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Effect of Tabletting on the Degree of Crystallinity and on the Dehydration and Decomposition Points of Cephalexin Crystalline Powder[1]

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Changes in the degree of crystallinity and in the dehydration and decomposition points of cephalexin (CEX) crystalline powder caused by tabletting were studied by means of X-ray diffraction analysis, infrared (IR) spectroscopy and differential thermal analysis (DTA). The degree of crystallinity of the compressed phase IV CEX was determined by the X-ray diffraction and IR-spectral methods, and the results agreed reasonably well. The maximum compression stress (MP) and the compression loss energy (LE) of phase IV CEX powder during tabletting compression were measured during compression in a single-punch tabletting machine. The degree of crystallinity of the compressed phase IV CEX decreased with increasing values of MP and LE, and was about 40% at LE = 1.75 kcal/mol. The dehydration and decomposition points of the compressed phase IV CEX fell with decreasing degree of crystallinity.

The plot of log (LE) against the degree of crystallinity showed a good straight line. The value of LE estimated by extrapolating the plot to zero crystallinity was 14.0 kcal/mol.

Keywords——cephalexin; tabletting; mechanical energy; crystallinity; mechanochemistry; thermal behavior; X-ray diffraction; IR spectra

Introduction

There are many reports[2] on mechanical studies of tabletting of organic medicinal powders, but there are few reports on the changes in physicochemical properties produced by tabletting compression.[3] The authors have reported previously on polymorphs, hydrates and noncrystalline solid of cephalexin (CEX) as well as on basic properties such as hygroscopicity, solubility and stability.[4,5] Further, the effects of grinding on the degree of crystallinity and the physicochemical properties of phase IV CEX were reported.[6,7] In a previous paper the compression stress, the compression loss energy, the hardness and the elasticity were determined, and the relation between the compression characteristics during the tabletting process and the physical properties of the tablet were studied.[8] In the present work, the relation between the compression parameters (stress and loss energy) and the physicochemical properties (the dehydration and decomposition points and the crystallinity) was investigated.

Experimental

Materials——CEX bulk powder (Larixin; Toyama Chemical Co., Ltd., lot HJ-595 E) was used. The bulk powder was identified as phase IV CEX and is a stable monohydrate under the usual conditions of temperature and relative humidity in the laboratory, as described in a previous paper.[4]

Tabletting Apparatus and Measurement of the Compression Loss Energy——A load cell and a noncontact displacement transducer mounted on a single-punch eccentric tabletting machine (type KS-2; Nichiei Seiko Co., Ltd.) with a flat-type punch having a diameter of 1.0 cm or 2.0 cm was used at 60 rpm, and the compression stress and distance between punches were measured as described in a previous paper.[8] The plots of compression stress against distance between punches showed a hysteresis; the area under the compression stress-displacement distance curve corresponds to the compression loss energy (LE), and was determined with a planimeter.

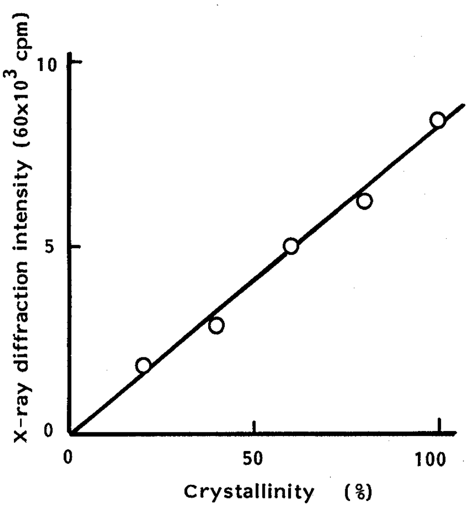

Fig. 1. Relation between the Degree of Crystallinity of the Standard Sample of CEX Powder and the X-Ray Diffraction Intensity at $2\theta=7.2°$

Preparation of Tablets——The punches and dies were smeared with 5% stearic acid solution in chloroform, and dried, then samples of 190 mg and 760 mg were put into the dies with tapping by hand (these sample weights are proportional to the punch cross-sectional area). The molded tablet was deagglomerated carefully by hand in an agate mortar with an agate pestle, and stored in a closed container at room temperature. The deagglomeration in an agate mortar corresponded to grinding about 20 times in a mortar, as shown in a previous paper.[6] The changes produced by this operation were less than about 5% in crystallinity, so the effect was neglected in the present study.

X-Ray Diffraction Analysis——The X-ray diffraction was measured at room temperature with a type JDX-7E diffractometer (Nihon Denshi Co., Ltd.). The measurement conditions were as described in a previous paper.[6] The degree of crystallinity (X_c) was determined as follows: about 80 mg of a standard sample obtained by physically mixing phase IV and the freeze-dried product[6] was loaded with a micro spoon into a glass holder without introducing a preferred orientation of the crystals. A plot of the area of the diffraction peak at $2\theta=7.2°$ *versus* the degree of crystallinity of the standard samples was linear (Figure 1). The degree of crystallinity of a sample was obtained by using this calibration plot.

Infrared (IR) Spectra——IR spectra were recorded as mulls in Nujol on an IR-2 infrared spectrophotometer (Nihon Bunko Co., Ltd.). The concentration of mulls was adjusted to give almost the same absorption intensity of the key band at each measurement. The IR spectral absorbance ratios of the peaks at 1580 cm^{-1} and 1750 cm^{-1} were measured, and the degree of crystallinity (X_c') according to the IR-spectral method was obtained by substituting the absorbance ratio into the calibration curve given in a previous paper.[6]

Thermal Analysis——The differential thermal analysis (DTA) curves were measured with a DTA (DT-20 B; Shimadzu Seisakusho Co., Ltd.) instrument. The measurement conditions were as follows: sample weight, about 5 mg; flow rate of N_2 gas, 30 ml/min; heating rate, 10 °C/min.

Results and Discussion

Results of X-Ray Diffraction Analysis, IR Spectroscopy and DTA Analysis of Compressed CEX Crystalline Powder

Figure 2 shows the X-ray diffraction profiles of intact crystalline phase IV, the product compressed at 2.03×10^9 dyn/cm^2 and the product ground in a centrifugal ball mill for 4 h.[6] The peak intensities in the X-ray diffraction profile of CEX were decreased by mechanical treatment, that is, compression and grinding, and the product ground for 4 h showed a halo pattern. This result suggests that compression destroyed the crystal structure and converted phase IV CEX into a noncrystalline state, as did grinding.

Figure 3 shows the IR spectra of CEX powders. In a previous paper[6] we reported that the IR spectral band at 1750 cm^{-1} is due to the β-lactam $\nu_{C=O}$ and that at 1580 cm^{-1} is due to the carboxylate $\nu_{C=O}$ of CEX, and we showed that the carboxylate is involved in intermolecular hydrogen bonding with water in the crystal lattice;[9] therefore, when the crystals are converted into a noncrystalline solid by grinding, the band is shifted. The IR spectral band at 1580 cm^{-1} of compressed phase IV CEX showed a broad peak, as it did after grinding.

Figure 4 shows the DTA curves of CEX powders. The DTA curve of phase IV showed an

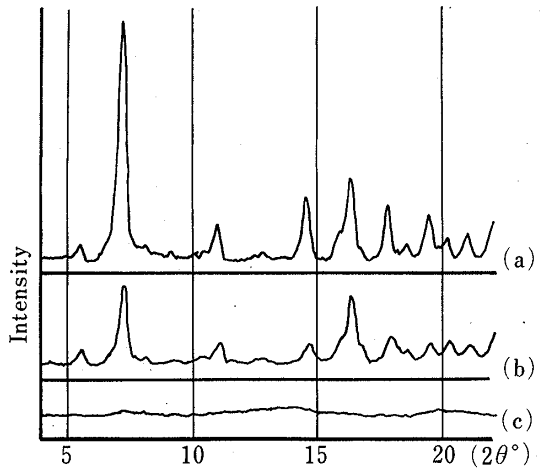

Fig. 2. Change of X-Ray Diffraction Profiles of Powders Caused by Mechanical Treatment

(a) intact phase IV CEX, (b) the product compressed at 2.03×10^9 dyn/cm^2 (punch diameter 1.0 cm), (c) the product ground for 4 h.

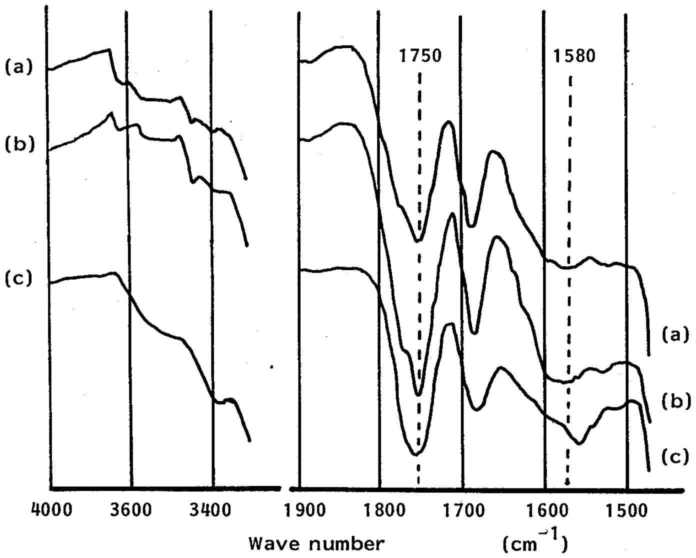

Fig. 3. Change of IR Spectra of CEX Powders Caused by Mechanical Treatment

(a) intact phase IV CEX, (b) the product compressed at 2.03×10^9 dyn/cm^2 (punch diameter 1.0 cm), (c) the product ground for 4 h.

endothermic peak at about 70 °C due to dehydration of 1 mol of water and an exothermic peak at about 190 °C due to decomposition. The DTA curve of the ground product showed a very broad endothermic peak at about 70 °C and an exothermic peak at 160 °C. The DTA curve of the compressed product showed a broad endothermic peak and an exothermic peak at about 180 °C. These results suggest that the dehydration and decomposition peaks of the compressed phase IV CEX are shifted to lower temperature when the crystals are converted into a noncrystalline state during tabletting.

Change of the Dehydration and Decomposition Points of CEX Powders Caused by Compression Stress during Tabletting

It was assumed that the dehydration and decomposition points are the intersection points between the tangents of the base line and peaks of the DTA curve. Figure 5 shows the relation between the maximum compression stress (MP) and the dehydration point of the compressed phase IV CEX. The dehydration point decreased with increasing MP, falling by about 5 °C on compression at $\mathrm{MP} = 0.5 \times 10^9$ dyn/cm^2, but its value thereafter stayed approximately constant at about 42 °C even under larger MP.

Figure 6 shows the relation between the MP and the decomposition point of the compressed phase IV CEX. The decomposition point decreased with increasing MP, falling by about 9 °C on compression at $\mathrm{MP} = 2 \times 10^9$ dyn/cm^2. These results suggest that the

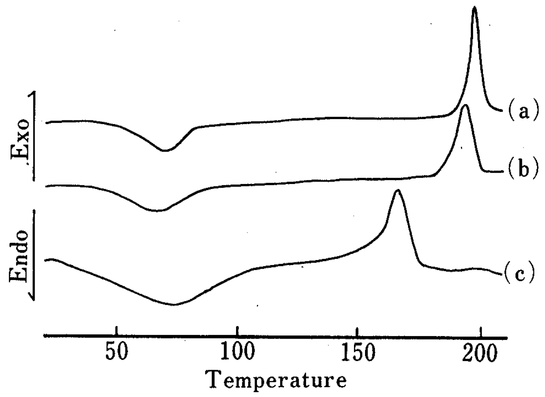

Fig. 4. Change of DTA Curves of CEX Powders Caused by Mechanical Treatment

(a) intact phase IV CEX, (b) the product compressed at 2.03×10^9 dyn/cm^2 (punch diameter 1.0 cm), (c) the product ground for 4 h.

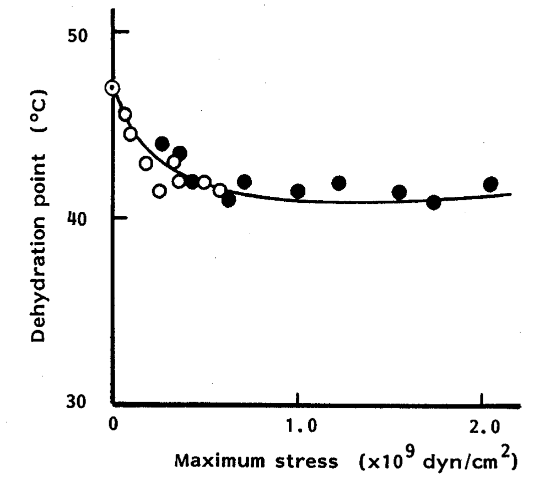

Fig. 5. Relation between Dehydration Point and Maximum Stress of CEX Powder

⊙, intact phase IV CEX; ●, punch diameter 1.0 cm; ○, punch diameter 2.0 cm.

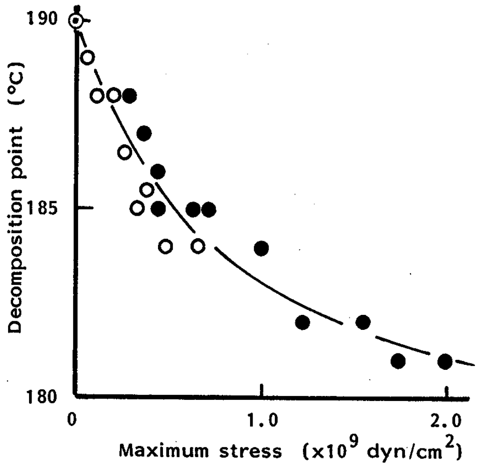

Fig. 6. Relation between Decomposition Point and Maximum Stress of CEX Powder

⊙, intact phase IV CEX; ●, punch diameter 1.0 cm; ○, punch diameter 2.0 cm.

dehydration and decomposition points of the compressed phase IV CEX were decreased by tabletting compression as a result of conversion of phase IV CEX into a noncrystalline state by the compression stress.

Change of the Degree of Crystallinity of CEX Powders Caused by Compression Stress during Tabletting

The degree of crystallinity (X_c) was obtained by the X-ray diffraction method (from Fig. 1). Figure 7 shows the relation between X_c and MP. The X_c of the compressed phase IV CEX decreased with increasing MP; at MP$=0.3 \times 10^9$ dyn/cm^2 it was about 55% and at MP$=2 \times 10^9$ dyn/cm^2 it was about 35%.

The degree of crystallinity (X_c') of the compressed phase IV CEX was obtained by the IR-spectral method.[6] Figure 8 shows the relation between X_c' and MP. The X_c' of CEX decreased with increasing MP; at 0.3×10^9 dyn/cm^2 it was about 50% and at MP$=2 \times 10^9$ dyn/cm^2 it was about 30%.

The X_c obtained by the X-ray diffraction method was in good agreement with the X_c' obtained by the IR-spectral method in each measurement. The crystallinity of the compressed phase IV CEX decreased rapidly at lower compression stress, since large particles were destroyed easily.

Change of the Degree of Crystallinity of CEX Powders in Relation to Compression Loss Energy

In a previous paper[8] we reported that in the tabletting process using the 1.0 cm and

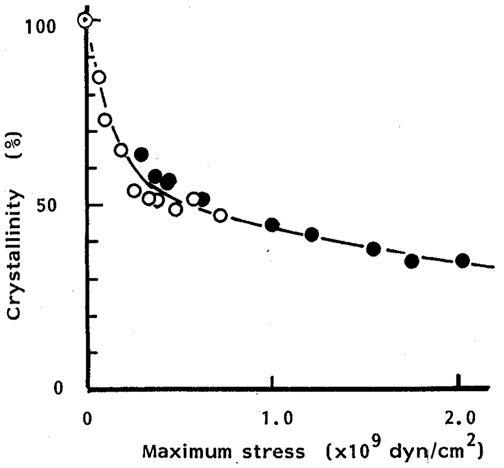

Fig. 7. Relation between the Degree of Crystallinity (X-Ray Diffraction Method) and Maximum Stress of CEX Powder

⊙, intact phase IV CEX; ●, punch diameter 1.0 cm; ○, punch diameter 2.0 cm.

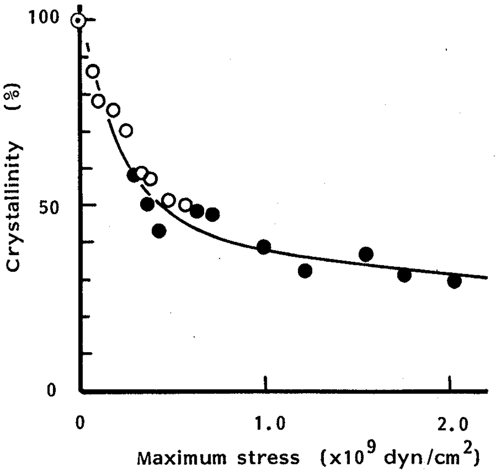

Fig. 8. Relation between the Degree of Crystallinity (IR-Spectral Method) and Maximum Stress of CEX Powder

⊙, intact phase IV; ●, punch diameter 1.0 cm; ○, punch diameter 2.0 cm.

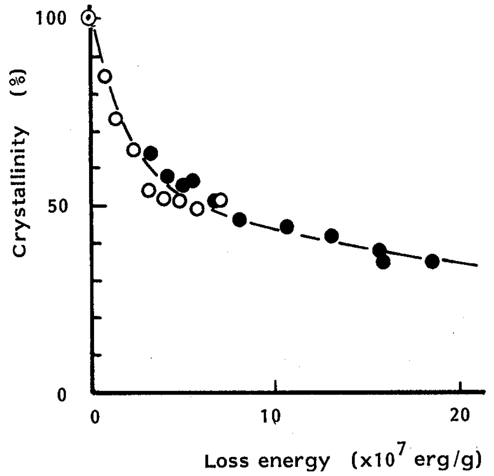

Fig. 9. Relation between the Degree of Crystallinity (X-Ray Diffraction Method) and Loss Energy of CEX Powder

⊙, intact phase IV; ●, punch diameter 1.0 cm; ○, punch diameter 2.0 cm.

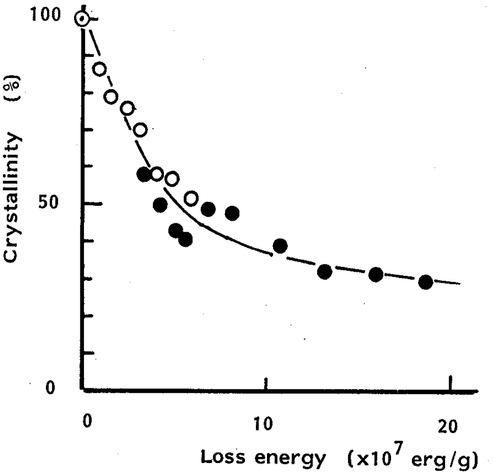

Fig. 10. Relation between the Degree of Crystallinity (IR-Spectral Method) and Loss Energy of CEX Powder

⊙, intact phase IV; ●, punch diameter 1.0 cm; ○, punch diameter 2.0 cm.

2.0 cm punches and dies, MP was proportional to the compression loss energy (LE). Figure 9 shows the relation between X_c and LE. The X_c of the compressed phase IV CEX decreased with increasing LE; at LE = 4×10^7 erg/g it was about 60% and at LE = 18×10^7 erg/g it was about 40%.

Figure 10 shows the relation between X_c' and LE. The X_c' of the compressed product decreased with increasing LE; at LE = 5×10^7 erg/g it was about 50% and at LE = 18×10^7 erg/g it was about 30%. These results suggest that about 60% of CEX crystals was converted into noncrystalline solid by a mechanical energy of less than about 2 kcal/mol (20×10^7 erg/g = 1.75 kcal/mol). In a previous paper[8] the compression energy of CEX powder was found to be approximately equal to LE in the pressure region used in the present study. It was assumed that the LE during the tabletting compression process was consumed for converting phase IV CEX to noncrystalline solid. The plots of log LE against X_c were linear, as shown in

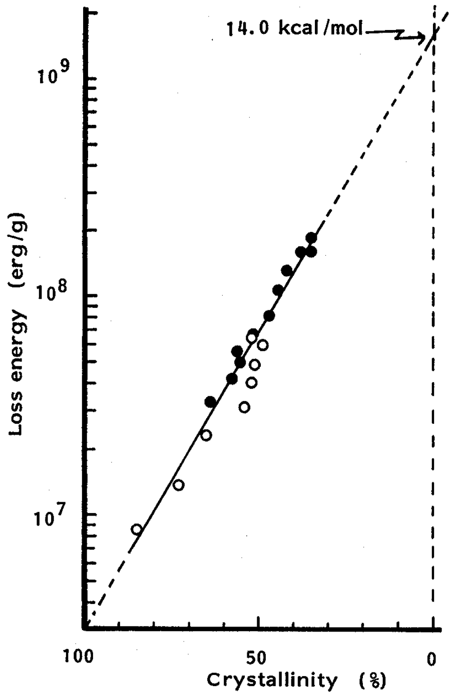

Fig. 11. Relation between Loss Energy and the Degree of Crystallinity of CEX Powder

●, punch diameter 1.0 cm; ○, punch diameter 2.0 cm.

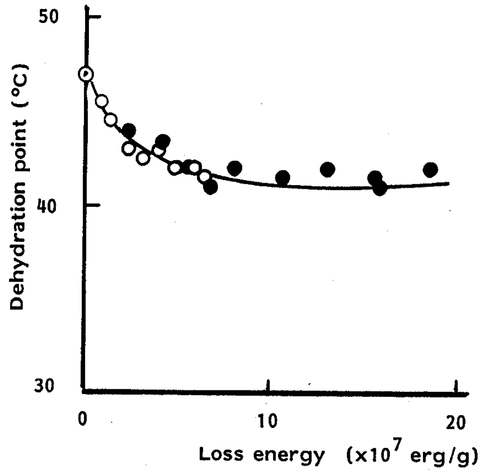

Fig. 12. Relation between Dehydration Point and Loss Energy of CEX Powder

⊙, intact phase IV; ●, punch diameter 1.0 cm; ○, punch diameter 2.0 cm.

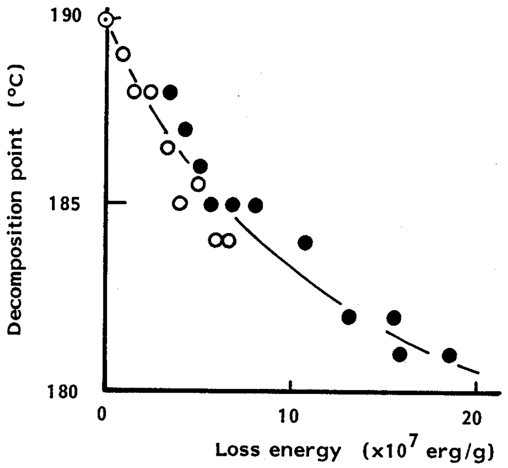

Fig. 13. Relation between Decomposition Point and Loss Energy of CEX Powder

⊙, intact phase IV; ●, punch diameter 1.0 cm; ○, punch diameter 2.0 cm.

Fig. 11, and the LE at $X_c = 0\%$ was estimated by extrapolarion to be 1.60×10^9 erg/g (14.0 kcal/mol) by the least-squares method. CEX is an ampho-ion having carboxylate and amine groups, and the CEX molecule shows hydrogen bonding with water in the monohydrate; such intermolecular hydrogen bonding acts as the main binding force in the crystal. The intermolecular hydrogen bond energy was estimated to be 1—10 kcal/mol.[10] The latent heat and the activation energy of dehydration of phase IV CEX are 7.13 kcal/mol and 15.67 kcal/mol, respectively,[11] and the adsorbed water seems to have an important role in the crystal structure. The product ground for 2 h in an agate centrifugal ball mill showed an X-ray diffractometrically noncrystalline state.[6] These results support the view that the estimated mechanical energy of 14.0 kcal/mol to convert phase IV CEX to noncrystalline solid is reasonable.

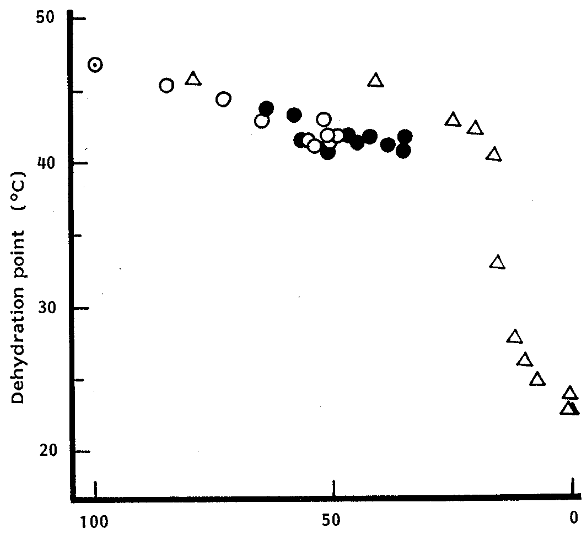

Fig. 14. Relation between the Degree of Crystallinity and Dehydration Point of Ground and Compressed Phase IV CEX

⊙, intact phase IV; △, the product ground in a ball mill; ●, the product compressed with a punch (diameter 1.0 cm); ○, the product compressed with a punch (diameter 2.0 cm).

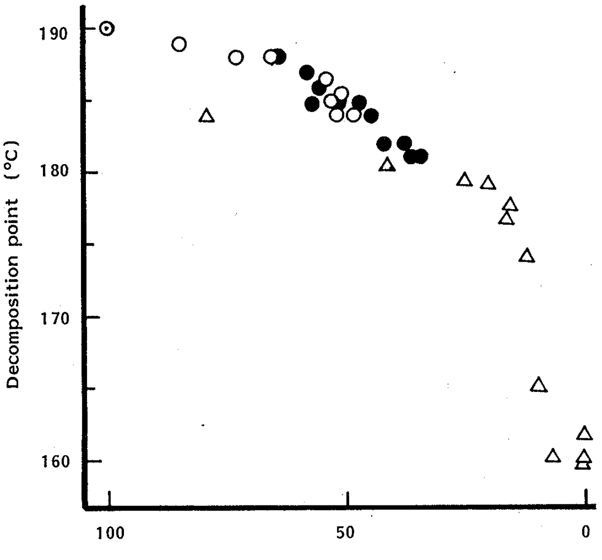

Fig. 15. Relation between the Degree of Crystallinity and Decomposition Point of Ground and Compressed Phase IV CEX

⊙, intact phase IV; △, the product ground in a ball mill; ●, the product compressed with a punch (diameter 1.0 cm); ○, the product compressed with a punch (diameter 2.0 cm).

Change of the Dehydration and Decomposition Points of the Compressed Product in Relation to Compression Loss Energy

Figure 12 shows the relation between LE and the dehydration point of the compressed phase IV CEX. The dehydration point fell by about 5 °C at $\mathrm{LE} = 5 \times 10^7$ erg/g, but its value remained constant with further increase of LE.

Figure 13 shows the relation between LE and the decomposition point of the compressed phase IV CEX. The decomposition point decreased with increasing LE, falling by about 9 °C at $\mathrm{LE} = 20 \times 10^7$ erg/g. These results suggest that the dehydration and decomposition points of CEX powders fall with increasing LE.

Relation between the Dehydration and Decomposition Points and the Degree of Crystallinity

Figure 14 shows the relation between the dehydration point of ground$^{6)}$ and/or compressed phase IV CEX and its crystallinity as obtained by the X-ray diffraction method. The dehydration point fell slightly with decreasing degree of crystallinity in the range of 100—20%, but fell rapidly when the degree of crystallinity was less than about 20%, and the dehydration point at zero crystallinity was about 23 °C.

Figure 15 shows the relation between the decomposition point of ground$^{6)}$ and/or compressed phase IV CEX and the degree of crystallinity as obtained by the X-ray diffraction method. The decomposition point fell gradually with decreasing value of degree of crystallinity at first, but fell rapidly when the degree of crystallinity decreased below about 20%, and the decomposition point at zero crystallinity was about 160 °C.

Conclusions

(1) CEX crystalline powder was converted to a solid with a low degree of crystallinity by tabletting compression, in the same way as by grinding in an agate centrifugal ball mill. The crystallinity of the compressed phase IV CEX was about 40% at LE = 1.75 kcal/mol.

(2) The dehydration and decomposition points of CEX were decreased by about 5 and 9 °C, respectively, by tabletting compression at the maximum value of MP (2.03×10^9 dyn/cm^2).

(3) The relation between the degree of crystallinity and log LE was linear, and the mechanical energy required to convert phase IV CEX into noncrystalline solid was found by extrapolation to be 14.0 kcal/mol.

References and Notes

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