Effect of Polymorphic Forms of Bulk Powders on Pharmaceutical Properties of Carbamazepine Granules

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The effects of polymorphic forms of bulk powder on the pharmaceutical properties of carbamazepine (CBZ) granules were investigated by using X-ray diffraction analysis, thermal analysis and Brunauer-Emmett-Teller surface area measurement. A mixture consisting of 50% CBZ forms I, II, III or IV (dihydrate) as a bulk powder, 35% crystalline α-lactose monohydrate and 15% corn starch was used as a pharmaceutical powder, with binder aqueous solutions containing 5% hydroxypropylcellulose (HPC). After kneading with the binder solution, granules were obtained using an extruding granulator. After granulation forms I, II and III were 2.5, 80.3 and 35.2% transformed into dihydrate, respectively. Next, the wet granules were dried at 60 °C for 24 h, and the transformed dihydrates were dehydrated into fine particles containing form III. The yield of granules obtained from forms I, II, III and IV was 73.8, 0.0, 0.0 and 76.3%, respectively. The lower granule yields of forms II and III appeared to be due to a lack of kneading water due to absorption of CBZ as crystalline water. Therefore, to the granules of forms II and III was added extra water (60 and 30 ml/kg) to the mixture, respectively, which improved yield markedly, (to 65.1 and 69.2%), indicating the decrease in granule yield was caused by the absorption of water on transformation of dihydrate. The specific surface area (Sw) results suggested that the granules obtained from form II bulk powder had the largest Sw, and those from form I the lowest. In the order of Sw and tablet hardness of the granules, the powders ranked form II>III>IV>I. This indicated that the mechanical strength of the tablet was proportional to the Sw of the particles. The dissolution profiles of the CBZ tablets were investigated in JP XIII, 1st fluid (pH 1.2, 37±0.5 °C), and the time required for 50% dissolution (T50) was measured. In the order of T50 the ranking was IV≤I<III<II. These results suggested that the polymorphic transformation during the granulation and drying processes induced a change in pharmaceutical properties.

Key words polymorphism; carbamazepine; preformulation study; an extruding granulation; specific surface area; polymorphic transformation

Preparations of high quality granules offer a number of potential advantages to the pharmaceutical industry in the production of beads or granules as both finished and intermediate products. As such, various kinds of formulations, techniques and equipment have been developed to obtain high quality granular materials.[1] However, the polymorphic form of insoluble drugs influences the bioavailability of preparations by affecting the dissolution rate.[2] Thus, the polymorphic forms affect the pharmaceutical properties of the preparations.[3] Carbamazepine (CBZ) is widely used as a potent anticonvulsant, and there have been reports concerning its polymorphic form.[4—6] The physicochemical stability of the polymorphic form at high humidity[7] and in suspension[8] has been investigated in formulation studies, and the method of preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic phase transformation of the bulk CBZ powder during the manufacturing process. In a previous study,[9] we investigated the effects of solvent systems on polymorphic transformation of CBZ during the extrusion-granulation process and the pharmaceutical properties of the granules. Their dissolution behaviors and the mechanical strength of the CBZ granules and/or tablets were affected by the characteristics of the solvent systems in the binder solution, since the metastable polymorphic form was transformed into other crystalline forms during granulation. In this study therefore, we investigated the effect of the polymorphic form of bulk CBZ powders on the pharmaceutical properties of granules and/or tablets obtained by extrusion-granulation.

Materials and Methods

Materials CBZ bulk powder of Japanese Pharmacopoeia (JP) XIII grade (lot No. CEE-9-5) was obtained from Katsura Chem. Co., Tokyo, Japan. The bulk powders were identified as polymorphic forms I, II, III and IV[7] by X-ray diffraction analysis and differential scanning calorimetry (DSC) measurement. Crystalline α-lactose monohydrate (Pharmatose 200M, DeMelkindustrie Veghel Co., the Netherlands) and corn starch (Matsuya Chem. Co., Japan) were used as a diluent and a disintegrator, respectively. Hydroxypropylcellulose (HPC) (HPC-L, Nihon Soda Co., Japan) and magnesium stearate (Kishida Chem. Co., Japan) were used as a binder and a lubricant, respectively. All other chemicals were of analytical grade.

Preparation of Polymorphs The CBZ bulk powder was identified as form I (anhydrate, monoclinic CBZ).[7] Form II (anhydride) was precipitated from a saturated chloroform solution of the drug by the addition of ethyl ether, and stirring for 1 h at room temperature. The separated crystals were then filtered and dried *in vacuo* in a desiccator containing P_2O_5 at room temperature for 3 h. Form III (anhydride) was obtained by heating dihydrate at 115 °C *in vacuo* for 6 h. Dihydrate form (form IV)[7] was obtained by recrystallization as follows: CBZ bulk powder was dissolved in 50% ethanol solution in a water bath at 70 °C, and filtered. After cooling the saturated CBZ solution to room temperature, the crystalline samples were filtered and dried in a desiccator containing silica gel at room temperature *under vacuo* for 3 h. All of the CBZ samples were passed through a No. 200 mesh (75 μm) screen.

Micrometric Characterization The true densities of the powders were determined using an air comparison pycnometer (model 930, Beckman–Toshiba Co., Tokyo, Japan). Specific surface area (Sw) measurement: The Sw was measured with a gas adsorption apparatus (one point method, Flow sorb, model 2300, Shimadzu Co.) using Brunauer-Emmett-Teller gas adsorption. The adsorption gas used for measurement contained 30% N_2 and 70% He. All values represent averages of 4 measurements.

X-Ray Powder Diffraction Analysis Diffractograms were taken at room temperature with an X-ray diffractometer (XD-3A, Shimadzu Co., Kyoto, Japan). The operating conditions were as follows: Target, Cu; filter, Ni; voltage 20 kV, current, 20 mA; receiving slit, 0.1 mm; time constant, 1 s; counting range, 1 kcps; scanning speed 4° 2θ/min.

Thermal Analysis DSC was performed with a type 3100 instrument

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(Mac Science Co., Tokyo). The operating conditions in the open-pan system were as follows: Sample weight, 5 mg; heating rate, 10 °C/min; N_2 gas flow rate, 30 ml/min.

Granulation Process The manufacturing process for CBZ granules and tablets is summarized in Chart 1. Two hundred and fifty grams of CBZ bulk powder, 175 g of crystalline lactose and 75 g of corn starch were mixed in a twin-shell type mixer (Model 5DMr, Sanei Ind. Co., capacity: 4.7 liters, mixing speed 28 rpm) for 60 min. The HPC binder solutions were obtained by mixing with 5 g of HPC and 100 ml of distilled water. After adding HPC binder solution (150 ml/kg), the mixed powder was kneaded at 107 rpm in a Multipurpose mixer (Shinagawa Ind. Co., 10 liter) for 10 min. The wet mass was immediately transferred to an extruding granulator equipped with a 0.5-mm mesh (Dorm Gran, Type DG-L1, Fuji Powdal Co., Japan) where the wet mass was extruded at 20 rpm. All procedures were performed at 25 °C, and 50±10% relative humidity (RH). Completed, processed granules were dried at 60 °C for 24 h. The sample granules between a No. 12 mesh screen (1400 μm) and a No. 42 mesh (355 μm) were used.

In order to evaluate the amount transformed dihydrate one gram of granule was sampled after granulation, and stored at 30 °C, 47% RH for 24 h to measure DSC.

Measurement of the Dihydrate Content of Granules The dihydrate (form IV) content of the granules was measured by DSC based on the endothermic peak at around 70 °C due to dehydration. Briefly, known quantities of standard mixtures were obtained by physically mixing anhydrate and dihydrate at various ratios (0, 25, 50, 75 and 100% crystal content) in a mortar. The DSC curves of the standard samples were measured in triplicate. The standard deviation of the data were within 5%. The plots gave good linear correlation and the linear regression equation is as follows:

$$Y=308.4X+5.8 \quad (R=0.998) \tag{1}$$

Y (J/g) is a latent heat due to dehydration of dihydrate CBZ. X is the dihydrate concentrations (%). R is the correlation coefficient.

Tabletting Compression Process Sample granules were mixed with 1.0% magnesium stearate in a twin-shell mixer (Tokujyu Ind. Co., Model V-1, capacity, 2 L, mixing speed, 28 rpm) for 10 min. A compression/tension tester (Autograph, model IS-5000, Shimadzu Co., Kyoto, Japan) was used at 25±1 °C. An 8-mm diameter die and punches compressed samples of 200 mg at 147 MPa (maximum upper punch pressure) at a flat surface compression speed of 15 mm/min. The tablet hardness was measured 3 times using a hardness tester (Toyama Co.).

Dissolution Test Drug dissolution was investigated in JP XIII 1st (pH 1.2) fluids. The sample tablet was introduced into 800 ml of dissolution medium at 37+0.5 °C. The test solution was stirred with a paddle (JP XIII) at 100 rpm. Aliquots (3 ml) of the solution were withdrawn through a 0.8 μm membrane filter at appropriate time intervals using a syringe and suitably diluted with dissolution medium for measurement of the CBZ concentration. The concentration of the drug was measured spectrophotometrically (model UV-160A, Shimadzu Co.) at 285 nm. The tablet disintegration time was evaluated by visible observation. All values are reproducible and represent the average of three runs.

Results and Discussion

Physicochemical Properties of CBZ Figures 1 and 2 shows the X-ray diffraction profiles and DSC curves of CBZ powders and excipients. CBZ was prepared by several means, as previously reported.[6,7] The X-ray diffraction patterns and the DSC curves of all crystalline CBZ forms were significantly different and identical to these reported.[6,7] The lactose was identical to α-crystalline monohydrate, and the corn starch was amorphous. The X-ray diffraction profiles and DSC curves of lactose and cornstarch did not change after granulation of the formulation without bulk CBZ powder.

Preparation of CBZ Granules from Polymorphic Forms of CBZ by Extrusion–Granulation The granule yield of all granules obtained by adding 150 ml/kg of the binder solution is shown in Table 1. The yield of granules obtained from each of the forms I and IV was more than 70%

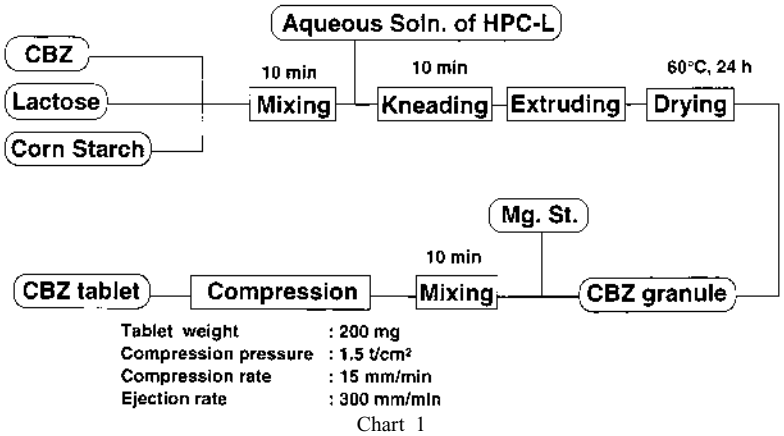

Chart 1

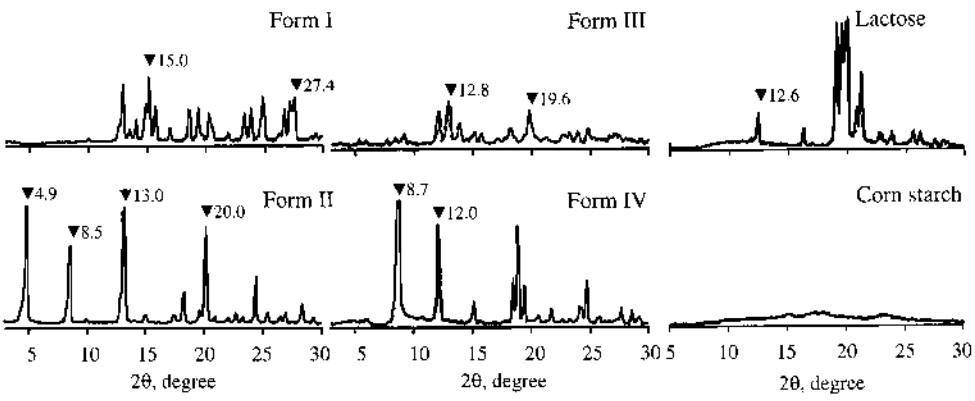

Fig. 1. Powder X-Ray Diffraction Profiles of CBZ Powders and Excipients

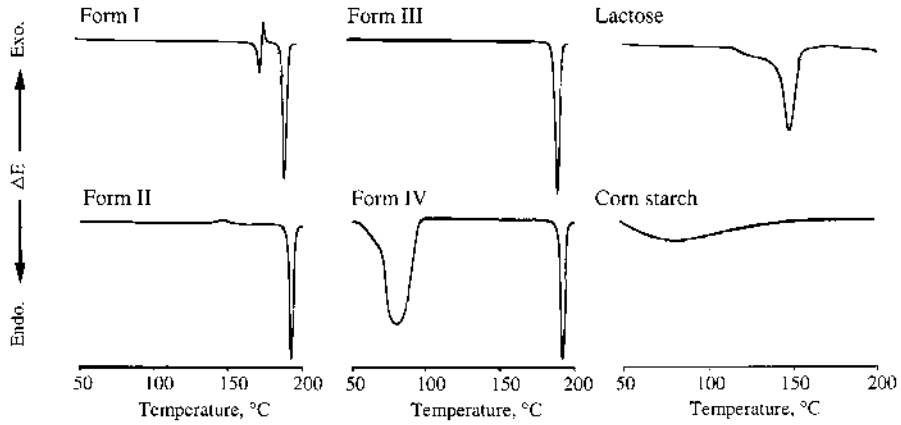

Fig. 2. DSC Curves of CBZ Powders and Excipients

Table 1. Yield of CBZ Granules by Extrusion–Granulation

Sample name	Crystalline form	Binder solution (ml/kg)	Added water (ml/kg)	Transformed (%)	Yield (%)
A	Form I	150	0	2.5	73.8
B	Form II	150	0	80.3	0.0
C	Form II	150	60	82.5	65.1
D	Form III	150	0	35.2	0.0
E	Form III	150	30	38.1	69.2
F	Form IV	150	0	98.8	76.3

The transformed value was based on the latent heat of dehydration in DSC, the yield is the percent amount of the sample granules that passed through a No. 12 mesh screen (1400 μm) but not a No. 42 mesh (355 μm).

yield. However, the yields of forms II and III were almost zero, since the mixed powders were not wet after kneading with the binder solution by the mixer, and did not mass even when treated with the granular instrument. Young *et al*.[8] reported first-order kinetics of CBZ polymorphic transformation in aqueous suspension, suggesting that anhydrate CBZ transformed into dihydrate in aqueous suspension. Anhydrate CBZ absorbed water into its crystalline structure and transformed into dihydrate during granulation, meaning that the decrease of free water in the wet powder mass made difficult the granulation process.

Figure 3 shows the DSC curves of the CBZ forms in the granules during granulation. After granulation forms I, II and III were 2.5, 80.3 and 35.2% transformed into dihydrate, respectively. Next, the wet granules were dried at 60 °C, after which the transformed dihydrate was transformed into form III, but form I did not change. Thus, CBZ was transformed into dihydrate, and dehydrated into fine particles of anhydrate form III, and the amount transformed depended on the stability of the crystalline phase of the bulk powder in water. The amount (Table 1) transformed suggested the order of the stability: CBZ form I>III≥II. Kaneniwa *et al*.[5] reported the rate of phase transition of forms I, II and III in distilled water at 20 °C by the rotating disk method to be 0.151, 0.369 and 0.130 min^{-1}, respectively, and suggested that CBZ form I was the most stable in distilled water. This result is partially consistent with the present data, but the order was not the same. This is because the previous results were obtained by the rotating disk method in distilled water, whereas the present results were obtained by the powder suspending method in water. The difference may be related to the variation between particle size and/or the shape of the forms. The results clearly indicated that the decrease of granule yields of forms II and III (samples B and D) were caused by a lack of kneading water due to absorption of CBZ as crystalline water. Therefore, to the granules of forms II and III (samples C and E) was added extra water in order to supplement that absorbed during the dihydrate transformation. The amount of water added was considered to represent the amount of dihydrate transformed during granulation, respectively. The granule yields of forms II and III (samples C and E) were improved markedly as shown in Table 1, indicating that the decrease of granule yield caused by the water absorption was due to transformation of dihydrate.

Characteristics of the Granules and Tablet Obtained from the Various CBZ Polymorphic Forms as Bulk Powders Table 2 shows the Sw of CBZ granules and their tablet hardness. The Sw result suggested that the granules obtained from form II bulk powder had the largest Sw, and those from form I the lowest. From the value of Sw of the granules, the powders are ranked as form II>III>IV>I. Sekiguchi *et al*. reported[10] that particle size reduction in several medical compounds was accomplished by forming solvates and then removing the solvent from the solvate. The present results suggested that the metastable forms transformed into fine monohydrate during granulation, and then the hydrate dehydrated and transformed into very fine anhydrate particles during the drying process. The particle size of the less stable CBZ was more reduced than that of the stable form after granulation and drying, since the amount of dihydrate transformed from the starting materials depended on the stability in the binder solution.

From the mechanical strength of the tablet obtained from the granules, the ranking was the same as that for the Sw: form II>III>IV>I. The relationship between the Sw and tablet is shown in Figure 4. The plot produced a linear line, indicating that the mechanical strength of the tablet was proportional to the Sw of the particles. The granules obtained from form II bulk powder had the highest tablet hardness and Sw values, and those from form I the lowest Sw and tablet hardness values. This is because most of form II was transformed into fine particles *via* dihydrate during the manufacturing process, but little of form I was transformed. Previously,[9] the effect of solvent systems in binder solution on the

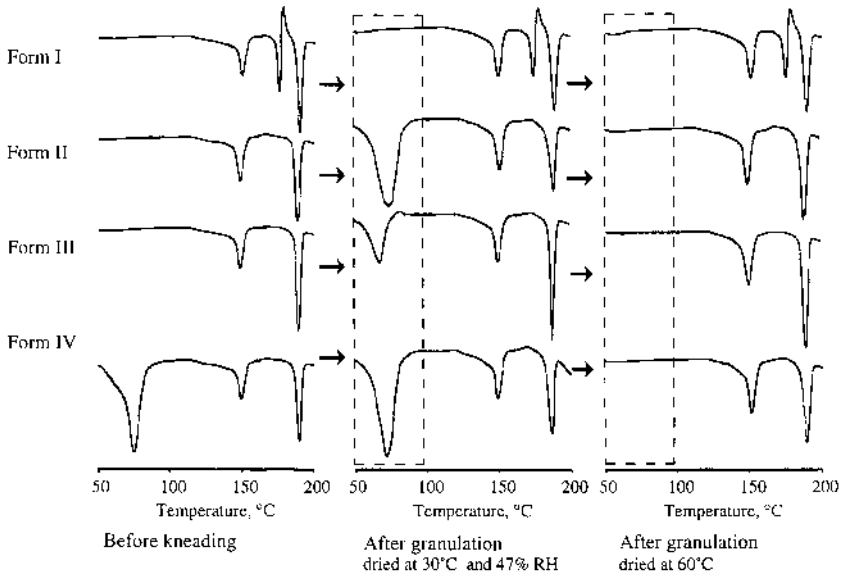

Fig. 3. Change of DSC Curves of CBZ Forms during Granulation and Drying Processes

Table 2. Pharmaceutical Properties of CBZ Granules and Their Tablet Obtained by Extrusion–Granulation.

Sample name	Crystalline form	Sw ($m^2/g \pm$S.D.)	Tablet hardness (kg±S.D.)	T50 (min±S.D.)	DT (min±S.D.)
A	Form I	0.952±0.021	7.7±0.2	3.2±0.2	2.1±0.2
C	Form II	2.87±0.016	14.6±0.3	64.4±5.2	72.2±6.1
E	Form III	2.075±0.025	12.1±0.2	9.8±1.3	11.4±2.2
F	Form IV	1.788±0.044	10.7±0.3	3.1±0.1	5.2±1.2

Sw, specific surface area of CBZ granules; T50, time required for 50% dissolution for tablets; DT, tablet disintegration time.

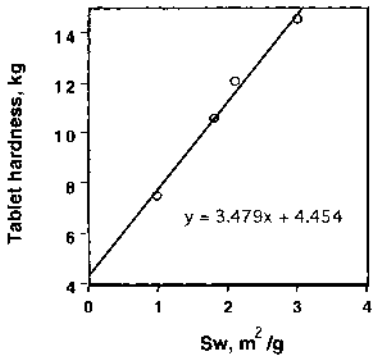

Fig. 4. Relationship between Sw and Tablet Hardness of the Granules Obtained from Various Polymorphic Forms of CBZ

tablet hardness of CBZ tablets was investigated. A large amount of the metastable CBZ (form I) was transformed into fine anhydrate particles *via* a dihydrate form in a soluble solution (50% ethanol) during extruding granulation, but this did not occur with distilled water or ethanol solutions in a less soluble solution. The tablet hardness improved by the phase change reflects the increasing of Sw. In the present study, the tablet hardness was affected by the stability of the CBZ polymorphic powders in the kneading solution, and depended on the amount of fine particle transformed during granulation and drying. The least stable crystalline form was the most effective in improving tablet hardness as a bulk powder for tablet production. This implies that the tablet hardness can be controlled by the degree of phase transformation.

Dissolution Behavior of the CBZ Tablets Obtained from the Various Polymorphic Forms Figure 5 shows the dissolution behavior of the CBZ tablets prepared by compressing the granules obtained from the polymorphic forms as starting bulk powder, and the times required for 50% dissolution (T50) are summarized in Table 2. The tablets A and F disintegrated and dissolved very rapidly, but tablet C dissolved very slowly. Since tablet C had a relatively large Sw, it seems that the geometrical structure of the tablet was more complex than that of the others. Tablet C has fine particles due to transformation of a large amount of form II, but tablets A, E and F do not.

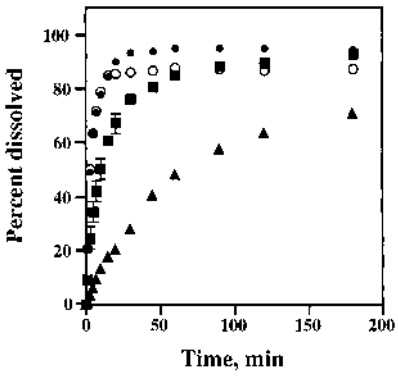

Fig. 5. Dissolution Profiles of the CBZ Granules Obtained from the Polymorphic Forms

●, Tablet A; ▲, tablet C; ■, tablet E; ○, tablet F.

In the order of T50, the ranking was table F≤A<E<C. Kaneniwa *et al.*[5] reported the solubility of forms I, II, III and IV to be 785, 531, 504 and 269 $\mu g \cdot ml^{-1}$ at 40 °C, respectively. In the present study, tablets C, E and F consisted of form III, but tablet A is of form I. The ranking of T50 of tablets is not consistent with that of the solubility of CBZ polymorphs. This result suggests that the dissolution rate for

the various CBZ tablets depends on the crystalline forms of the starting material, which is clearly consistent with the results for Sw and hardness of tablet.

Conclusions

The pharmaceutical properties and yield of granules and/or tablets containing metastable polymorphic forms of CBZ as bulk powder were affected by the stability of crystalline transformation during the manufacturing processes. Because the free water content changed depending on the extent of absorption during the transformation to dihydrate, the granulation process was affected. On the other hand, particle size was reduced by forming the hydrate and removing the crystalline water. The particle size reduction changed the mechanical strength of the tablet and their dissolution behavior. The nature of the bulk powders and excipients, such as polymorphic form, particle size and distribution, crystallinity *etc*., reflect the history of the chemical and physical treatments of the raw materials. Therefore, to prepare better quality granules it is necessary to monitor and control the characteristics of the powder materials.

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