Effect of Tablet Geometrical Structure on the Dehydration of Creatine Monohydrate Tablets, and Their Pharmaceutical Properties

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Yukoh Sakata,[1] Sumihiro Shiraishi,[1] and Makoto Otsuka[2]

[1]Healthcare Research Institute, Wakunaga Pharmaceutical Co, Ltd, 1624 Shimokotachi, Kodacho, Takatagun, Hiroshima 739-1195, Japan

[2]Department of Pharmaceutical Technology, Kobe Pharmaceutical University, 4-19-1 Motoyama-Kitamachi, Higashi-Nada, Kobe 658, Japan

ABSTRACT

The effects of compression and pulverization on the dehydration kinetics and hardness of creatine monohydrate tablets were studied using a variety of kinetic equations and physical models. The dehydration behavior of unpulverized and pulverized tablets was investigated by using differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). The hardness of both unpulverized and pulverized monohydrate tablets was significantly decreased after dehydration. The relationship between the degree of dehydration and the tablet hardness of both unpulverized and pulverized monohydrate tablets formed a straight line. The results suggest that the reduction in tablet hardness is dependent on the dehydration of crystal water, and the values of the slopes indicate that the bonding energy of the unpulverized sample was stronger than that of the pulverized sample. The dehydration kinetics of the unpulverized and pulverized monohydrate tablets were evaluated by analyzing the fit of the isothermal DSC data using a variety of solid-state kinetic models. The dehydration of the unpulverized tablets at various levels of compression pressure followed the 3-dimensional growth of nuclei mechanism. In contrast, although the dehydration kinetics of pulverized monohydrate tablets compressed at 500 and 750 kg/cm^2 followed the 3-dimensional diffusion mechanism, those compressed at 1000 kg/cm^2 followed the 3-dimensional growth of nuclei mechanism. The PXRD analysis indicated that the diffraction intensity of the pulverized monohydrate powder was significantly lower than that of the unpulverized powder. The diffraction peaks of the (h00) planes and the micropore structure of the unpulverized monohydrate tablets were affected by pulverization and compression force, respectively.

KEYWORDS: unpulverized creatine, pulverized creatine, dehydration kinetics, crystal orientation, compression force.

Corresponding Author: Yukoh Sakata, Healthcare Research Institute, Wakunaga Pharmaceutical Co, Ltd, 1624 Shimokotachi, Kodacho, Takatagun, Hiroshima 739-1195, Japan. Tel: +81-826-45-2331; Fax: +81-826-45-4351. E-mail: sakata_y@wakunaga.co.jp

INTRODUCTION

The presence of crystal water in crystalline structures is common in both organic and inorganic compounds. More than 90 hydrates are listed in the *United States Pharmacopoeia*.[1] Since the stability of all hydrates is not the same,[2,3] hydrate formation and dehydration might occur during the manufacture, processing, or storage of pharmaceutical compounds.[4] Knowledge of the hydration and dehydration behaviors of the hydrate drugs is essential for the development of stable formulations because the physicochemical, mechanical (during processing), and biological properties of the hydrates are significantly different from those of anhydrates. The differences in stability are attributable to the interaction between crystal water and the crystalline structure of the drug, which is based on hydrogen bonding. Shefter and Higuchi[5] found that the apparent dissolution rate and solubility of the anhydrous form of several drugs, such as theophylline, caffeine, and glutethimide, are higher than those of the hydrate. Utsumi et al[6,7] reported that the disintegration time and appearance of tablets containing several drug hydrates, such as pentobarbital calcium and calcium pyruvate isoniasone were significantly different from those of anhydrates. Since the crystalline-phase transitions of hydrates or anhydrates during the manufacturing process and storage periods were accompanied by a change in the pharmaceutical properties of the preparations, it was concluded to be important to understand the mechanisms of the transition and the fate of pharmaceutical preparations under various conditions. However, there has been little research into the phase transition kinetics of pharmaceutical drugs in tablet form during storage.[8,9]

Creatine is used in the treatment of adenosine triphosphate (ATP)-yielding substrates in muscle under anaerobic conditions and exists as both a monohydrate and an anhydrate. In a previous study using thermogravimetric analysis (TGA), dehydration of creatine monohydrate powder was affected by particle size, and the dehydration was accelerated by pulverization. This was attributed to the fact that the surface area of the powder determined the dehydration rate. The dehydration of unpulverized and pulverized powders followed a zero-order mechanism.[10] On the other hand, Otsuka et al[9] reported that the dehydration kinetics of

theophylline monohydrate tablets were affected by their geometrical structure, such as porosity and shape. Moreover it was concluded that the geometrical characteristics of the tablet governed the hydration kinetics based on the dehydration observed in a pure theophylline monohydrate tablet system. However, there has been no previous study of the effect on a practical formulation tablet system. In the present study, therefore, in order to clarify the effect of tablet geometrical factors on the dehydration kinetics of a tablet's formulation, the dehydration of a creatine monohydrate tablet formulation was analyzed using the solid-state kinetic method.

Materials and Methods

Materials

Creatine monohydrate was purchased from Yukigosei Yakuhin Industries (Tokyo, Japan). The fine powder form of creatine monohydrate was pulverized with an atomizer (pulverizing machine, Hitachi, Tokyo, Japan). Dibasic calcium phosphate anhydrous (Fujicalin, Fuji Chemical Industries Co, Ltd, Toyama, Japan) and microcrystalline cellulose (Avicel PH101, Asahi Chemical Industries, Tokyo, Japan) were used as an excipient. Magnesium stearate (Taihei Chemical Industries, Osaka, Japan) and anhydrate silicic acid (Maikon F, Tomita Pharmaceuticals, Tokushima, Japan) were used as a lubricant and a glidant, respectively.

Methods

Preparation of Tablets

Tablets containing the model drug, creatine (100 mg/tablet), were prepared by direct compression at 500, 750, and 1000 kg/cm^2 using a circular die of 9.0 mm in diameter and a standard concave punch on a tablet machine (Kikusui Engineering, Kyoto, Japan). The formula of the tablets (250 mg/tablet) containing creatine was as follows: anhydrous dibasic calcium phosphate, 75 mg/tablet; microcrystalline cellulose, 65 mg/tablet; magnesium stearate, 2.5 mg/tablet; anhydrate silicic acid, 7.5 mg/tablet.

Storage Conditions

Unpulverized and pulverized creatine monohydrate were 100% transformed into the anhydrate, respectively, at more than 40ºC and 30ºC under conditions of 30% ± 2% relative humidity.[10] (The unpluverized creatine monohydrate was 100% transformed into anhydrate, and pulverized monohydrate was also 100% transformed into anhydrate.) On the other hand, the anhydrate was 100% transformed into the hydrate, respectively, at more than 53% relative humidity at 25ºC. (The unpluverized anhydrate was 100% transformed into hydrate, and pulverized anhydrate was also transformed 100% into hydrate.) The dehydration behavior of unpulverized and pulverized creatine monohydrate tablets was tested at various storage temperatures from 40ºC to 60ºC ± 1ºC and under conditions of 30% ± 2% relative humidity.

Dehydration Studied by Differential Scanning Calorimetry

Thermal analysis of the samples was performed using differential scanning calorimetry (DSC) (EXSTRA 6000 with measuring cell DSC 30E, Seiko, Tokyo, Japan). Approximately 10 mg of sample was weighed into the DSC pan. The pan was not sealed and was placed into the sample side of the instrument. An identical reference pan was placed in the reference side. Scans were performed at a rate of 10ºC/min and at temperatures of between 25ºC and 300ºC, using a nitrogen gas purge at 50 mL/min.

Powder X-ray Diffraction Analysis

Powder X-ray diffraction (PXRD) analysis was performed at room temperature with a type Rint2550VHF diffractometer (Rigaku, Tokyo, Japan). Measurement conditions were as follows: target, copper; filter, Kα; voltage, 40 kV; current, 450 mA; time constant, 1 second; step slit, 1.0º; counting time, 1.0 second; measurement range, 2 θ = 5º to 2 θ = 30º. The loosely packed sample was prepared by pouring the powder into the holder without compressing.

Thermogravimetric Analysis

The TGA curves were measured using a thermogravimetric analyzer (TGA EXSTRA 6000 with measuring cell DSC 30E, Seiko). Approximately 10 mg of sample was weighed with accuracy into the DSC pan. The pan was not sealed and was placed into the sample side of the instrument. An identical reference pan was placed in the reference side. Scans were performed at a rate of 10ºC/min and at temperatures between 25ºC and 300ºC, using a nitrogen gas purge at 50 mL/min.

Dehydration of the Tablets

The tablets (250 mg/tablet) were heated in an oven at 40ºC to 60ºC, removed at predetermined intervals, and then ground to prepare powder samples. The powder samples were subjected to DSC, PXRD, and TGA.

Measurement of Thickness, Diameter, and Specific Volume of Tablets After Dehydration

After dehydration, the thickness and diameter of each tablet were measured 10 times with a slide caliper, and the mean was calculated. The micropore volume distribution of each

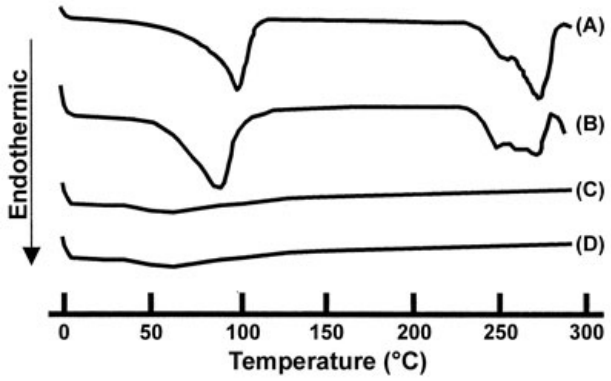

Figure 1. DSC thermographs of (A) unpulverized creatine monohydrate powder, (B) the tablet, (C) before storage of fillers and (D) after storage of fillers.

tablet was measured immediately after compression using mercury porosimetry (Porosimeter type 2000, Carlo Erba Instruments, Milan, Italy). The contact angle and surface tension of mercury were 141.3º and 480 dyne/cm, respectively. The pore radius ranged from 6×10^{-3} to 300 μm.

Results and Discussion

Typical DSC Curves of Creatine Monohydrate, Tablets Containing Creatine Monohydrate and Excipients, Before and After Storage of Excipients

The dehydration of tablets might be affected by the dehydration characteristics of bulk powders and additives in the formulation. Therefore, DSC profiles of the bulk powder of creatine and excipients were measured as follows.

Figure 1A and B show the DSC profiles of unpulverized creatine monohydrate and creatine monohydrate tablets containing excipients. The DSC curves of unpulverized creatine monohydrate and its tablet showed endothermic peaks at 88.3ºC and 66.5ºC due to dehydration, and dehydration and vaporization of water respectively, and endothermic peaks at 234.7ºC and 229.6ºC due to intramolecular cyclization of creatine anhydrate with a loss of 1 mol of water, respectively. The absorption peaks of dehydration and the melting point of creatine monohydrate powder were slightly affected by excipients.

Figure 1C and D show the DSC profiles of excipients before and after storage at 60ºC for 24 hours. The thermal behavior of excipients before and after storage did not differ significantly. Also, the water contents calculated using the TGA of excipients did not differ significantly before and after storage. This result indicated that the excipients were not hydrated under the experimental conditions. Moreover, there was a uniformly linear relationship between the degree of dehydration calculated using the DSC and the water content calculated using the TGA of creatine monohydrate tablets. Since the dehydration of creatine monohydrate tablets was not affected by addition of excipients, it was presumed that the degree of hydration of creatine monohydrate in the tablet could be evaluated based on the latent heat in the DSC curve of the tablet formulation sample powder.

Dehydration Kinetics of Creatine Monohydrate Tablets and Their Tablet Geometrical Structure

Since the dehydration of pharmaceuticals affects the bioequivalence and stability of the products, it is important to clarify the dehydration kinetics of a practical tablet formulation in order to predict the stability of the product. Figure 2A and B show the typical isothermal dehydration plots of unpulverized and pulverized creatine monohydrate

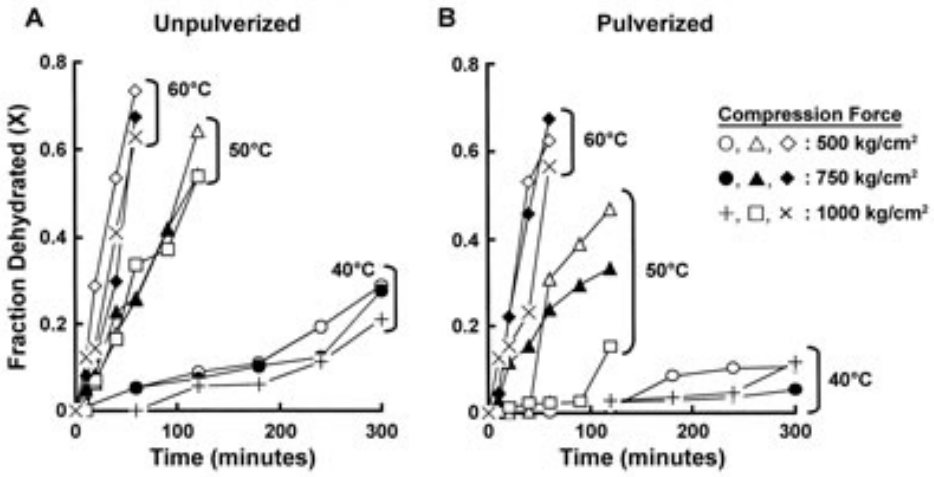

Figure 2. Plot of dehydration fraction against time for the dehydration of unpulverized and pulverized creatine monohydrate tablets under isothermal conditions.

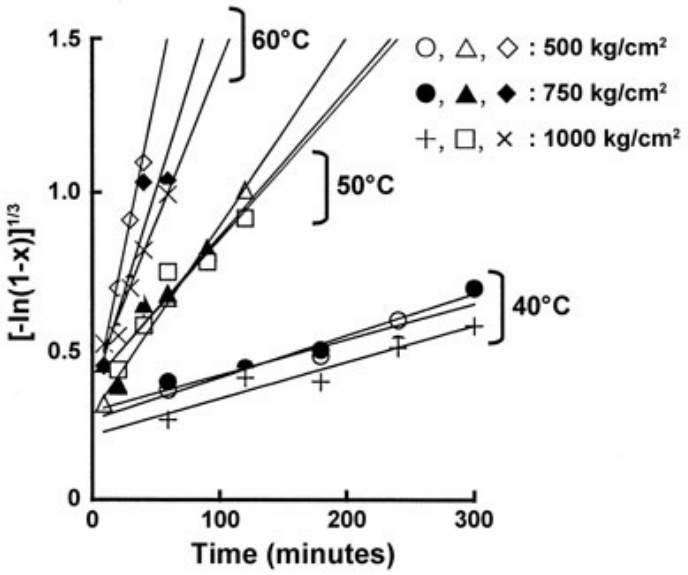

Figure 3. Dependence of g(x) on time for dehydration of unpulverized creatine monohydrate tablets prepared by various compression forces. $g(x)=[-\ln(1-x)]^{1/3}$

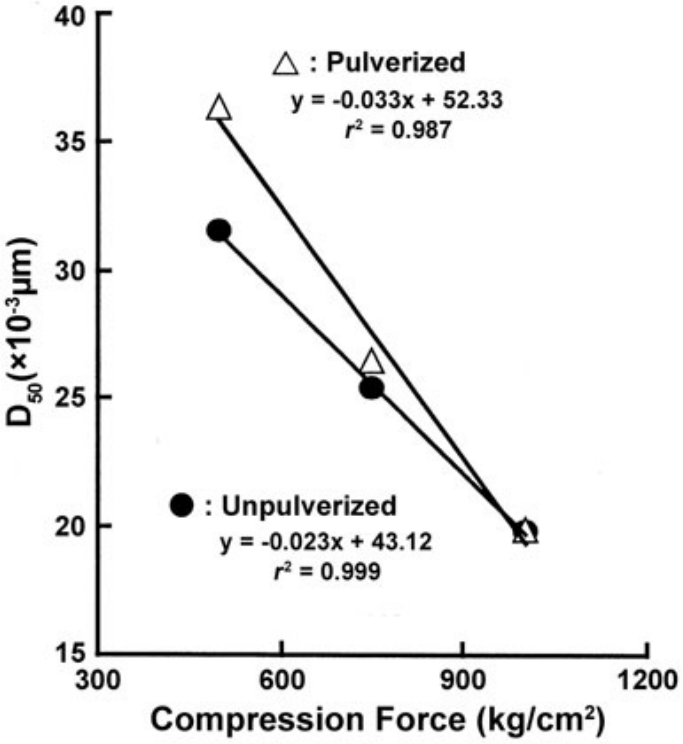

Figure 5. The relationship between compression force and average micropore radius of unpulverized and pulverized creatine monohydrate tablets.

tablets. The dehydrated fraction, *x*, of the sample tablets at fixed temperatures covering the range 40ºC to 60ºC was obtained by calculating the heat of dehydration from the creatine monohydrate DSC curves. The value of *x* of the unpulverized or pulverized samples was plotted as a function of time, *t*, according to the kinetic model of the reaction mechanisms known to occur in the solid state.[11-17] The correlation coefficient squared, r^2, was determined to test the extent to which the data conform to the kinetic models. At all temperatures tested, dehydration rate increased with increasing storage temperature. The dehydration behavior of unpulverized sample tablets was analyzed with the aid of various solid-state reaction equations. It was found that the dehydration kinetics of unpulverized monohydrate tablets were best fitted to the 3-dimensional growth of nuclei equation, as shown in Figure 3 and below. In contrast, Figure 4 shows the effect of various compression forces on the dehydration kinetics of the pulverized monohydrate tablets. The dehydration curves of pulverized creatine monohydrate changed significantly with increasing compression force. Figure 4A and B show that the dehydration kinetics at 500 to 750 kg/cm^2 were best described by the 3-dimensional diffusion equation (D4)

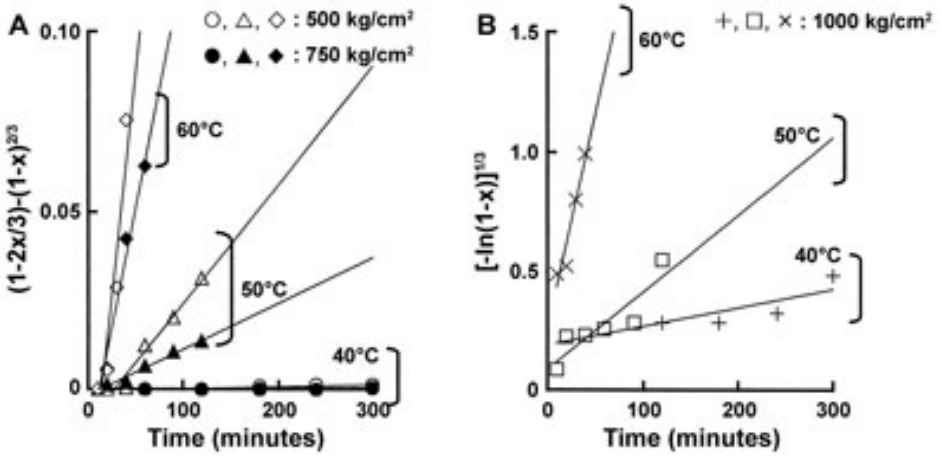

Figure 4. Dependence of g(x) on time for dehydration of pulverized creatine monohydrate tablets prepared by various compression forces. A: $g(x) = (1-2x/3)-(1-x)^{2/3}$, B: $g(x) = [-\ln(1-x)]^{1/3}$

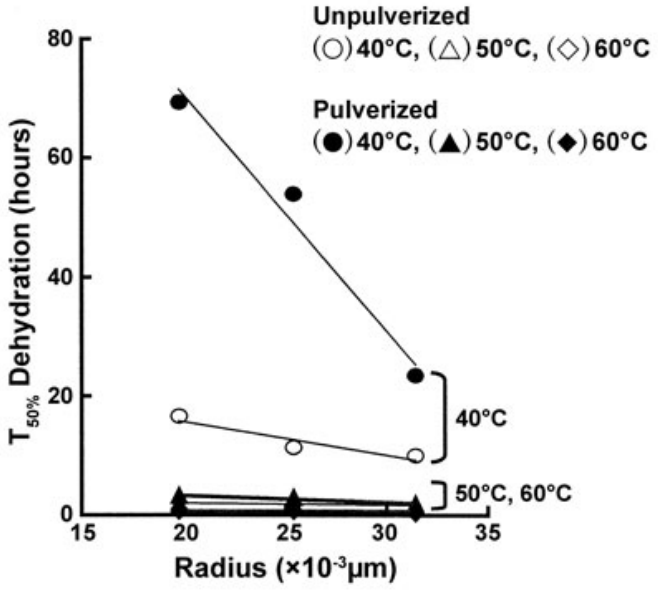

Figure 6. Effect of temperature on the relationship between average micropore radius and the time required for 50% dehydration ($T_{50\%}$) of unpulverized (open symbols) and pulverized (closed symbols) creatine monohydrate tablets.

and at 1000 kg/cm^2 by the 3-dimensional growth of nuclei equation.

$$[-ln(1-x)]^{1/3} = kt,\ k;\ \textit{rate constant}$$

Figure 5 shows the relationship between average micropore radius in the tablets, as calculated from the profiles of specific volume and compression force. The average radius of unpulverized and pulverized tablets decreased with increasing compression force, the relationship exhibiting a straight-line correlation. These results suggest that unpulverized tablets have a lower apparent volume than pulverized tablets.

Figure 6 shows the relationship between the 50% dehydration time ($T_{50\%}$) and micropore radius of both unpulverized and pulverized creatine monohydrate tablets. The $T_{50\%}$ of unpulverized and pulverized tablets decreased with increasing micropore radius, the relationship exhibiting a straight-line. The slope of the plots decreased with increasing storage temperature. These results suggest that the dehydration of the tablets is dependent on both particle size and the mechanical strength of the tablet. The pulverized creatine monohydrate tablets compressed at 500 and 750 kg/cm^2 had significantly higher tablet hardness and tablet porosity than unpulverized tablets compressed at 500 and 750 kg/cm^2 as shown in Table 1. It seems that the hydrate tablets, which have enough mechanical strength and high original porosity did not show significant change on their porosity as a result of water vapor during dehydration. The porosity of tablets that have weak mechanical strength and lower tablet porosity might be significantly increased during dehydration. Moreover, the porosity of unpulverized and pulverized creatine monohydrate tablets at a compression force of 1000 kg/cm^2 was similar (Table 1). Otsuka et al[8,9] reported that the dehydration kinetics of tablets were governed by the diffusion process of water vapor in tablet micropores. These results suggest, therefore, that the dehydration kinetics are affected by the mechanical strength of the particles and heat conduction.

Effect of Dehydration on Pharmaceutical Properties of the Creatine Monohydrate Tablets

A previous study demonstrated that the dehydration of creatine monohydrate was affected by particle size and was accelerated by pulverization. However, the results of the present tablet dehydration study (Figure 2) indicate that the dehydration kinetics of the tablet are not controlled only by dehydration of the bulk powder particles in the tablet, as reported by Otsuka et al.[9] In the Dehydration Kinetics of Creatine Monohydrate Tablets and Their Tablet Geometrical Structure section, the results (Figures 3 and 4) indicated that the diffusion of water vapor in tablet micropores determined the dehydration rate. Moreover, the dehydration behavior significantly affected the pharmaceutical properties of creatine monohydrate tablets, such as tablet hardness and tablet expansion.

Figures 7A and B show the relationship between the degree of dehydration, as calculated using DSC, and the hardness of unpulverized and pulverized creatine monohydrate tablets, respectively. As shown in Table 2, they were each

Table 1. Geometric Factor of Creatine Monohydrate Tablets*

Tablet Type	CF (kg/cm^2)	T (mm)	D (mm)	R	SV (mm^3/g)	Radius ($\times 10^{-3}$ μm)
Unpulverized	500	3.67	9.06	2.47	**141.9**	31.50
	750	3.54	9.05	2.55	**109.2**	25.40
	1000	3.49	9.05	2.59	**90.8**	19.80
Pulverized	500	3.76	9.06	2.41	**153.8**	36.39
	750	3.63	9.04	2.49	**116.7**	26.50
	1000	3.47	9.04	2.60	**87.2**	19.90

*CF indicates compression force; T, thickness; D, diameter; R, ratio of tablet diameter to tablet thickness, and SV, specific volume.

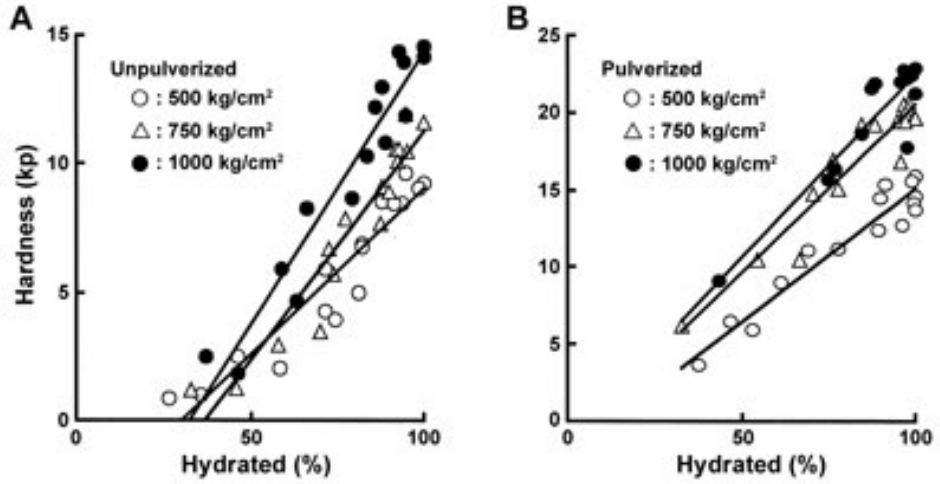

Figure 7. Effect of compression force on the relationship between dehydration and hardness of unpulverized and pulverized creatine monohydrate tablets.

significantly correlated, suggesting that tablet hardness is dependent upon the degree of dehydration of the hydrate. The slope calculated from the straight-line relationship of pulverized creatine monohydrate tablets was higher than that of the unpulverized creatine monohydrate tablets (Table 2). These results suggest that the phase change due to dehydration of the tablets contributes to the reduction in tablet hardness, and that the relationship between the degree of dehydration and tablet hardness for the unpulverized creatine monohydrate tablets has a more significant relationship than for pulverized tablets.

Figure 8 shows the percentage expansion of the thickness and diameter of unpulverized and pulverized creatine monohydrate tablets after dehydration for 5 hours. The expansion ratio of the thickness and diameter of the tablets increased and decreased with increasing compression force, respectively. Furthermore, the thickness and diameter of unpulverized and pulverized creatine monohydrate tablets expanded by 3% to 20% and 2% to 8%, respectively, after dehydration. Since expansion in the thickness of the tablets exceeded expansion in the diameter, tablet expansion was

Table 2. Slopes and Correlation Coefficients of Calorimetric Measurements of Crystallization Water and the Hardness of Unpulverized and Pulverized Creatine Monohydrate Tablets*

Tablet Type	CF (kg/cm^2)	Slope (kp/%)	Correlation Coefficient (r^2)
Unpulverized	500	**0.129**	**0.927**
	750	**0.179**	**0.908**
	1000	**0.213**	**0.935**
Pulverized	500	**0.172**	**0.925**
	750	**0.217**	**0.907**
	1000	**0.237**	**0.925**

*CF indicates compression force.

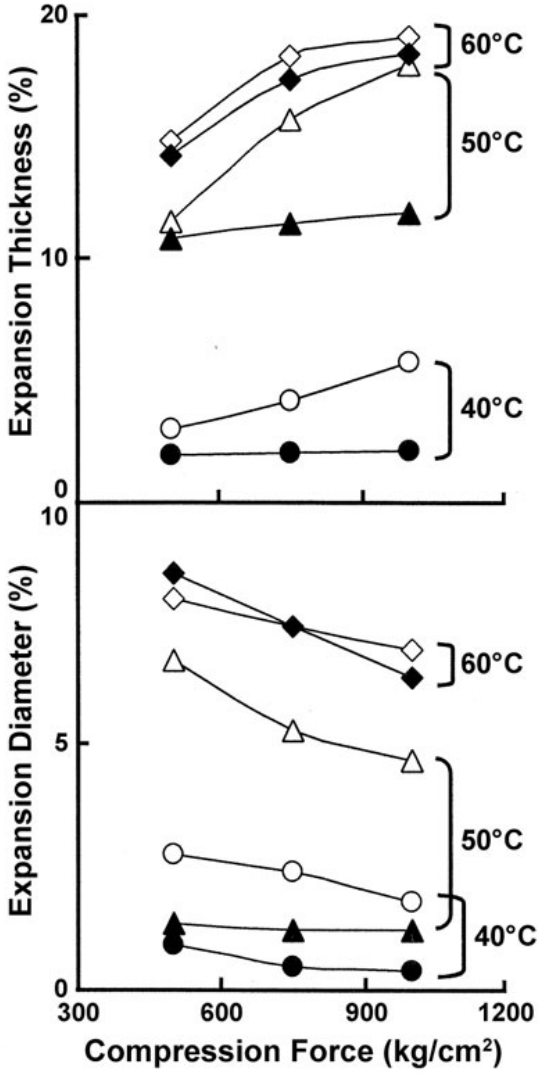

Figure 8. The effects of storage temperature and compression force on the expansion thickness and diameter of unpulverized (open symbols) and pulverized (closed symbols) creatine monohydrate tablets.

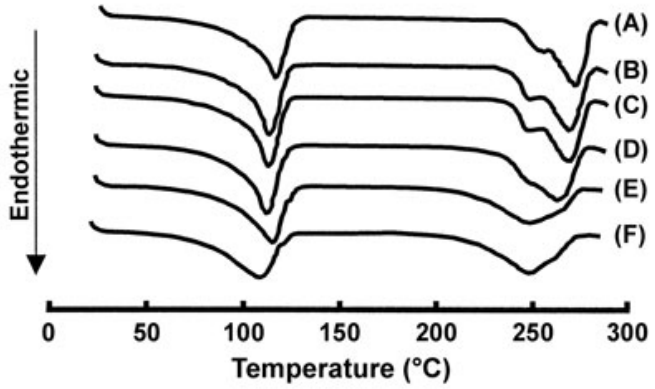

Figure 9. DSC thermograph of unpulverized and pulverized creatine monohydrate under various compression forces. (A) Unpulverized monohydrate powder, (B) Unpulverized at 500 kg/cm^2, (C) Unpulverized at 1000 kg/cm^2, (D) Pulverized monohydrate powder, (E) Pulverized at 500 kg/cm^2, and (F) Pulverized at 1000 kg/cm^2.

not uniform. The present results suggest that unpulverized creatine monohydrate tablets expand more than pulverized creatine monohydrate tablets when subjected to dehydration. The mechanical strength of dehydrated tablets decreased, and the tablets disintegrated after dehydration.

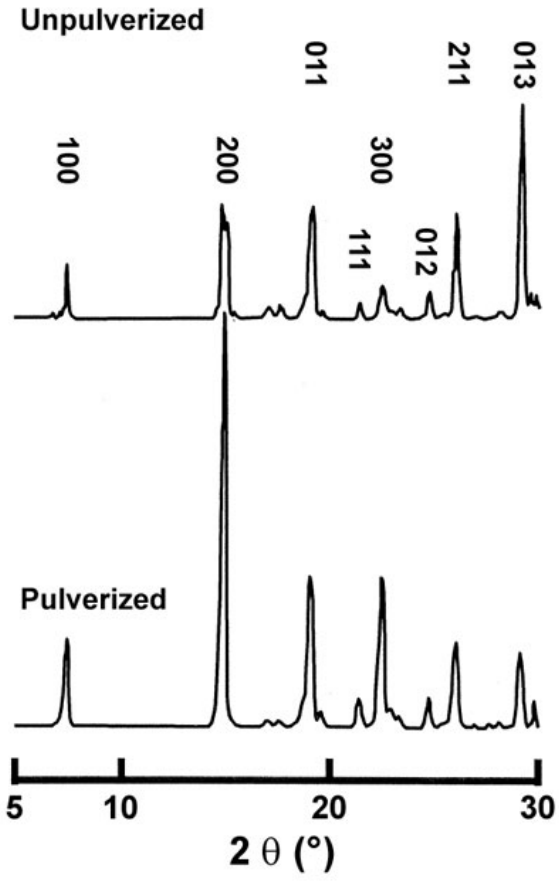

Figure 10. PXRD patterns of unpulverized and pulverized creatine monohydrate.

Thus, a relationship exists between tablet hardness and dehydration kinetics: there is a reduction in hardness with tablet expansion. Both kinds of creatine monohydrate tablets studied here expanded more in thickness than in diameter after dehydration. These results suggest that the difference of unpulverized and pulverized tablet properties might depend on the characterization of their monohydrate powder by means of mechanical force.

Figure 9 shows the DSC profiles of unpulverized and pulverized creatine monohydrate powder following tableting performance. The absorption peaks of dehydration and the melting point of unpulverized and pulverized creatine monohydrate were significantly different than those of their powder, with some of their absorption peaks reduced with increased compression force. However, the heat of fusion of the unpulverized and pulverized creatine monohydrate tablets and their powder remained unchanged following compression.

Figure 10 shows the PXRD profiles of the crystal structure of unpulverized and pulverized creatine monohydrate samples. The PXRD pattern and main diffraction angles of the unpulverized and pulverized creatine monohydrate powder agreed with data described in a previous study.[18] However, the intensities of the diffraction peaks at 2θ = 7.4°, 14.9°, and 22.5° due to the (100), (200), and (300) planes of pulverized creatine monohydrate, respectively, were much stronger than those of the unpulverized powder sample (Table 3). Therefore, the peak intensity of the (*h*00) plane of the unpulverized creatine monohydrate was increased by mechanical force during pulverization. Furthermore, compared with the intensities of the peaks at 2θ = 23.3° and 28.9° due to the (012) and (013) planes, respectively, unpulverized creatine monohydrate appeared to be much stronger than pulverized creatine monohydrate.

Unpulverized and pulverized monohydrate tablets comprise long needle-shaped and cubic particles, respectively (data not shown). Since the needle-shaped particles have a

Table 3. Intensities of Diffraction Peaks in Powder X-ray Diffraction Patterns of Unpulverized and Pulverized Creatine Monohydrate*

		Peak Intensity(×10^4 cps)	
2 θ (º)	(hkl)	Unpulverized	Pulverized
7.4	(100)	**3.43**	**5.95**
14.9	(200)	**7.07**	**26.64**
19.1	(011)	**7.91**	**10.97**
21.4	(111)	**1.28**	**2.29**
22.5	(300)	**2.76**	**10.48**
23.3	(012)	**1.09**	**0.65**
26.0	(211)	**7.15**	**6.45**
28.9	(013)	**15.02**	**5.75**

*hkl indicates the Miller indices.

tendency to pack into a sample holder together in a fixed direction, the difference in PXRD intensity between unpulverized and pulverized samples may therefore be attributable to the crystal particle orientation in the sample holder. As shown in Figure 10, the crystals of creatine monohydrate oriented themselves in the (*h*00) and (01*l*) planes into monoclinic shapes after pulverization. This finding suggests that compression forces may cause crystals of creatine monohydrate within a tablet to orient in a particular way. Nakagawa et al[19] reported that the preferred orientation of aspirin crystals, which are thin and plate-like, within a tablet after compression have a strong tendency to orient in a particular direction at an early stage of compression, is to orient in a particular direction at an early stage of compression. These results and those gleaned from our present PXRD data suggest that the microstructure of pulverized creatine monohydrate tablets is not as uniform as in the unpulverized samples, because the pulverized creatine monohydrate contains more isotropic particles than the unpulverized sample. Thus, compression causes the crystals in the tablets to become oriented along a specific plane, such as (*h*00), resulting in nonuniformity of the mechanical strength of the tablets. These results suggest that the difference in the hardness of unpulverized and pulverized monohydrate tablets is attributable to differences in crystal shape and particle size. The expansion thickness and diameter of the unpulverized creatine monohydrate tablets were greater than those of the pulverized creatine monohydrate tablets (Figure 8), presumably because the deformed crystals of unpulverized creatine monohydrate tend to orient themselves more during compression than do the pulverized creatine monohydrate crystals. Thus, the crystal orientation of unpulverized creatine monohydrate was affected significantly by mechanical force during pulverization.

Furthermore, the results of a previous study indicated that dehydration kinetics of unpulverized and pulverized creatine monohydrate powder followed the R1 equations.[10] In contrast, in the present study the demonstrated kinetics of unpulverized and pulverized creatine monohydrate tablets suggest that tablet dehydration occurs in a manner different to that of the bulk powder and is affected by the structure of the dosage form (ie, whether it is unpulverized or pulverized). The dehydration of creatine monohydrate tablets involves water vapor diffusion and other reaction processes. Since the dehydration of the bulk powder occurs much faster than in the tablets, the rate-determining step of the dehydration of creatine tablets might be the process of diffusion from the micropores.

On the other hand, the hardness of unpulverized and pulverized creatine monohydrate tablets decreases with the degree of dehydration, and the dehydration kinetics might be affected by the changes in the porosity during dehydration. We have reported previously that the particle size of creatine monohydrate powder decreases with dehydration,[10] and tablet thickness and diameter expand with increases in the surface area of the particles. Moreover, we reported that the dehydration kinetics of unpulverized and pulverized creatine monohydrate powder are not dependent on the crystal orientation,[10] although the crystal orientation of unpulverized and pulverized creatine monohydrate might differ according to the compression force, as shown in Figure 9. The dehydration kinetics of unpulverized and pulverized creatine monohydrate tablets indicated the same pattern at a compression force of 1000 kg/cm^2. As shown in Table 1, tablet thickness and the radius of unpulverized and pulverized creatine monohydrate tablets were similar at a compression force of 1000 kg/cm^2. These results suggest that the dehydration kinetics of unpulverized and pulverized creatine monohydrate depend on the porosity of the tablets immediately after compression.

Moreover, these studies indicated that the dehydration kinetics of unpulverized and pulverized creatine monohydrate tablets were not affected by excipients because water of crystallization is probably inactive with excipients in tablet formulations. These results suggest that the dehydration kinetics of hydrate tablets can be estimated using a tablet formulation instead of the pure hydrate tablet.

CONCLUSION

The dehydration kinetics of creatine monohydrate tablets were affected by tablet geometrical factors, such as tablet hardness and porosity. Moreover, the dehydration kinetics of hydrate tablet were previously established for the pure hydrate tablet. In the present study, it was possible to estimate the dehydration of creatine monohydrate tablet for practical use by the solid-state kinetics method. Therefore, in the future, it may be possible to estimate the fate, stability, and pharmaceutical properties of various hydrate drugs in practical formulations by the thermal kinetics method.

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