Influence of Particle Design on Oral Absorption of Poorly Water-Soluble Drug in a Silica Particle–Supercritical Fluid System

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The physicochemical characteristics and oral absorption of a poorly water-soluble drug, K-832, adsorbed onto porous silica (Sylysia 350), were compared with those of K-832 adsorbed onto non-porous silica (Aerosil 200). K-832 and silica were treated with supercritical CO_2 ($scCO_2$) to produce K-832-Sylysia 350 and K-832-Aerosil 200 formulations. Scanning electron microscopy, polarizing microscopy, powder X-ray diffraction, and differential scanning calorimetry results suggested that K-832 mainly existed in an amorphous state in both formulations. The specific surface area of both formulations was much larger than that of pure K-832 crystals. The dissolution rate of K-832 from both formulations was considerably greater than that from corresponding physical mixtures due to rapid wetting of the hydrophilic carrier surfaces and amorphous state, the dissolution from the K-832-Sylysia 350 formulation being the fastest. *In vivo* absorption tests on the two formulations indicated no significant differences in their peak concentration (C_{max}) and the area under their plasma concentration–time curve (*AUC*), while the concentrations of K-832 in the K-832-Sylysia 350 formulation were significantly higher than those in the K-832-Aerosil 200 formulation 1 h and 1.5 h after administration of these formulations ($p<0.05$). This could be attributed to the different dispersion states of K-832 in the formulations due to their different three-dimensional structures (porous and non-porous). In physical stability tests, the amorphous drugs in both formulations were stable at room temperature for at least 14 months. Thus, the absorption of poorly water-soluble drugs could be greatly improved by adsorption onto porous silica using $scCO_2$.

Key words porous silica; non-porous silica; supercritical carbon dioxide; dissolution; absorption; amorphous state

Drug adsorption onto a high-surface-area carrier is known to be a useful approach for improving the dissolution rate and absorption of poorly water-soluble drugs.[1—6] Monkhouse and Lach reported such improvements for drugs such as indomethacin when dissolved in an organic solvent such as acetone and deposited onto a high-surface-area carrier such as fumed silica.[1] Friedrich *et al.* reported the use of non-toxic, non-volatile solvents such as PEG 400 and 2-pyrrolidone as solvents for adsorbing a solution of drugs onto large surface-area carriers.[5]

In our previous work, we investigated the utility of a new solid dispersion system—comprising a high-surface-area silica, Sylysia 350, as a carrier and supercritical CO_2 ($scCO_2$) as a solvent—for poorly water-soluble drugs.[7] In this system, a pharmaceutical preparation (drug adsorbed onto the high-surface-area silica using $scCO_2$) with no residual solvent is obtained because CO_2 is easily eliminated from the products.

Various types of adsorbents can be used as carriers. These adsorbents include montmorillonite clay,[2] porous calcium silicate,[3,6] and various kinds of silica with different particle structures, *e.g.* fumed silica,[1,5] porous silica,[6] and mesoporous silica such as MCM 41[4] and FSM-16.[8] Each type of silica consists of simple SiO_2 but has a different specific surface area and pore diameter depending on the intended use and the manufacturing method. However, the design of the carrier particle used in the $scCO_2$ method for enhancing the oral absorption of the drug has not been studied in detail thus far.

With this background, the aim of this study is to investigate the influence of carrier particle design on the oral absorption of a poorly water-soluble drug when silica particles with different structures are used in the $scCO_2$ method. In our preliminary screening of porous type silica, three silicas with specific surface areas of 90, 300, and 700 m^2/g were examined. The 300 m^2/g-silica showed improved dissolution and fastest dissolution rate of the drug. In the case of the 90 m^2/g-silica, although the surface area is sufficiently large for that of the drug (less than 1 m^2/g), the dissolution rate of the drug was not improved. Finally, in the case of the 700 m^2/g-silica, although the dissolution rate of the drug was improved, the resultant formulation exhibited sustained-release features. As a result, 300 m^2/g-silica (Sylysia 350) was selected.

Further, non-porous type silica is also known to be a potential carrier for poorly water-soluble drugs. Wang *et al.*[9] reported faster dissolution of nitrendipine from solid dispersion using Aerosil 200 as a carrier. Therefore, in this study, porous silica Sylysia 350 and non-porous silica Aerosil 200, which are both used as inactive ingredients in pharmaceutical products, were used as drug carriers. Their properties are listed in Table 1. Sylysia 350 has a porous structure, an aver-

Table 1. Physical Properties of Sylysia 350 and Aerosil 200

Silica	Structure type	Particle size (μm)	Specific surface area (m^2/g)	Pore size (nm)	Pore volume (ml/g)
Sylysia 350	Porous structure	3.9	300	21.0	1.6
Aerosil 200	Non-porous structure	0.012	200	—	—

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age particle diameter of 3.9 μm, and an average pore diameter of 21 nm; Aerosil 200 has a non-porous structure and an average primary particle diameter of 0.012 μm. The poorly water-soluble drug chosen for this study (including the preliminary screening) was 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2*H*-pyridazin-3-one (K-832), which exhibits the useful property of inhibiting the production of interleukin-1β, a cytokine, and is effective as a preventive and therapeutic drug for immune, inflammatory, and ischemic diseases.[10,11]

Experimental

Materials K-832 (melting point, 155—159 °C) was sourced from Kowa Co., Ltd., and Sylysia 350 was supplied by Fuji Silysia Chemical Ltd. (Japan). Aerosil 200 was purchased from Nippon Aerosil Co., Ltd. Liquid CO_2 was purchased from Fujisanso Industry Co., Ltd.

Preparation The experimental apparatus consisted mainly of a CO_2 tank, a CO_2 pump, a pressure-resistant vessel (0.5 l) with a jacket, a paddle stirrer, pressure gauges, valves, and a safety valve.[7] Four hundred milligrams of K-832 and 4.0 g of silica (K-832 : silica = 1 : 10 (by weight)) were put into the pressure-resistant vessel. The vessel was closed and heated to 60 °C, following which, CO_2 was added to the mixture. After it reached a pre-selected pressure (18 MPa), the temperature and pressure were maintained constant for 5 h under stirring at 500 rpm. Thereafter, CO_2 was gradually discharged from the vessel through the valve to yield the K-832-Sylysia 350 or K-832-Aerosil 200 formulation.

Morphology The morphology of the samples was investigated using a scanning electron microscope (SEM; Hitachi S-3000N, Japan) and a polarizing microscope (Olympus BX51, Japan).

Crystallinity Evaluation The crystallinity of K-832 was evaluated using a powder X-ray diffractometer (PXRD; Rigaku RINT2000, Japan) with CuKα radiation at 40 kV and 20 mA and a differential scanning calorimeter (DSC; Shimadzu DSC-60, Japan). For the PXRD measurements, samples were scanned from 5° to 35° (2θ) at a scanning speed of 5°/min. The DSC data was collected at a heating rate of 10°C/min under a N_2 gas flow (20 ml/min).

Measurement of Specific Surface Area and Pore Volume The specific surface area and pore volume were measured by the N_2 adsorption method using a TriStar 3000 (Micromeritics Instrument Corp., U.S.A.) after degassing the samples at 120 °C for 15—20 h.

Dissolution Test The dissolution test was carried out by means of the paddle method at 50 rpm, which is a general test method specified in the Japanese Pharmacopoeia. The sample amount was equivalent to 5 mg of K-832. The dissolution medium was 900 ml of water containing 0.1% Triton X-100[12] at 37±0.5 °C. The amount of K-832 dissolved in the test solution (reported in percentage) was determined by high-performance liquid chromatography (HPLC; Shimadzu LC-10A, Shimadzu, Japan) using a reversed-phase column (Inertsil ODS-2, GL Sciences Inc., Japan). The flow rate of the mobile phase (acetonitrile/water (7 : 3, v/v)) was 1.1 ml/min. The eluent was detected using a UV detector at 280 nm.

Oral Absorption Study in Dogs HRA beagle dogs (male; body weight, 9.2—13.7 kg; Japan Laboratory Animals Inc.) were housed in the animal facility of Fuji Research Laboratories, Kowa Co., Ltd., with free access to water throughout the day and free access to food until about 17 h before administration. Animal care and related procedures were conducted in accordance with the Regulations for Animal Experiments of Kowa Co., Ltd. The study was approved by the Ethics Committee on Animal Research of Kowa Co., Ltd. The K-832-silica formulation suspended in 30 ml of water was administered orally with 20 ml of water to male beagle dogs *via* a Nelaton catheter (dose, 10 mg/kg as K-832). Blood (1.0 ml) was drawn from the antebrachial vein using heparinized syringes 0.5, 1, 1.5, 2, 3, 5, 8, and 24 h after administration and centrifuged immediately. The plasma obtained was stored at −20 °C until assay. The plasma samples (400 μl) were then mixed with 1 ml of internal standard solution, 750 μl of 1 mol/l glycine buffer solution (pH 10), and 5 ml of methyl *tert*-butyl ether, and centrifuged. The supernatant fluid was dried at 40 °C under a N_2 gas flow. The residue was dissolved in 250 μl of the mobile phase (methanol/0.05 mol/l formic acid buffer solution (pH 3)/acetonitrile (12 : 5 : 2, v/v)), and 80 μl was subjected to HPLC analysis for K-832 on the LC-10A system using an Inertsil ODS-P column (GL Sciences Inc.). The flow rate of the mobile phase was 0.8 ml/min. The eluent was detected using a UV detector at 280 nm.

Physical Stability Test For stability analysis, the K-832-Sylysia 350 and K-832-Aerosil 200 formulations were stored in closed glass vials at room temperature for 14 months and then tested for crystallinity and drug dissolution.

Statistical Analysis Statistical analysis was performed *via* Student's *t*-test, and a significance level of less than 0.05 was considered statistically significant.

Results

Preparation Silica particles have low bulk density (density of solids) and are thus generally difficult to handle. Further, because Sylysia 350 has higher bulk density than Aerosil 200, the bulk densities of the corresponding formulations share the same relationship. In addition, both formulations tend to be easily charged.

Morphology Figures 1 and 2 show, respectively, the SEM and polarizing microscope images of K-832, Sylysia 350, Aerosil 200, physical mixtures, and the K-832-Sylysia 350 and K-832-Aerosil 200 formulations. The SEM images confirm that Aerosil 200 particles existed as aggregates (Fig. 1e). The K-832 particles (crystals) are clearly distinguishable from the silica particles in the polarizing microscope photographs (Figs. 2a, b, e). In addition, the K-832 particles are

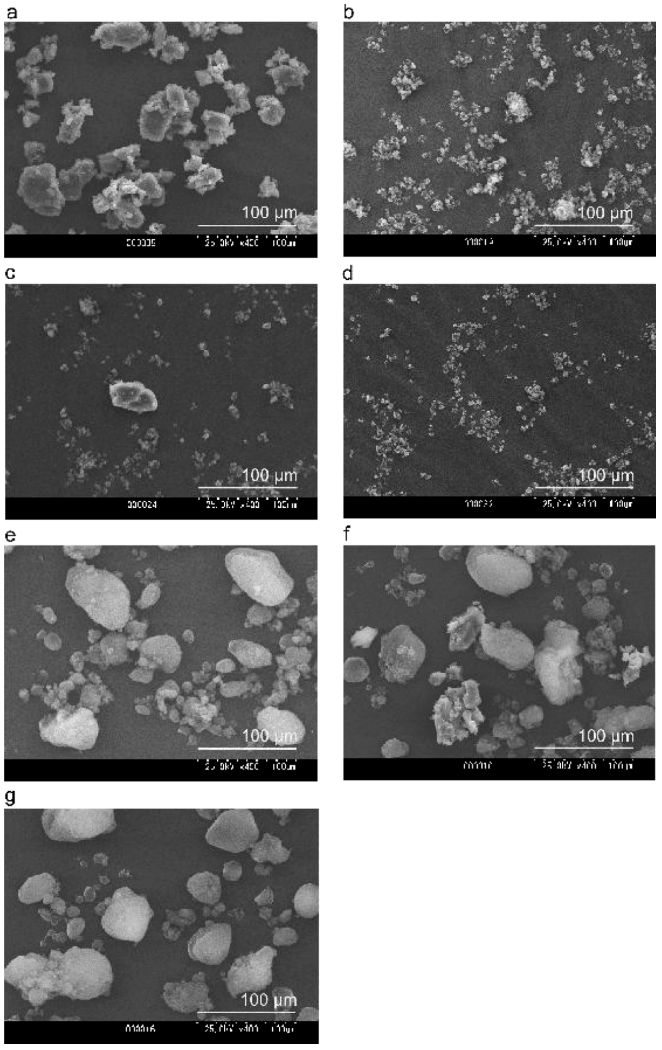

Fig. 1. SEM Images (×400, 25 kV) of (a) K-832 Crystal, (b) Sylysia 350, (c) Physical Mixture with Sylysia 350, (d) K-832-Sylysia 350 Formulation, (e) Aerosil 200, (f) Physical Mixture with Aerosil 200, and (g) K-832-Aerosil 200 Formulation

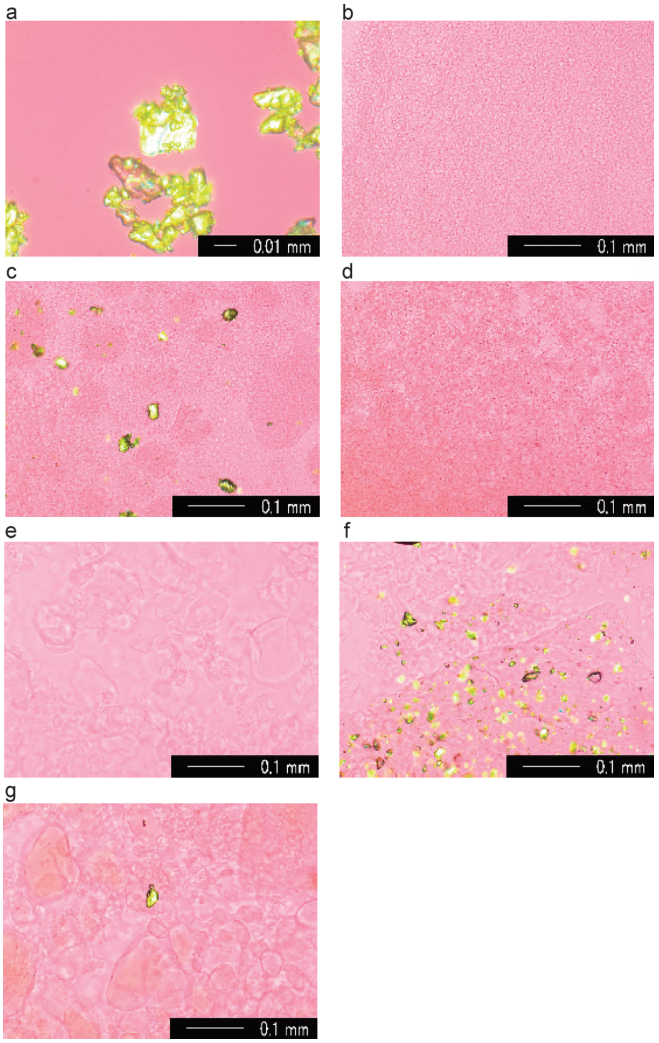

Fig. 2. Polarizing Microscope Images of (a) K-832 Crystal, (b) Sylysia 350, (c) Physical Mixture with Sylysia 350, (d) K-832-Sylysia 350 Formulation, (e) Aerosil 200, (f) Physical Mixture with Aerosil 200, and (g) K-832-Aerosil 200 Formulation

clearly observed to coexist with silica particles in the physical mixture (Sylysia 350, Figs. 1c, 2c; Aerosil 200, Figs. 1f, 2f). By contrast, although a few individual K-832 particles are observed in the K-832-Aerosil 200 formulation (Fig. 2g), none are observed in the K-832-Sylysia 350 formulation (Fig. 2d).

Crystallinity Evaluation PXRD patterns of pure K-832 crystals, Sylysia 350, Aerosil 200, the physical mixtures, and the K-832-Sylysia 350 and K-832-Aerosil 200 formulations are shown in Fig. 3. Pure K-832 crystals show many distinctive diffraction peaks, which indicate high crystallinity (Fig. 3a). The physical mixtures (Figs. 3c, f) retain the distinctive peaks, although with a marked decrease in intensity compared with pure crystals. By contrast, the K-832-Sylysia 350 (Fig. 3d) and K-832-Aerosil 200 (Fig. 3g) formulations retain no diffraction peaks and instead show a halo pattern. The DSC curves of these samples are shown in Fig. 4. The endothermic peak of the K-832 crystal was observed at 157.4 °C (Fig. 4a, −103.23 J/g). The heat absorbed at the endothermic peak (155—159 °C) for each sample is listed in Table 2. Corresponding peaks were also observed for physical mixtures with Sylysia 350 (Fig. 4c, −5.30 J/g) and

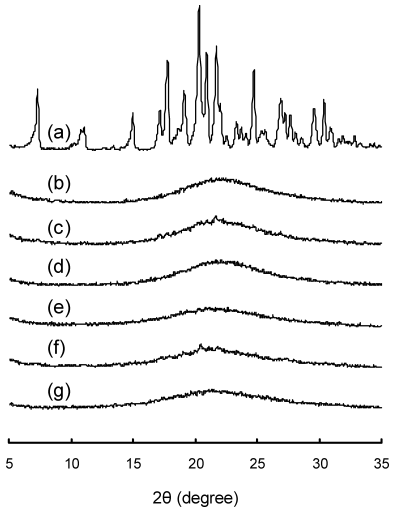

Fig. 3. Powder X-Ray Diffraction Patterns of (a) K-832 Crystal, (b) Sylysia 350, (c) Physical Mixture with Sylysia 350, (d) K-832-Sylysia 350 Formulation, (e) Aerosil 200, (f) Physical Mixture with Aerosil 200, and (g) K-832-Aerosil 200 Formulation

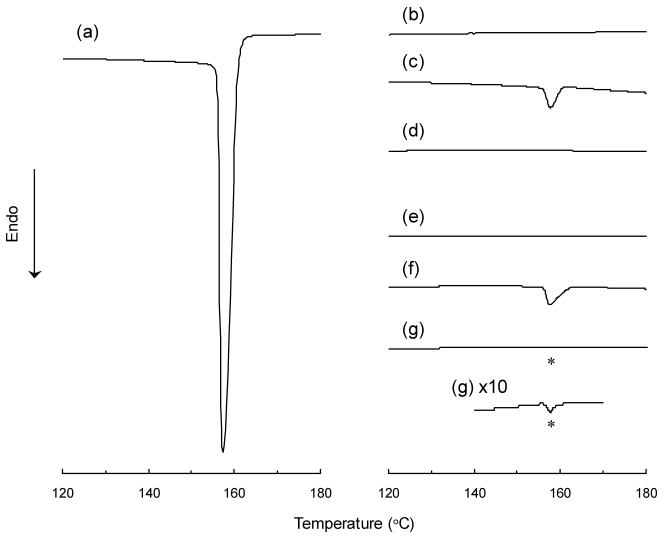

Fig. 4. DSC Curves of (a) K-832 Crystal, (b) Sylysia 350, (c) Physical Mixture with Sylysia 350, (d) K-832-Sylysia 350 Formulation, (e) Aerosil 200, (f) Physical Mixture with Aerosil 200, and (g) K-832-Aerosil 200 Formulation

g×10, *i.e.* the intensity of g is magnified tenfold.

Table 2. Heat of Fusion of K-832 Crystal, Sylysia 350, Aerosil 200, Physical Mixtures, and K-832-Silica Formulations

Sample	Heat of endothermic peak (J/g)
K-832 crystal	−103.23
Sylysia 350	0.00
Aerosil 200	0.00
Physical mixture with Sylysia 350	−5.30
Physical mixture with Aerosil 200	−6.38
K-832-Sylysia 350 formulation	0.00
K-832-Aerosil 200 formulation	−0.24

Aerosil 200 (Fig. 4f, −6.38 J/g). However, this endothermic peak was not observed in the K-832-Sylysia 350 formulation (Fig. 4d), although a small peak was observed in the K-832-Aerosil 200 formulation (Fig. 4g×10, −0.24 J/g, 3.8% of K-

832).

Specific Surface Area and Pore Volume The specific surface area and pore volume of pure K-832 crystals, the physical mixtures, and the two formulations are listed in Table 3. The specific surface area of the physical mixture with Sylysia 350 (243.18 m^2/g) was larger than that with Aerosil 200 (163.15 m^2/g) simply because the specific surface area of Sylysia 350 is larger (300 m^2/g *vs.* 200 m^2/g for Aerosil 200). However, the specific surface areas of both formulations were considerably larger than that of pure K-832 (0.82 m^2/g). The specific surface area of the K-832-Sylysia 350 formulation (239.61 m^2/g) was slightly smaller than that of the corresponding physical mixture (243.18 m^2/g), but the pore volume (1.419 ml/g) was equal to that of the corresponding physical mixture (1.415 ml/g). The specific surface area of the K-832-Aerosil 200 formulation (164.26 m^2/g) was equal to that of the corresponding physical mixture (163.15 m^2/g).

Dissolution Test The dissolution profiles of K-832, shown in Fig. 5, illustrate that 77.4% and 44.1% of K-832 were released from the K-832-Sylysia 350 and K-832-Aerosil 200 formulations within just 5 min, whereas only 3.5% and 1.9% were released from corresponding physical mixtures even after 60 min. Thus, clearly, the $scCO_2$ treatment remarkably enhanced the dissolution rate. In particular, dissolution from the K-832-Sylysia 350 formulation was much faster than that from the K-832-Aerosil 200 formulation (5 min, $p<0.001$; 60 min, $p<0.01$).

Oral Absorption Study in Dogs Plasma concentrations of K-832 in beagle dogs after oral administration and the pharmacokinetic parameters are shown in Fig. 6 and Table 4, respectively. The plasma concentration of K-832 after dosing with the K-832-Sylysia 350 formulation was greater than that after dosing with the K-832-Aerosil 200 formulation. One hour and 1.5 h after administration, the concentrations of K-832 in the K-832-Sylysia 350 formulation were significantly higher than those in the K-832-Aerosil 200 formulation ($p<0.05$). The C_{max} values of the K-832-Sylysia 350 and K-832-Aerosil 200 formulations were 0.56±0.10 and 0.32±0.05 μg/ml, respectively. The *AUCs* of the K-832-Sylysia 350 and K-832-Aerosil 200 formulations were 2.88±0.89 and 1.79±0.45 μg h/ml, respectively. Statistical analysis results showed no significant differences in the C_{max} and *AUC* values between the two formulations.

Physical Stability The DSC curves of the K-832-Sylysia 350 and K-832-Aerosil 200 formulations stored for 14 months at room temperature are shown in Fig. 7. The curves did not change for either formulation (K-832-Sylysia 350 formulation—14 months, 0 J/g; K-832-Aerosil 200 formulation—14 months, −0.30 J/g). The dissolution profiles of the K-832-Sylysia 350 and K-832-Aerosil 200 formulations

Table 3. Specific Surface Area and Pore Volume of K-832 Crystal, Physical Mixtures, and K-832-Silica Formulations

Sample	Specific surface area (m^2/g)	Pore volume (ml/g)
K-832 crystal	0.82	0.001
Physical mixture with Sylysia 350	243.18	1.415
K-832-Sylysia 350 formulation	239.61	1.419
Physical mixture with Aerosil 200	163.15	—
K-832-Aerosil 200 formulation	164.26	—

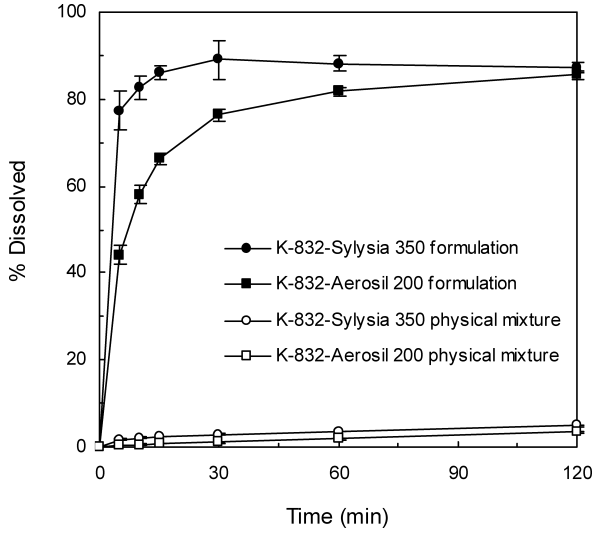

Fig. 5. Dissolution Profiles of K-832 in 900 ml of Water Containing 0.1% Triton X-100

Mean±S.D., $n=3$.

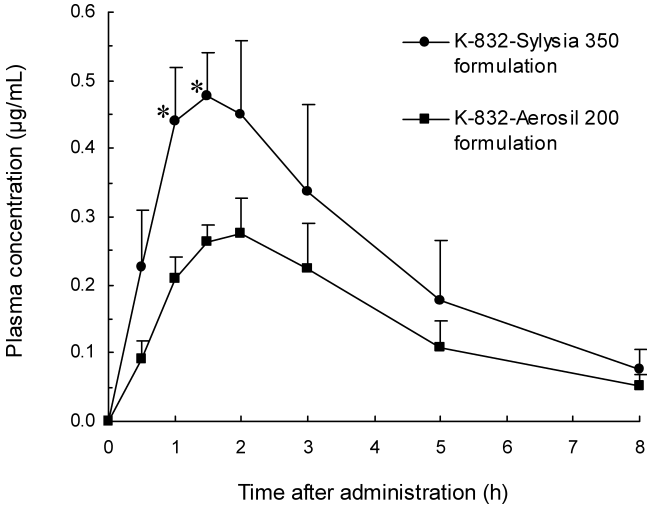

Fig. 6. Plasma Concentration–Time Profiles of K-832 in Beagle Dogs after Oral Administration of K-832-Sylysia 350 and K-832-Aerosil 200 Formulations

Dose: 10 mg/kg, $*p<0.05$, each point represents the mean±S.E.M. ($n=5$—6).

Table 4. Pharmacokinetic Parameters of K-832 after Oral Administration to Beagle Dogs at the Dose of 10 mg/kg of K-832-Sylysia 350 and K-832-Aerosil 200 Formulations

Sample	T_{max} (h)		C_{max} (μg/ml)		*AUC* (μg·h/ml)	
K-832-Sylysia 350 formulation	1.4±0.3	N.S.	0.56±0.10	N.S.	2.88±0.89	N.S.
K-832-Aerosil 200 formulation	1.8±0.3		0.32±0.05		1.79±0.45	

Each value represents the mean±S.E.M. ($n=5$—6). N.S.: not significantly different.

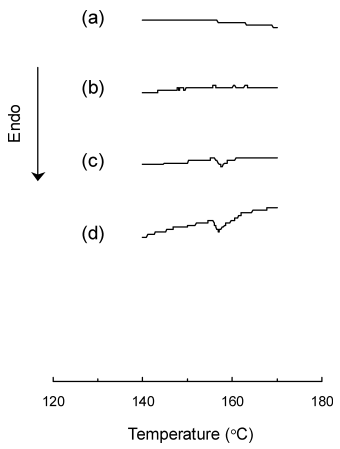

Fig. 7. DSC Curves of K-832-Sylysia 350 and K-832-Aerosil 200 Formulations before and after Storage at Room Temperature for 14 Months

(a) K-832-Sylysia 350 formulation–initial, (b) K-832-Sylysia 350 formulation–14 M, (c) K-832-Aerosil 200 formulation–initial, (d) K-832-Aerosil 200 formulation–14 M. The intensities of all samples are magnified tenfold.

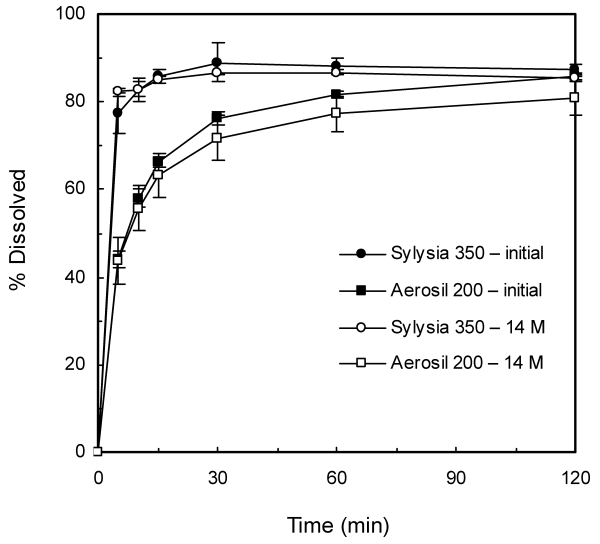

Fig. 8. Dissolution Profiles of K-832 in K-832-Sylysia 350 and K-832-Aerosil 200 Formulations before and after Storage at Room Temperature for 14 Months

In 900 ml of water containing 0.1% Triton X-100, mean±S.D., $n=3$.

stored for 14 months at room temperature are shown in Fig. 8. Over this long storage period, no significant decrease in the dissolution rate of either sample was observed. Therefore, the K-832-Sylysia 350 and K-832-Aerosil 200 formulations were physically stable for at least 14 months.

Discussion

No evidence for the existence of K-832 crystals in the K-832-Sylysia 350 formulation was found from the SEM, polarizing microscope, PXRD, and DSC measurements. When only K-832 was treated with $scCO_2$ without silica, K-832 was obtained in the crystalline state, not in the amorphous state. As a result, the dissolution rate of K-832 was not found to improve. Thus, in this system, the silica carrier is necessary for amorphization and improvement in the dissolution of the drug. Hence, it is believed that all of K-832 was well adsorbed on the extensive surface of Sylysia 350 and existed in an amorphous state. In addition, it is believed that most of the K-832 added was adsorbed on the internal surfaces of the Sylysia 350 particles, because the internal surface area is much larger than the outer surface area. By contrast, though the drug–silica mixture ratio was the same for the Aerosil 200 system, a polarization image derived from the K-832 crystal (Fig. 2g) and an endothermic peak that indicated melting of K-832 crystals (Fig. 4g×10, *) were observed. The amount of K-832 existing in the crystalline state was estimated to be 3.8% from the DSC endothermic peak. Accordingly, it was considered that approximately 96% of K-832 was adsorbed onto Aerosil 200. Thus, we conclude that the porous structure of the Sylysia 350 system improves drug adsorption from the $scCO_2$ solution.

In addition, the dissolution of K-832 from both formulations was much greater than that from the corresponding physical mixtures. Because K-832, which is a hydrophobic compound, has extremely poor aqueous wettability and dispersibility, K-832 particles float on the surface of the dissolution medium. By contrast, Sylysia 350 and Aerosil 200 are hydrophilic compounds with good aqueous wettability and dispersibility because of the silanol group (–Si–OH) on the surface of silica. Furthermore, drugs adsorbed onto high-surface-area carriers are known to assume an amorphous state, and the activity in the amorphous state is higher than that in the crystalline state. Consequently, in the $scCO_2$ method, the improved dissolution rate from the two formulations could be due to the rapid wetting and dispersion of the formulations by drug adsorption onto the hydrophilic carrier surfaces and also due to the fact that less energy is required for dissolution of the amorphous form than the crystalline form.

It is generally considered that smaller particles afford better dissolution rates because the contact area with the dissolution medium is greater.[13] The average particle diameters of the Sylysia 350 and Aerosil 200 particles are 3.9 μm and 0.012 μm, respectively. Therefore, by conventional reasoning, the dissolution rate of the Aerosil 200 system should be faster. Wang *et al.* have also reported faster dissolution from the Aerosil system for solid dispersions of nitrendipine, a poorly water-soluble drug, with various grades of Aerosil and Sylysia produced by the melt-mixing method.[9] However, in our case, the reverse (faster dissolution from the Sylysia system) was observed. This discrepancy may be due to the fact that the dispersion state of the drug in our system might be different from that in Wang *et al.*'s system because of the difference in the manufacturing methods ($scCO_2$ method *vs.* melt-mixing method). In the melt-mixing method, the formulation of drug with silica (solid dispersion) is prepared by heating the physical mixture of drug and silica at a temperature greater than the melting point of the drug (180 °C in the case of nitrendipine). Therefore, the drug is expected to remain only on the surface of the silica particle, near the region where the drug melts. Hence, in the melt-mixing method, most of the drug remains in pores close to the outer surface of the Sylysia particles. By contrast, as mentioned previously, it is believed that in the $scCO_2$ method, the drug infiltrates internal pores. This could also be attributed to the gas-like diffusibility of $scCO_2$. As reported by Takeuchi *et al.* and Uchino *et al.*, the dispersion[14] or molecular[15] state of the drug in the solid dispersion, as well as its dissolution rate, differs based on the pore diameter of the silica carrier particles. In fact, formulations of K-832 with silica particles hav-

ing small pore diameters (*e.g.* 2.5 nm) have slow dissolution rates (unpublished results, Miura *et al.*). Wang *et al.* reported that the dissolution profile of nitrendipine from a solid dispersion system using Sylysia 350 (pore size, 21 nm) was the same as that of nitrendipine from a system using Sylysia 730 (pore size, 2.5 nm).[9] These results support the hypothesis that the drug remains in the immediate vicinity of the outer surface of the particle in the melt-mixing method. Therefore, it is considered that the dissolution rate of the drug is strongly affected by where the drug resides in the drug–carrier system rather than the diameter of the carrier particle. The selection of the manufacturing method on the basis of where the drug resides in the obtained formulation is important for improving the dissolution rate of a poorly water-soluble drug.

Previous studies have reported that after administration of K-832 crystals, the plasma concentration did not increase due to the extremely poor absorbability of the crystal. In this study, the plasma concentrations of K-832 were markedly greater with both formulations than with the corresponding drug crystals. It is believed that the quantity of drugs dissolved in the gastrointestinal tract drastically increased because of the good wettability of the silica and the amorphous state of the drug.

As mentioned previously, the statistical analysis results showed no significant differences in the C_{max} and *AUC* values between the two formulations. Although the drug absorption *in vivo* is affected by the properties of the drug and the carrier that affect the drug dissolution, it is also affected by physiological factors; hence, the absorption behaviour *in vivo* may not always correspond with the release behaviour *in vitro*. Therefore, the similarities in the C_{max} and *AUC* values of the two formulations may be attributed to physiological factors.

On the other hand, 1 h and 1.5 h after administration, the plasma concentrations of K-832 in the K-832-Sylysia 350 formulation were significantly higher than those in the K-832-Aerosil 200 formulation ($p<0.05$). This difference between the plasma concentrations of the two formulations was attributed to the difference between the dissolution rates of K-832 in the formulations. Both formulations were created by adsorbing the drug onto high-surface-area carriers in mainly an amorphous state; hence, the reason for this difference between the dissolution rates remains uncertain. Nevertheless, it is believed that the thickness of the amorphous drug on the silica surface differs between the porous silica (Sylysia 350) and non-porous silica (Aerosil 200). Because Sylysia 350 has 21 nm pores, the thickness of the amorphous drug layer becomes equal to or less than 21 nm in its pores. As for Aerosil 200, the thickness does not have the limit of 21 nm due to its non-porous structure. Therefore, the difference in the dissolution rates of the drug from the formulations might be because of the fact that the amorphous drug layer on the surface of Aerosil 200 is thicker than that in the 21 nm pores of Sylysia 350. Our results suggest that the selection of the type of silica is important in the $scCO_2$ method and that the silica carrier having an appropriate pore enables faster dissolution and superior absorbability of a poorly water-soluble drug. In conclusion, our study showed that porous Sylysia, which adsorbs the drug in its pores and maintains it in an amorphous state over a long term, facilitates absorption of a poorly water-soluble drug from a solid dispersion system produced using $scCO_2$.

Conclusion

The influence of particle design on the oral absorption of a poorly water-soluble drug, K-832, was investigated using porous silica (Sylysia 350) and non-porous silica (Aerosil 200). Sylysia 350 is a promising carrier for poorly water-soluble drugs. Further, oral absorption is found to greatly improve by preparing a solid dispersion system using the $scCO_2$ method.

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