Effect of Structural Relaxation on the Physical and Aerosol Properties of Amorphous Form of FK888 (NK1 Antagonist)

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FK888 (NK1 antagonist) is a candidate drug for migraine and selected as a model of amorphous drug. FK888 was micronized to develop as dry powder inhalers (DPIs) taking into consideration of its water insoluble property. The glass transition temperature (Tg) and fragility (*m*) were 90 °C and 118, respectively, and it was categorized as a fragile glass based on Angell's concept. FK888 was structually relaxed by aging below Tg, then the effect of aging on their physical and aerosol properties were investigated. The investigation on the moisture sorption–desorption isotherms of FK888 indicated that aged FK888 adsorbed less amount of water than that of unaged FK888. This unique moisture sorption–desorption behavior of the aged sample is explained by structural relaxation accompanying decrease of free volume and/or increase of density. As for the dissolution rate of unaged and aged FK888, they showed the similar value, suggesting that there would be no difference in bioavailability. In relation to the stability, FK888 DPIs prepared by unaged and aged FK888 were stored at 70 °C, and the respirable fraction of FK888 DPIs was evaluated by using multistage cascade impactor (USP apparatus 3). As a result, the respirable fraction of FK888 DPIs prepared by unaged sample was significantly decreased compared to the aged sample, suggesting that agglomeration may occur in the unaged sample during the storage. This phenomenon was supported by that the unaged sample showed a significant decrease in the surface area compared to that of the aged sample when stored at various conditions.

Key words amorphous solid; structural relaxation; FK888; dry powder inhaler; physical stability; fine particle dose

The use of amorphous form of drug substances to improve solubility, accelerate dissolution, and promote therapeutic activity has been very important for the development for water insoluble solids as pharmaceutical dosage forms.[1] However, not only chemical degradation[2] but also physical change such as crystallization[3,4] and aggregation[5,6] of amorphous solids even below their glass transition temperature (Tg) were reported, and these instabilities of most amorphous solids preclude their more widespread use in pharmaceutical dosage forms. Such advantages and disadvantages are offered due to excess properties of amorphous systems in terms of enthalpy and free energy. These high energy systems are unstable and tend to spontaneously revert back to the thermodynamically stable state. Thus, amorphous solids may crystallize, or even if crystallization does not occur on pharmaceutical shelf life, amorphous solids will 'relax' toward the equilibrium supercooled liquid state as shown in Fig. 1. As a glass moves towards the equilibrium state, energy decreases, free volume decreases, and structural order increases, *i.e.*, configurational entropy decreases. Thus, this process is called structural relaxation. As the intact amorphous state indicated in Fig. 1 is of higher enthalpy than the equilibrium state, heat is given off during the relaxation process, and this process is known as enthalpy relaxation. This process has strong temperature dependence, and the relaxation rate is maximal close to the Tg while negligible relaxation occurs at temperatures far below it. This means that relaxation of the amorphous materials would occur during pharmaceutical unit operations involving thermal or mechanical stresses. For glassy polymers, time dependent changes in physical and mechanical properties are often attributed to relaxation.[7] This includes increase in density, yield stress, and modulus and decrease in creep and stress relaxation rate.[8] Aging procedure is also known to increase the brittleness and lower the impact strength of glasses.[9] Thus, there is a large possibility that aging should affect the physical properties of amorphous solids, and those studies in pharmaceutical systems have focused on the measurement of relaxation times in relation to the stability prediction based on their molecular mobility.[10,11] Despite that amorphous drug substances can take various enthalpy states, there are few studies[12] to investigate its effect on their properties.

FK888 (NK1 antagonist) is a candidate drug for migraine, and is developed as dry powder inhalers (DPIs) to avoid the first-pass effect and minimize unwanted side effects. The solid state of FK888 drug substance is adopted to be amorphous considering its low solubility in aqueous solution, and it is confirmed that the amorphous state is obtained constantly in industrial scale size. In the dosage form of DPIs, because the respirable fraction of the emitted dose is largely dependent on the geometric size of bulk drug particles, not

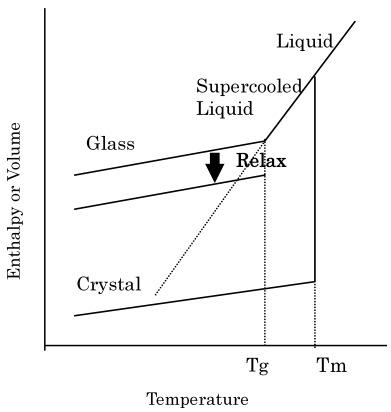

Fig. 1. Schematic Representation of Enthalpy of a Material in the Amorphous and Crystalline States

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only chemical stability but also physical stability of the drug particles are key factors to obtain constant product characteristics.

The objective of this work is to clarify the effect of aging procedure accompanying the enthalpy relaxation on the physical and aerosol properties of amorphous form of FK888.

Experimental

Materials FK888 ((4*R*)-4-Hydroxy-1-[(1-methyl-1*H*-indol-3-yl)carbonyl]-L-propyl-*N*-benzyl-*N*-methyl-3-(2-naphthyl)-L-alaninamido) was prepared by Fujisawa Pharmaceutical Company (Fig. 2). It was obtained as an amorphous solid by precipitation process from the ethanol/water solvent system. The obtained substance was stored in a refrigerator. The amorphous state was confirmed by powder X-ray diffraction (MPD-1880, Philips). Karl Fisher titration (MKS-210, Kyoto Electronics) showed water content of about 0.5%. Lactose (325 mesh) was purchased from DMV International, and all other chemicals used were reagent grade.

Specific Surface Area Determination The adsorption of nitrogen gas to the sample was measured using an automatic surface area analyzer (Gemini 2375, Micromeritics). The specific surface area was calculated from the nitrogen isotherm using the BET equation.

Particle Size Distribution The particle size distribution was measured using a laser particle size distribution analyzer (LA-920, HORIBA Ltd.). FK888 saturated Tween80 solution (0.1 w/v) was used as the dispersant. The measurement was carried out by stirring the sample solution with a magnetic stirrer.

Differential Scanning Calorimetry Approximately 5 mg of sample was taken in aluminum open pan and analyzed under a dry nitrogen purge in a differential scanning calorimeter (Seiko DSC6200) fitted with an automated liquid nitrogen cooling accessory. Unless otherwise noted, heating rate of 10 °C/min was used. The DSC was calibrated for temperature and enthalpy using indium standards. The endothermic recovery peak located at the end of glass transition region, reflecting enthalpy relaxation, was analyzed (Fig. 3). As indicated in Fig. 3, the area of the endotherm (enthalpy recovery) was determined by constructing a tangent to the heat curve in the region above Tg and extrapolating to lower temperatures.

Preparation of Micronized FK888 Particles As FK888 has a glass transition temperature at around 90 °C, 100 g of FK888 was aged at 60 °C for 5 d to obtain an amorphous solid with high relaxation enthalpy (Fig. 3). The unaged and aged solids were milled with a jet mill (Powlex 100 AS, Powlex Corporation), and DSC measurement revealed that the enthalpy recoveries of unaged and aged FK888 were 0.9 J/g (hereafter Sample A) and 6.3 J/g (hereafter Sample B), respectively. The surface area and particle size distribution of Sample A were 10.31 m^2/g and 3.6 μm (D50), respectively, and those of Sample B were 10.21 m^2/g and 3.9 μm (D50), respectively.

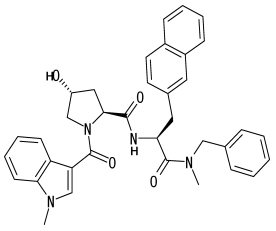

Fig. 2. Chemical Structure of FK888

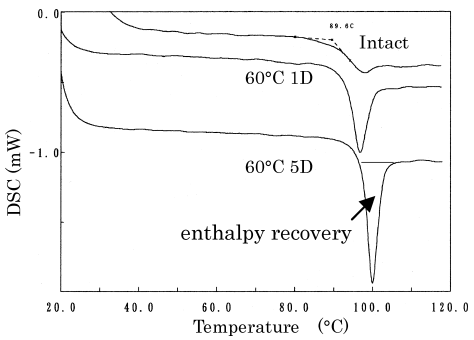

Fig. 3. DSC Thermograms of FK888 Aged at 60 °C

Water Vapor Sorption–Desorption Isotherms Water sorption–desorption studies were conducted on an integrated microbalance system (MB-300W, VTI Corporation) with about 10 mg each of Sample A and Sample B. Relative humidity was increased from 5 to 95% with 10% RH increments. Each successive increment was initiated when the change in weight at given RH was smaller than 0.01%.

Intrinsic Dissolution Rate The intrinsic dissolution rate was measured by rotating disk method. Sample A and Sample B were compacted with a KBr tabulating instrument for IR measurement (HORIBA Ltd.), and the diameter of the disk was 6 mm. The disk was set to the drive shaft for USP apparatus 1 with white petrolatum and rotated at 100 rpm at 37 °C in 900 ml of aqueous solution with 0.15 w/v% or 0.30 w/v% of sodium lauryl sulfate (SLS). At appropriate intervals, an aliquot was withdrawn automatically through the filter (F-72, Toyama Sangyo Co. Ltd.) and drug release was spectrophotometrically determined at 287 nm (UV-1600, Shimadzu Corporation).

Preparation of Drug Product Lactose (325 mesh) was added to both of Sample A and Sample B so that lactose content was 35 w/w%, and these were mixed well. Mixed powders were then filled into HPMC capsules (size 2) manually such that each capsule contained about 40 mg of FK888 (about 53 mg of powders).

Respirable Fraction (Fine Particle Dose) Determination Fine particle dose of the drug product was determined by using multistage cascade impactor (USP28 ⟨601⟩ Aerosols apparatus 3). E-haler was used as the device to inhale. Flow rate and the duration of the flow were set to be 40 l/min and 6 s based on the flow resistance of the device according to the USP. FK888 deposited from induction port to stage 1, or FK888 deposited from stage 2 to filter stage (its aerodynamic particle size was less than 5.8 μm) were extracted together by methanol, respectively, and then quantified spectrophotometrically at 287 nm (UV-2400, Shimadzu Corporation). The latter was stipulated as fine particle dose, and sum of these two was stipulated as delivered dose. Respirable fraction was calculated according to the following equation to remove the influence of the difference of delivered dose.

$$\text{respirable fraction (\%)} = \{(\text{fine particle dose})/(\text{delivered dose})\} \times 100 \quad (1)$$

Results and Discussion

Characterization of Amorphous Form of FK888 Amorphous materials can be described in terms of their fragility, which is a measure of the temperature dependence of the molecular mobility in the region of their glass transition temperature (Tg). Fragility (m) and strength parameter (D) were obtained by using the following equations.

$$m = \Delta H^* \eta / 2.303 R\mathrm{Tg} \quad (2)$$

$$D = 666/(m-17) \quad (3)$$

Where $\Delta H^* \eta$ is activation energy for viscous flow, R is gas constant. ΔH^* was obtained from heating rate dependence of Tg.

$$d \ln q / d(1/\mathrm{Tg}) = -\Delta H^*/R \quad (4)$$

Where q is heating rate of thermal analysis.[13,14]

FK888 was heated through Tg to 140 °C with various heating rate (2— 30 °C/min), and Tg values of each heating rate condition were determined. As a result, it appeared that the relationship between Tg and heating rate for FK888 showed a good linearity (see Fig. 4).

The calculated values of fragility (m) and strength parameter (D) were 118 and 6.6, respectively. It has been reported that fragile amorphous solids, citric acid, sorbitol, and indomethacin, for example, have the m value of 135, 93 and 77, respectively.[14] Based on these results and Angell's concept, FK888 is considered to be a fairy fragile glass.[13] Therefore, FK888 is reorganized to have a structure that fluc-

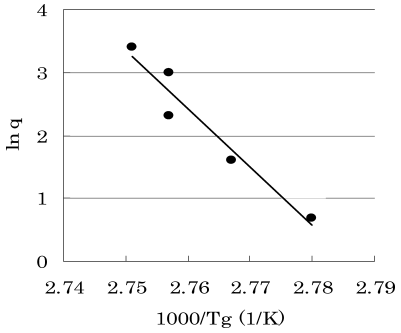

Fig. 4. The Relationship between Tg and Heating Rate for FK888

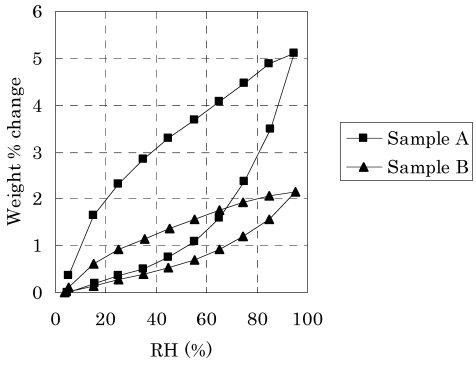

Fig. 5. Water Sorption–Desorption Isotherms for Sample A and Sample B at 25 °C

tuates over a variety of orientation and would show a catastrophic change in structure near Tg.

As FK888 was confirmed to have a typical property as a glass solid in the DSC analysis, the molecular mobility of FK888 was evaluated whether FK888 shows a similar relaxation behavior like indomethacin, poly(vinylpyrrolidone) or sucrose. The obtained DSC curve for the aged sample stored at 60 °C for 5 d is shown in Fig. 3. As it was confirmed that the aged sample showed no crystallization and chemical degradation during the aging periods by powder X-ray and HPLC analysis (data are not shown), a large endothermic peak observed at around the glass transition temperature should be due to the structural relaxation. The size of the recovery endotherm accompanying the glass transition increased with storage period reflecting greater structural relaxation of the glass towards the equilibrium supercooled liquid state. As the characteristic recovery endotherm was observed in FK888, it could exist as an amorphous solid with various energy states. Therefore, FK888 may show time dependent and/or temperature dependent changes in physical and mechanical properties. Considering that the morphology or physical property changes due to moisture adsorption as well as heat stresses may affect drug delivery from dry powder inhalers, unique insights into the performance of FK888 DPIs are necessary.

Moisture Sorption–Desorption Isotherms of FK888 It has been reported that adsorbed water plasticises the amorphous solids, leading to a greater probability of chemical or physical instability.[15] In case of FK888, it showed a typical decrease in Tg from 89 to 57 °C when it adsorved 4.5% of moisture.[16] This Tg lowering phenomenon due to moisture sorption may lead to molecular mobility at around room temperature, which would cause morphology changes of FK888 fine particles during storage or manufacturing processes. In case of FK888, it has appeared that FK888 might exist as glass states with different enthalpy recovery values according to the manufacturing or storage conditions. Thus, moisture sorption–desorption behavior of Sample A and Sample B were evaluated, since it was suggested that unaged and aged FK888 would show some different physical properties. Figure 5 shows the moisture sorption–desorption isotherms of Sample A and Sample B at various relative humidity at 25 °C.

As shown in Fig. 5, experimentally measured moisture sorption isotherms for Sample A and Sample B showed a typical isotherm of type II, commonly reported for water insoluble hydrophilic polymers.[17] It is suspected that hydroxyl groups in the FK888 solid may have a similar role to that of water insoluble hydrophilic polymers.

In addition, it appeared that the moisture sorption–desorption isotherms of Sample A and Sample B exhibited a hysteresis, showing that the amounts of water associated with the samples are greater for the desorption isotherm than for the adsorption isotherm at the given relative humidity. This phenomenon is also observed for water insoluble hydrophilic polymers, and it is recognized by the formation/destruction of hydrogen bonding.

In case of FK888, as the adsorption process proceeds, the interhydroxyl hydrogen bonds would be broken and the new hydrogen bonds formed between hydroxyl-groups and water molecules. Thus, at high relative humidity, more sites are available for the interaction between water molecules and hydroxyl-groups on the sample during the desorption process than the adsorption process. In the hysteresis of the moisture isotherms for Sample A and Sample B, much larger amount of water was observed in the desorption process of Sample A compared to that of Sample B. Considering that there was no difference in the surface area (about 10 m^2/g) as well as particle size distribution for these samples (D50: about 4 μm), these distinctly different moisture sorption–desorption behaviors can be explained by that Sample A has much larger sites where water molecules penetrate deeply into the particles compared to Sample B when stored it under high humidity conditions.

Precise comparison of water sorption profiles between Sample A and Sample B indicates that their water contents up to 55%RH were almost same. However, under high humidity conditions more than 55%RH, adsorbed amount of water to Sample A was much larger than that of Sample B, supporting that there would be some differences in the surface properties of Sample A (unaged sample) and Sample B (aged sample). The similar moisture sorption behavior was reported for freeze-dried (amorphous) trehalose with different ΔH (intact and aged samples), and the aged sample sorbed less water than the unaged trehalose at RH values ranging from 0 to 40% (25 °C).[12] In this case, it was confirmed that there was no difference in the particle size and morphology, suggesting that the observed differences were attributed to enthalpy relaxation. These phenomena observed for amorphous trehalose were explained by that the major consequence of aging is decrease in free volume and increase in density, resulting in the decreasing of the amount of sorbed water to the aged sample compared to the intact sam-

ple. Regarding the moisture sorption behavior of FK888, Sample A and Sample B showed a significant increase in water content at relatively high humidity compared to amorphous trehalose. This difference is considered to be due to the hydrophobic property of FK888, since it has only one hydroxyl group while trehalose has totally 8 hydroxyl groups in its structure.

Therefore, these results suggest that this different water sorption behavior observed for unaged and aged FK888 may be explained by the decrease in free volume of aged FK888 accompanying with the increase in density. From these water sorption–desorption studies, the aged sample of FK888 is much preferable for drug substance applied to DPIs product according to the stability and handling point of view.

Effect of Structural Relaxation on Dissolution Rate of FK888 It has been reported that small changes in physical properties such as crystallinity of water insoluble compound strongly affect the dissolution rate or solubility. Thus, it is suspected that the effect of aging procedure may change the dissolution rate, since the structure relaxation observed for FK888 was confirmed to cause some physical changes such as decrease in the free volume and increase in the density. Figure 6 shows the dissolution rate of Sample A and Sample B. In this dissolution studies, sodium lauryl sulfate (SLS) was adopted as the surfactant since the solubility of FK888 in water is very low. The SLS concentrations of 0.15% and 0.30% were selected taking into consideration of its CMC value (0.2%).

As shown in Fig. 6, the dissolution rate of Sample A was a little bit faster than that of Sample B not depending upon the concentration of SLS. However, it was considered that there would be no significant difference in the bioavailability between FK888 DPIs product prepared by Sample A and that by Sample B, since these small differences in the dissolution rates of Sample A and Sample B would be negligible compared to the dissolution rate differences reported in many pharmaceutical polymorphs.[18] From these results, it was expected that the aging process (structural relaxation) might not affect the bioavailability of FK888, even though the particle and/or physical properties of FK888 were confirmed to be changed by aging process.

Effect of Structural Relaxation on Physical Stability (Specific Surface Area) Generally, physical or particle properties such as surface area, particle morphology and particle size distribution are recognized to be important for DPIs product, since solid particles are directly administrated into the human lung and the product performance is strongly affected by physical/particle properties of drug substance. This means that the changes of surface area or particle size distribution of FK888 would affect the performance of DPIs product during storage periods or manufacturing processes. Considering that the heat stress below Tg causes physical changes as described above (decrease in the free volume and increase in the density of FK888 particles), it should be very important to know the effect of heat and humidity stresses on the physical or particle properties of FK888 for the development of the DPIs product. Thus, Sample A and Sample B were stored under the various storage conditions tabulated in Table 1. Although analyses of surface area and/or particle size distribution are very common to evaluate the physical or particle properties of fine particles, there was a difficulty in testing for the particle size distribution of FK888 due to its adhesive property. Therefore, specific surface area was selected as the indicator of its physical property. The obtained results of specific surface areas of Sample A and Sample B stored under the various conditions are shown in Fig. 7 and Table 1.

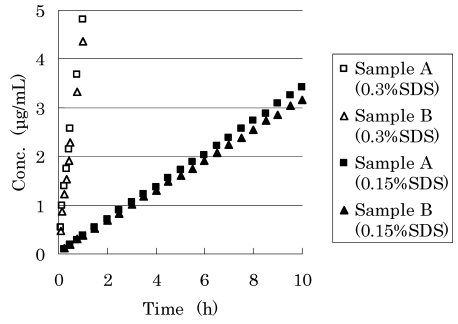

Fig. 6. Dissolution Rate for Sample A and Sample B

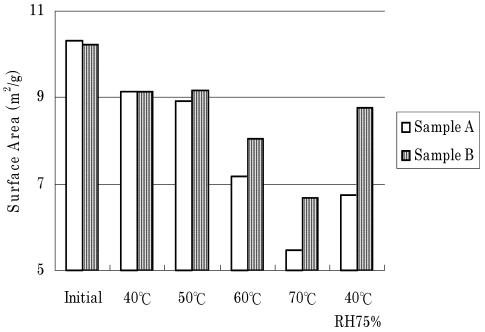

Fig. 7. Specific Surface Area for Sample A and Sample B Stored under Various Storage Conditions for 1 Month

Table 1. Change in Specific Surface Area for Sample A and Sample B Stored under Various Storage Conditions

Storage condition and period		Specific surface area (m^2/g)	
		Sample A	Sample B
Initial		10.31 (100)	10.21 (100)
40 °C	2 weeks	9.49 (92)	9.74 (95)
	1 month	9.14 (89)	9.12 (89)
50 °C	2 weeks	9.64 (94)	9.97 (98)
	1 month	8.91 (86)	9.18 (90)
60 °C	2 weeks	8.91 (86)	10.04 (98)
	1 month	7.17 (70)	8.04 (79)
70 °C	2 weeks	6.22 (60)	8.19 (80)
	1 month	5.47 (53)	6.68 (65)
40 °C RH75%	2 weeks	7.74 (75)	8.55 (84)
	1 month	6.73 (65)	8.76 (86)

( ): [(surface area after storage)/(surface area of initial)]×100.

As shown in Table 1, the specific surface area of Sample A was the same as that of Sample B before storage. However, it was found that the reduction percentage of surface area for Sample A after storage at 40, 50, 60 and 70 °C for 1 month were 89, 86, 70, and 53%, respectively. On the other hand, the reduction percentage of Sample B even stored at 70 °C was 65%, which was milder than that of Sample A (53%). Furthermore, the reduction percentage of specific surface

area of Sample B stored at 40 °C 75%RH for 1 month was 86%, which was much stable compared to that of Sample A (65%). In the comparison of the test results between Sample A and Sample B, it appeared that the surface property of Sample A was strongly affected by storage conditions. This result can be explained by that Sample B is almost fully relaxed by aging and molecular mobility is considered to be restrained compared with Sample A. Therefore, it can be concluded that the aged FK888 particles is physically more stable than the intact FK888 particles, suggesting that the aged sample has preferable physical/particle properties for the DPIs product.

Effect of Structural Relaxation on Aerosol Property An multistage cascade impactor (USP apparatus 3) was used to determine the aerosol properties of FK888 DPIs product. The cascade impactor provides an *in vitro* system for estimating the potential depth of penetration of aerosols into the human lung. The device consists of series of flat plates arranged perpendicular to an airflow, such that particles deposit stagewise in accordance with their aerodynamic diameter, which is critically dependent on the cross-sectional area, density, and morphology of the particles. Therefore, there is a high possibility that the respirable fraction of DPIs product prepared by Sample A would be decreased by heat stress, since the above described results revealed that the physical properties (such as specific surface area) of Sample A were confirmed to be changed by high temperature or humidity storage conditions. To evaluate the effect of storage temperature on respirable fraction of FK888 DPIs product, FK888 capsules filled with Sample A or Sample B was stored at 70 °C for 2 weeks. The obtained respirable fractions for Sample A and Sample B are shown in Table 2.

Table 2. Change in Respirable Fraction of DPIs Manufactured with Sample A and Sample B (70 °C 2 Weeks)

Storage condition and period	Run No.	Respirable fraction (%)			
		Sample A		Sample B	
Initial	1	56.6	Ave.: 59.6 (100)	59.7	Ave.: 60.2 (100)
	2	61.7		58.8	
	3	61.0		60.6	
	4	60.3		59.1	
	5	58.6		62.7	
70 °C 2 weeks	1	34.2	Ave.: 32.8 (55)	49.8	Ave.: 51.5 (86)
	2	32.5		52.4	
	3	31.7		52.2	

( ): [(respirable fraction after storage)/(respirable fraction of initial)]×100.

Although it was confirmed that aging process gave rise to small changes in density and free volume of FK888 particles, the initial drug product of Sample A and Sample B showed almost the same respirable fraction as shown in Table 2. However, as indicated in Table 2, the drug product of Sample A stored at 70 °C showed a significant decrease (55%) in respirable fraction compared to that of Sample B (86%). Therefore, it was confirmed that the unaged FK888 particles aggregated or showed a morphology changes in the capsules during the storage periods, and resulted in the decrease in respirable fraction. On the contrary, the aged FK888 particles was confirmed to be relatively stable in terms of DPIs performance compared to unaged FK888.

Conclusions

FK888 was confirmed to be a typical glass and categorized as a fragile glass based on Angell's concept. DSC study indicated that FK888 may have various energy states depending upon the aging conditions, since FK888 showed a large recovery endotherm reflecting a structural relaxation. The unaged and aged FK888 solids were micronized to prepare for dry powder inhalers. The physicochemical comparison of these unaged and aged FK888 particles revealed that they showed a significant difference in the moisture sorption–desorption isotherms. That is, much less amount of moisture adsorbed to the aged sample under high humidity conditions (>55%RH) compared to the unaged sample. This moisture sorption–desorption behavior of aged FK888 is explained by that the major consequence of aging is decrease in free volume and increase in density. Investigation on the respirable fraction (fine particle dose) indicated that unaged FK888 filled into the capsules with lactose showed the lower results after storage at 70 °C for 2 weeks compared to that of initial sample. On the other hand, aged FK888 did not show a significant decrease in the respirable fraction after the same storage condition, suggesting that fine particle agglomeration or morphology changes should be prevented. This result was supported by that the surface area of unaged FK888 was significantly reduced compared to that of aged FK888 by heat or humidity stresses. Since the dissolution rate of unaged FK888 was confirmed to be very similar to that of aged FK888, it was considered that there should be no significant difference in the bioavailability between FK888 DPIs prepared by aged FK888 and that by unaged FK888. Therefore, it can be concluded that the aged FK888 particles are much preferable to prepare for the stable DPIs than the unaged FK888 particles.

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