005b). To investigate the effects of the pore size, pore volume of Sylysia, and SPI concentration on the crystalline characteristics of SPI, solid dispersions of SPI with Sylysia 350 and Sylysia 730 in various weight ratios were prepared and their PXRD patterns were determined. Fig. 4 shows the PXRD patterns of the Sylysia : SPI system in various mixing ratios. In the Sylysia 350 system, diffraction peaks due to SPI crystals were observed in the solid dispersion in a weight ratio of 1 : 2 (Fig. 4–(8)). However, no diffraction peaks due to SPI crystals were observed in the solid dispersions in a weight ratio of 1 : 1 and 2 : 1 (Fig. 4–(4) and (6), respectively). From these results, it was found that the decrease in the SPI concentration increased with the amorphous fraction of SPI in the solid dispersion with Sylysia 350.

The effect of the pore size and pore volume on SPI characteristics were investigated using Sylysia 730. Although no X-ray diffraction peaks due to SPI crystals in the solid dispersion in a weight ratio of 2 : 1 were observed (Fig. 4–(3)), the diffraction peaks due to SPI crystals in the solid dispersions in a weight ratio of 1 : 1 and 1 : 2 still remained (Fig. 4–(5) and (7), respectively).

These results indicated that the mean pore diameter and specific surface area of an additive are some of the important factors for the amorphization of SPI crystals by the solvent method.

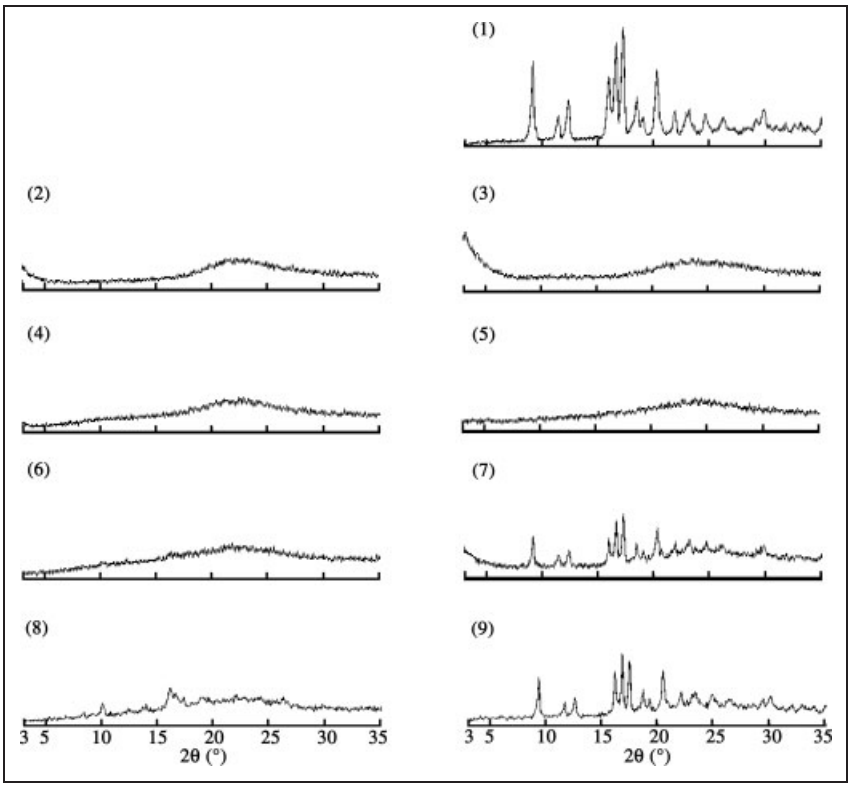

Fig. 4: PXRD patterns of Sylysia 350 : SPI systems: (1) SPI crystal; (2) Sylysia 350 intact; (3) Sylysia 730 intact; (4) Solid dispersion of Sylysia 350 : SPI (weight ratio of 2 : 1); (5) Solid dispersion of Sylysia 730 : SPI (weight ratio of 2 : 1); (6) Solid dispersion of Sylysia 350 : SPI (weight ratio of 1 : 1); (7) Solid dispersion of Sylysia 730 : SPI (weight ratio of 1 : 1); (8) Solid dispersion of Sylysia 350 : SPI (weight ratio of 1 : 2); (9) Solid dispersion of Sylysia 730 : SPI (weight ratio of 1 : 2)

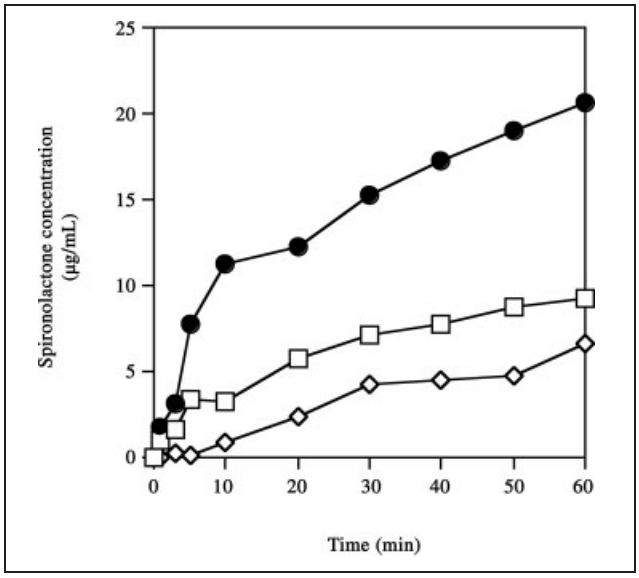

Fig. 5: Dissolution profiles of SPI from solid dispersion with Sylysia 350 or 730 at 37 °C:
●: Solid dispersion of Sylysia 350 : SPI (weight ratio of 1 : 1); □: Solid dispersion of Sylysia 730 : SPI (weight ratio of 1 : 1); ◇: SPI crystal

2.3. Dissolution behavior of SPI from solid dispersions

The dissolution behavior of SPI from the solid dispersion in the JP XV 2nd fluid (pH 6.8) was studied according to the JP XV paddle method (Fig. 5). SPI crystals exhibited a low dissolution rate for poor water solubility and poor wettability. The enhancement of the dissolution of SPI from the solid dispersions with Sylysia 350 and Sylysia 730 was observed in comparison with crystalline SPI. These results indicated that the SPI molecules entrapped in the pores of the Sylysia in the solid dispersion had low crystallinity and dissolved more rapidly than SPI crystals. The dissolution rate of the SPI from the solid dispersions with Sylysia 350 was faster than that of the SPI from the solid dispersions with Sylysia 730. It was considered that there was a difference in the dissolution rate of SPI depending on the Sylysia species because the SPI in the solid dispersion with Sylysia 350 had an amorphous state while the SPI in the solid dispersion with Sylysia 730 remained crystalline as shown in Fig. 4.

2.4. Stability of amorphous SPI in solid dispersion

Figure 6 shows the stability of the amorphous SPI in the solid dispersion with Sylysia 350. Amorphous SPI without Sylysia showed crystalline diffraction peaks due to SPI after storing at 0% RH and 25 °C for 2 weeks. On the other hand, the solid dispersion of SPI with Sylysia (weight ratio of 1 : 1) was maintained in the amorphous state. It was reported that Sylysia 350 has a strong stabilizing effect on the metastable tolbutamide in solid dispersions (Takeuchi et al. 1992). Therefore, this stabilizing effect of Sylysia 350 might be ascribed to the interaction between SPI and Sylysia 350.

2.5. Conclusion

Solid dispersions of SPI with porous silica (Sylysia 730 and Sylysia 350) were prepared by the solvent method. In the AFM study, the surface of the solid dispersion of the Sylysia 350 : SPI system (weight ratio of 1 : 1) was rather smooth as compared with that of the Sylysia 350 intact. The results of XRD and DSC indicated that SPI adsorbed on the surface of Sylysia and the molecular state of the adsorbed SPI changed from crystalline to amorphous. Although the decrease in the SPI concentration increased with the amorphous fraction in the solid dispersion, the diffraction peaks due to SPI crystals still remained in the solid dispersion of the Sylysia 730 : SPI system in a weight ratio of 1 : 1, indicating that the mean pore diameter and specific surface area of an additive are some of the important factors for the amorphization of SPI crystals. The dissolution property of the SPI from the solid dispersions was remarkably improved in comparison with that of SPI crystals. The amorphous state of the SPI in the solid dispersion of the Sylysia 350 : SPI system in the weight ratio of 1 : 1 was maintained for 2 weeks at 0% RH and 25 °C.

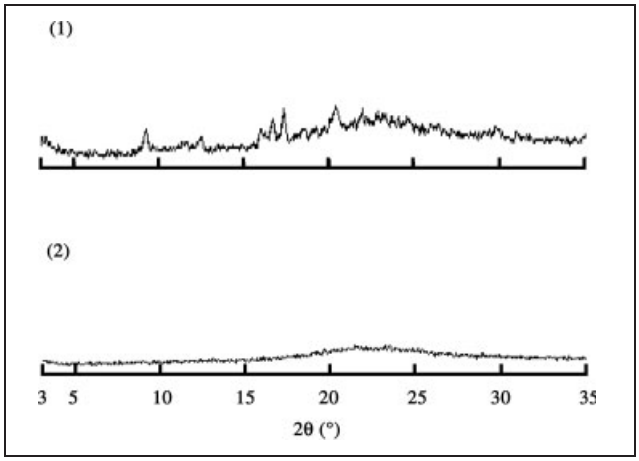

Fig. 6: Stability of amorphous SPI and solid dispersion of Sylysia 350 : SPI (weight ratio of 1 : 1) stored at 0% RH and 25 °C for 2 weeks.
(1) Amorphous SPI without Sylysia 350; (2) Solid dispersion of Sylysia 350 : SPI (weight ratio of 1 : 1)

3. Experimental

3.1. Materials

SPI (SIGMA) was used without further purification. The two kinds of porous silica (Sylysia 350 and 730) were purchased from Fuji Silysia Chemical Ltd., Japan. The physicochemical properties of porous silica are shown in the Table. Before use, these porous materials were dried at 100 °C in a vacuum for 3 h.

3.2. Methods

3.2.1. Sample preparation

In the preparation of the solid dispersion, SPI was dissolved in acetone and Sylysia was added and the suspensions were evaporated at room temperature. The prepared samples were dried in the vacuum at room temperature for 3 h to remove the acetone. Amorphous SPI without Sylysia was prepared by grinding 2 g of SPI crystals for 30 min using a vibration mill (model TI-200, CMT, Tochigi, Japan). The grinding cell was made of aluminum oxide. All the samples were stored in desiccators at 0% RH (P_2O_5 powder) at 25 °C before use.

3.2.2. Scanning electron microscopy (SEM)

The morphology of Sylysia and the solid dispersion was observed by SEM at a voltage of 15 kV (Hitachi Model S-4100, Hitachi, Tokyo).

Table: Physicochemical properties of Sylysia 730 and 350

Porous silica	Mean pore diameter (nm)	Specific surface area (m^2/g)	Mean particle size (μm)
Sylysia 730	2.5	730	4.0
Sylysia 350	21	350	3.9

3.2.3. Atomic force microscopy (AFM)

The AFM measurement was carried out using SPM-9500-J3 (Shimadzu, Kyoto, Japan) to observe the surface of Sylysia and the prepared solid dispersion. The sample was embedded in resin, and the measurement was performed in the tapping mode at room temperature with a silicon cantilever. The scanning area was 1.25×1.25 μm.

3.2.4. Powder X-ray diffraction (PXRD)

The powder X-ray diffractograms were measured using a Rigaku MiniFlex diffractometer (Cu-Kα, voltage: 30 kV, current: 15 mA, scanning speed: 4°/min).

3.2.5. Differential scanning calorimetry (DSC)

The DSC study was performed on MAC Science 3100 (Japan) using an aluminum pan. The measurement was carried out from 30 to 250 °C at a heating rate of 5 °C/min under a nitrogen gas flow (50 mL/min).

3.2.6. Dissolution studies

The dissolution studies were performed according to the JP XV paddle method. The JP XV 2nd fluid (pH 6.8) was used as the dissolution medium. A powdered sample (SPI content: 60 mg) was introduced into 500 mL of the dissolution medium thermostated at 37 °C. The revolution speed of the paddle was adjusted to 100 rpm. At definite intervals, 1 mL of the solution was pipetted out and filtered through a 0.45 μm membrane filter. The cumulative dilution caused by the sampling was corrected by replacing the sample with an equal volume of the original medium. The concentration of SPI in solution was determined by HPLC. The mobile phase (acetonitrile : distilled water, 85 : 15, v/v) was delivered at a flow rate of 1.0 mL/min through a Pegasil ODS column (4.6 mm ID × 250 mm; Senshu Scientific Co., Ltd., Japan) at 40 °C. The detection wavelength was 240 nm.

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