Effect of Polymorphic Transformation During the Extrusion-Granulation Process on the Pharmaceutical Properties of Carbamazepine Granules

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The effects of a solvent system on the pharmaceutical properties of carbamazepine (CBZ) granules containing a polymorphic form of bulk powder were investigated by X-ray diffraction analysis, thermal analysis, mercury porosimetry and Brunauer-Emmett-Teller (BET) surface area measurement. A powder mixture consisting of 20% CBZ form I, as a bulk powder, 56% crystalline α-lactose monohydrate and 24% corn starch was used as a pharmaceutical powder, with the three kinds of binder solutions (distilled water, 50% aqueous ethanol and ethanol) containing 5% hydroxypropylcellulose (HPC). After kneading with a binder solution, the granules were obtained using an extruding granulator. The X-ray diffraction and differential scanning calorimetry (DSC) results of the granules indicated that form I with 50% ethanol solution transformed into a dihydrate form during extruding granulation, but this did not occur with the distilled water or ethanol solutions. The order of hardness and specific surface area (Sw) of the granules was distilled water > 50% ethanol > ethanol and 50% ethanol > ethanol > distilled water. The stress-thickness profiles of the tabletting compression processes of CBZ granules obtained using various binder solution systems were measured, and the initial compression process due to particle rearrangement was affected by the characteristics in the granules. The total pore volume of tablets obtained from 50% ethanol was the lowest, and their order was ethanol > distilled water > 50% ethanol. Their order of tablet hardness reflected the total pore volume of the tablet, and was 50% ethanol > distilled water > ethanol. All pharmaceutical properties of the granules and/or tablets containing CBZ were affected by the characteristics of the solvent systems in binder solution.

Key words carbamazepine; polymorphic form; preformulation study; extruding granulation; solvent

Granulation is a key process in the production of many pharmaceutical dosage forms. Various formulations, techniques and equipment have been developed to obtain granular materials.[1] The preparation of higher quality granules offers a number of potential advantages to the pharmaceutical industry in the production of beads or granules as either finished or intermediate products.

On the other hand, the polymorphic form of bulk powders of drugs affects their bioavailability of preparations by affecting the dissolution rate. Thus, the pharmaceutical design of drugs, especially those of a polymorphic form which are practically insoluble in water, is important.[2,3] Carbamazepine (CBZ) is widely used as a potent anticonvulsant, and there have been many reports concerning its polymorphic form.[4] The dissolution rate[5] and bioavailability[6] of CBZ in humans, and the physicochemical stability of its polymorphic forms at high humidity[7] and in suspension[8] have been investigated in formulation studies. In addition, the method of CBZ preparation has been shown to affect a drug's pharmaceutical properties through the polymorphic phase transformation of the bulk CBZ powder during manufacturing processes. However, there have been no reports concerning the effect of the CBZ crystalline form on its pharmaceutical properties during manufacturing processes. In this study, therefore, we investigated the effects of various solvent systems on the polymorphic transformation of CBZ during the extrusion-granulation process and the pharmaceutical properties of their granules.

Experimental

Materials Bulk CBZ powder of JP grade (lot No. CEE-9-5) was obtained from Katsura Chem. Co., Tokyo, Japan, and the bulk powder was identified as polymorphic form I[7a] by X-ray diffraction analysis and DSC measurement. Crystalline α-lactose monohydrate (DeMelkindustrie Veghel Co., Netherlands) and corn starch (Mitsubishi Co., Japan) were used as a diluent and a disintegrator, respectively. Hydroxypropyl cellulose (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.

Granulation Process Twenty grams of CBZ bulk powder (form I), 56 g of crystalline lactose and 24 g of corn starch were mixed in a twin-shell type mixer (Model 5DMr; Sanei Ind. Co., capacity: 4.7 l, mixing speed 28 rpm) for 10 min. The three kinds of HPC binder solutions were obtained by it mixing with 5 g of HPC and 100 ml of distilled water, 50% aqueous ethanol or ethanol. After adding various kinds of HPC binder solution (150 ml/kg), the mixed powder was kneaded for 10 min at 25 °C and 50% relative humidity (RH), and the wet mass was immediately transferred to an extruding granulator equipped with a 0.5-mm mesh screen (Dorm Gran, Type DG-L1; Fuji Powdal Co., Japan) where the wet mass was extruded at 20 rpm. Completed, processed granules were dried at 35 °C and 50% RH for 12 h. The sample granules were prepared and sieved to a 370—1410 μm sized fraction (12 and 42 mesh screens).

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 of the bulk powders was measured by the air permeability method (SS-100; Shimadzu Co., Kyoto, Japan), assuming the particles were spherical. The specific surface area diameter was calculated from the value of Sw. The Sw of the granules was measured with a gas adsorption apparatus (one point method; flow sorb, model 2300, Shimadzu Co.) using BET gas adsorption. The adsorption gas used for measurement contained 30% N_2 and 70% He, and all values represent

Table 1. Micrometrics of Raw Powders

Sample	Sw[a] (cm^2/g)	d[b] (μm)	δ_t[c] (g/cm^3)
CBZ bulk powder	1664± 4	31.4±0.1	1.15±0.01
α-Lactose	2558±11	16.4±0.1	1.43±0.01
Corn starch	3546±37	12.2±0.1	1.38±0.01

a) The air permeability method. *b*) Particle diameter calculated from the Sw obtained by the air permeability method. ($d=6/(\mathrm{Sw}\ \delta_t)$). *c*) True density.

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averages of 4 measurements. The angle of repose was measured 5 times using a 4 cm diameter table.

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 Differential scanning calorimetry (DSC) was performed with a type 3100 instrument (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, 50 ml/min.

Solubility Test An excess of bulk powder sample (100 mg) was introduced into 10 ml of various kinds of dissolution media in a test tube with a cap at 25±0.5 °C, then tube was shaken horizontally at 90 strokes/min. All the solutions were filtered with a 0.2-μm membrane filter at 6, 12 and 24 h, and suitably diluted with dissolution medium. The concentration of the drug was measured spectrophotometrically (model UV-160A; Shimadzu Co.) at 285 nm. The solubilities are summarized in Table 2.

Granule Hardness The granule hardness was measured using a granule hardness test apparatus (Grano Type I; Okada Seiko, Inc., Japan). All values represent averages of 20 measurements.

Tabletting Compression Process Sample granules were mixed with 0.5% 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) with two load cells (upper and lower punches) and a displacement transducer was used to measure the upper and lower compression force and displacement at 25±1 °C. Samples of 200 mg were compressed by an 8-mm die and punches with a flat surface at 147 MPa (maximum upper punch pressure) at a compression speed of 15 mm/min.

Tablet Hardness The tablet hardness was measured 3 times using a hardness tester (Toyama Co.).

Micropore Distribution Measurement Micropore distribution of the tablet was measured by means of mercury porosimetry (type 2000, Carlo Erba Strumentazione, Italy). The contact angle and surface tension of mercury were 141.3 deg. and 480 dyn/cm, respectively. The pore radius ranged from 300 to 6×10^{-3} μm.

Table 2. Solubility of CBZ Form I in Various Solvent Systems at 25 °C

Solvent system	Solubility (mg/l)
Distilled water	230
50% ethanol	8500
Ethanol	18700

Results and Discussion

Polymorphic Transformation of CBZ During the Extrusion of Granules Figure 1 shows the X-ray diffraction profiles of CBZ granules obtained by adding binder solutions made using various solvent systems. The X-ray diffraction profiles of the granules obtained from ethanol solutions showed almost the same pattern as the physical mixture containing form I CBZ. However, their diffraction pattern from distilled water was almost the same as the physical mixture, but the peak intensity at $2\theta = 19.8°$ due to α-lactose decreased. Since X-ray diffraction profiles of α-lactose monohydrate and corn starch showed no changes on treatment with distilled water, 50% ethanol or ethanol solution, most of CBZ form I was not transformed into other crystalline phases under the granulation conditions. In contrast, the granules obtained from 50% ethanol solution had a significant diffraction peak at $2\theta = 8.7°$ due to dihydrate.[7]

Figure 2 shows the DSC curves of CBZ granules obtained from various kinds of binder solutions. The endothermic peaks at 150 °C, 177 °C and 195 °C in DSC of the physical mixtures were due to dehydration of the monohydrate of α-lactose, phase transformation of CBZ form I to form III and the fusion of CBZ form III, respectively.[7] The DSC curve of the granules obtained from distilled water and/or ethanol solutions showed almost the same pattern as that of the physical mixture, except for a decrease in the endothermic peak due to the fusion of CBZ in the DSC of granules obtained from ethanol. In contrast, the granules obtained from the 50% ethanol solution had a broad endothermic peak at 70 °C due to dehydration, and the peak at 177 °C disappeared.

These X-ray diffraction and DSC results indicate that

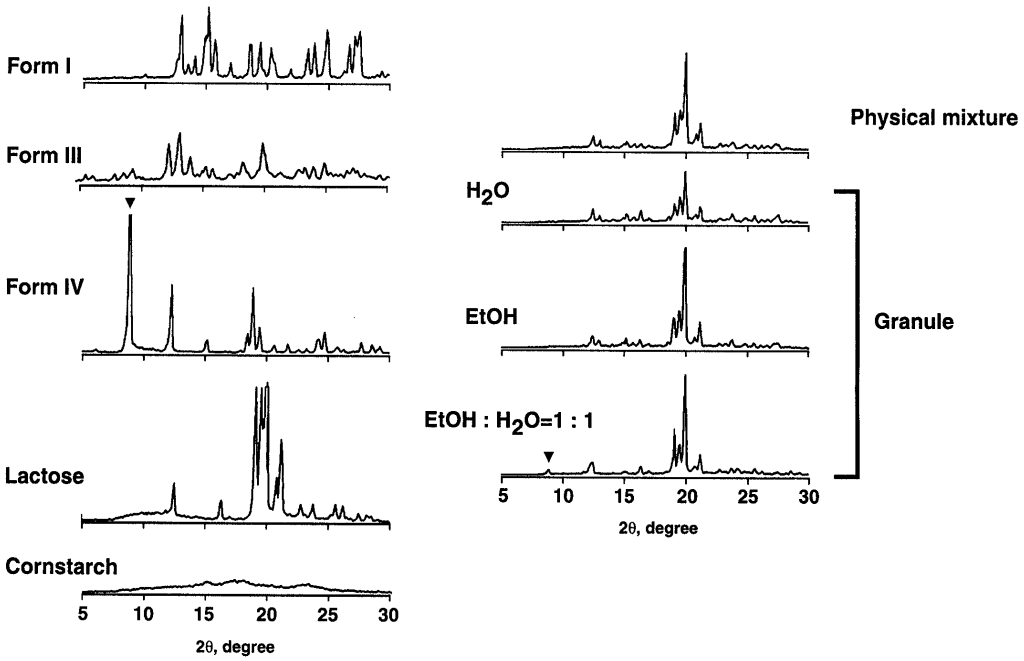

Fig. 1. Powder X-Ray Diffraction Profiles of CBZ Granules Obtained by Adding Binder Solutions Consisting of Various Solvent Systems

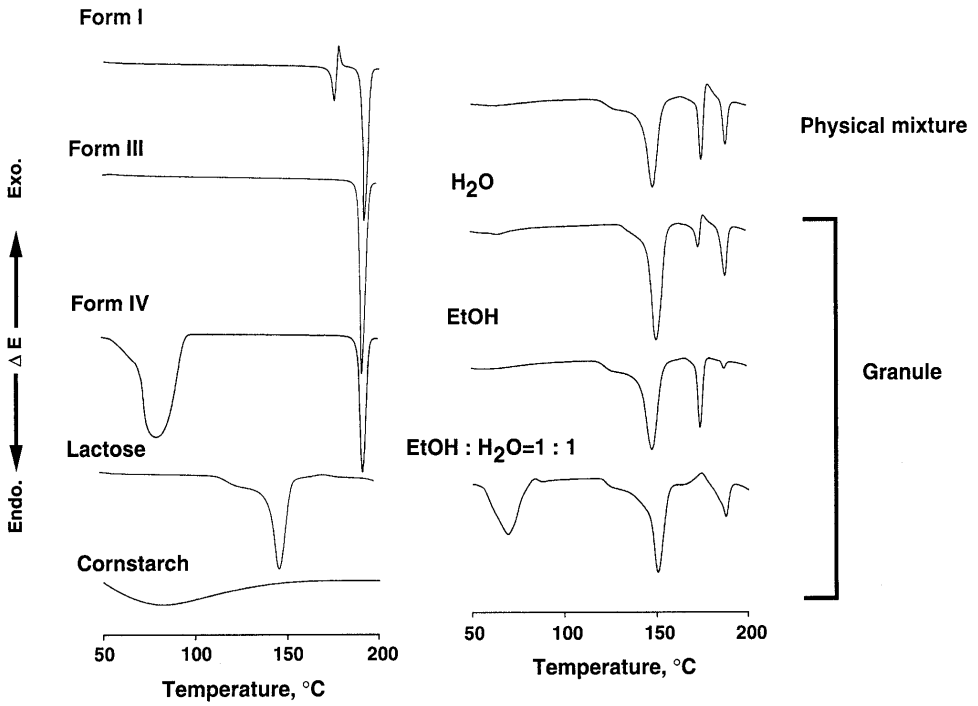

Fig. 2. DSC Curves of CBZ Granules Obtained by Adding Binder Solutions Consisting of Various Solvent Systems

form I with 50% ethanol solution was transformed into dihydrate during extruding granulation, but not with the distilled water or ethanol solutions. Since the solubility of CBZ in 50% ethanol was 37-fold higher than that in distilled water, as shown in Table 2, the transformation was accelerated in 50% ethanol, but not in distilled water.

Ling *et al.*[8] reported that the kinetics of CBZ polymorphic transformation in aqueous suspension (3 g/200 ml distilled water), as well as the transformation from form I to dihydrate (form IV), followed first-order kinetics (Eq. 1),[15] and 60% of form I transformed into dihydrate after 10 min at 25 °C.

$$1-x=A\exp(-kt) \qquad \text{Eq. 1}$$

x, fraction of transformed solid at time t; A, frequency factor; k, transformation rate constant.

If it is assumed that the polymorphic transformation of form I CBZ to dihydrate during granulation follow first-order kinetics (Eq. 1) and is calculated based on the kinetic parameter data ($A=0.972$, $k=0.071\,\mathrm{min}^{-1}$) reported by Ling *et al.*,[8] the amount of dihydrate transformed in the present experiment (10 min for kneading and 10 min for granulation processes) should be estimated to be around 75.8%, but the actual amount of dihydrate estimated from a latent heat on DSC was less than 3%. In the present study, the solution contained a polymer, HPC, as a binder, the powder ratio against solution (20 g/15 ml) in aqueous suspension was higher than Ling's data, and their contact time with water was also relatively short (20 min). Since it is well known that polymer, such as polyvinyl pyrrolidone and gelatin, inhibit recrystallization in solution,[10] it seems that the amount of CBZ transformed into the dihydrate was limited during the granulation process.

Characteristics of CBZ Granules Obtained from Various Kinds of Binder Solution Systems Figure 3 shows the

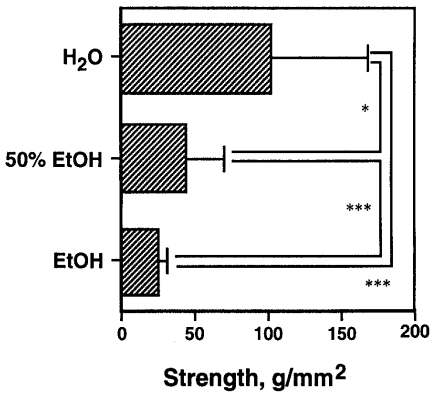

Fig. 3. The Mechanical Strength of CBZ Granules Obtained by Adding Binder Solutions Consisting of Various Solvent Systems

All data are the mean, and ±S.D. is reported. Student's t-test was used to determine the significance of difference. $*p<0.05$, $***p<0.005$, $n=15$—24.

mechanical strength of CBZ granules. The order of hardness of the granules was distilled water > 50% ethanol > ethanol. Figure 4 shows the Sw of CBZ granules. The order of Sw of the granules was 50% ethanol > ethanol > distilled water. These results suggests that the hardness and Sw of all tablets were significantly different, and the granules from distilled water had the highest hardness and lowest Sw, whereas those granules from 50% ethanol had the largest Sw and low hardness, indicating that the granules from 50% ethanol might be formed by weak binding with fine particles.

Tabletting Processes of CBZ Granules Obtained from Various Binder Solution Systems and the Properties of Their Tablets Figure 5 shows dynamic compression and decompression processes of CBZ granules obtained from various kinds of binder solutions. The compression processes for tabletting are divided into three stages: particle rearrangement, compression and depression.[11,12] In the

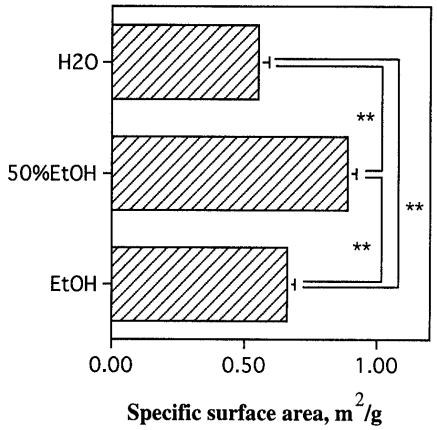

Fig. 4. S_w of CBZ Granules Obtained by Adding Binder Solutions Consisting of Various Solvent Systems

All data are the mean of 4 different experiments and ±S.D. is reported.

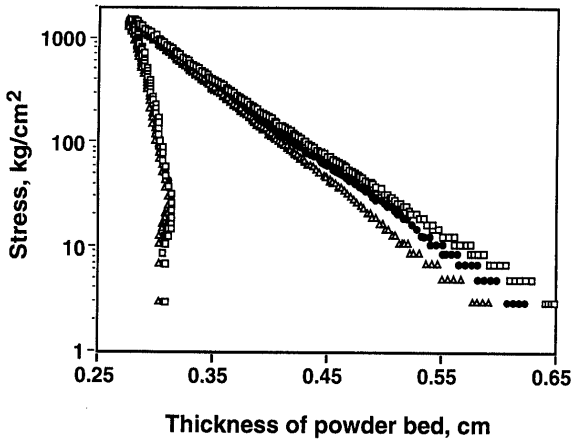

Fig. 5. Dynamic Tabletting Process of CBZ Granules Obtained by Adding Binder Solutions Consisting of Various Solvent Systems

□, H_2O; △, EtOH; ●, 50% EtOH.

Table 3. Micrometrics of Granules

Sample granules	Sw[a] (m^2/g)	δ_a[b] (g/cm^3)	δ_i[c] (g/cm^3)	Angle of repose (degree)
Distilled water	0.552±0.041	0.362±0.005	1.27±0.01	38.8±1.3
50% ethanol	0.889±0.033	0.385±0.004	1.28±0.07	35.9±1.0
Ethanol	0.662±0.028	0.374±0.003	1.24±0.01	42.1±1.9

a) The BET gas adsorption method. *b*) Apparent density. *c*) True density.

stress-thickness profiles for the CBZ granule tabletting process, specific differences were observed in the initial compression process due to particle rearrangement, and thereafter, the compression and depression processes were almost the same. The order of stress at the initial compression stage was granules obtained from distilled water > 50% ethanol > ethanol. The angle of repose and apparent density of granules are shown in Table 3, and the order of the angle of repose was granules obtained from ethanol > distilled water > 50% ethanol, but that of the apparent density was 50% ethanol > ethanol > distilled water, indicating that the initial powder bed thickness was in the order of the granules from distilled water > ethanol > 50% ethanol. Since the physical properties of the primary

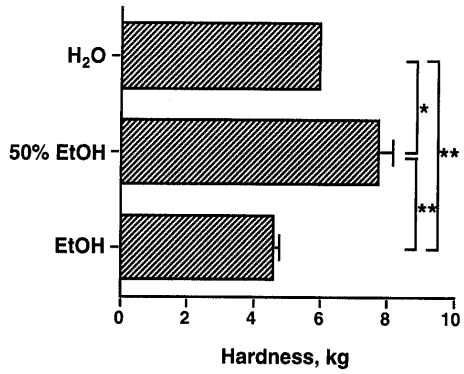

Fig. 6. Hardness of Tablets Obtained from Various CBZ Granules

All data are the mean of three different experiments and ±S.D. is reported. Student's *t*-test was used to determine the significance of difference. $*p<0.05$, $**p<0.01$, $n=3$.

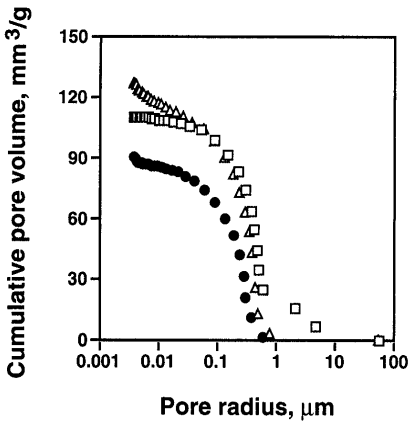

Fig. 7. Micropore Distribution of CBZ Tablets Obtained from Various Kinds of Granules

□, H_2O; △, EtOH; ●, 50% EtOH.

particles in granules, such as the crystalline form, geometrical structure, mechanical strength and agglomeration, affected the pharmaceutical properties of granules, such as flowability, mechanical strength and apparent density, the tabletting compression behaviors depended on the characteristics of the granules obtained during the preparation.

Figure 6 shows the hardness of tablets obtained from various kinds of CBZ granules. The hardness of the tablets from granules obtained in 50% ethanol was the highest, and their hardness order was 50% ethanol > distilled water > ethanol.

Figure 7 shows the micropore distribution of CBZ tablets obtained from various granules. Tablets obtained from distilled water had a higher volume, with pores of around 1—10 μm in diameter, compared with the others. The total pore volume of tablets obtained from 50% ethanol was the lowest, and their order was ethanol > distilled water > 50% ethanol. There have been many reports concerning the relationship between tablet compressibility and granule strength,[13] as well as studies on the effects of concentration,[14] types and/or viscosity[15] of binders and solvents[16] on the mechanical properties of granules. As reported previously,[13-16] the mechanical strength of tablets obtained from the hard granules was lower than that from soft granules, because the hard granules resisted compression during the initial particle

rearrangement process, resulting in high porosity of the tablets. The results of the present study suggested that the granules obtained from ethanol were rearranged more easily than those from distilled water, because the granules from distilled water were 4-fold harder than those from ethanol, and the order of granular hardness affected the initial stage of the compression behaviors of CBZ granules.

On the other hand, it is well known that tablet mechanical strength is related to Sw of the original powder and tablet porosity. Therefore, the tablet hardness increased with increasing Sw and/or decreasing the total volume in the tablets, reflecting an increasing contact area between the particles in the tablets.

Conclusions

All of the pharmaceutical properties of CBZ granules and/or tablets containing metastable polymorphic bulk powder were affected by characteristics of the solvent systems in binder solution. Since polymorphic transformation of the bulk powder during granulation affected on the Sw and the mechanical strength of the granules, to prepare higher quality granules it is necessary to monitor and control the characteristics of the bulk powder. It is also possible to regulate the quality of pharmaceutical preparations, *e.g.* producing tablets with high Sw and sufficient mechanical strength, through polymorphic transformation during granulation by using metastable CBZ polymorphs.

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