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Effects of grinding and compression on crystal structure of anhydrous caffeine

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Summary

The extent of the polymorphic transformation of anhydrous caffeine has been studied as a function of grinding time and compression pressure by using quantitative X-ray diffraction analysis. The measurements show that both grinding and compression induce the transformation from the metastable form I into the stable form II. The transformation can be observed even after 1 min grinding or by using a compression pressure of about 50 MPa in tableting. The degree of transformation is greater near the surface than in the middle part of the tablet.

Introduction

Two or more crystals having identical atomic composition but different arrangements or structures are called polymorphs. Different polymorphs have different physical properties like solubility, dissolution rate, melting point, density, hardness and crystal form. One polymorph is always the stable form at a given temperature and pressure, others are metastable forms. The metastable form transforms to the stable modification spontaneously. The kinetics of this process are determined by the activation energy. When the activation energy is high the transition happens slowly. Also the mechanical treatment may induce the transition if the amount of energy brought to the system is sufficient.

Investigations dealing with the polymorphism of the drug substances have usually been concentrated on the characterization of the different forms and on the determination of different physical properties of the forms. The properties of the metastable form might be useful from the biopharmaceutical point of view (Haleblian and McCrone, 1969; Rosenstein and Lamy, 1969; York, 1983; Matsuda and Tatsumi, 1990). The metastable forms, however, turns to the stable form and therefore the kinetics of this process should be known. Although the spontaneous transformation may be sluggish the transformation induced by

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the mechanical treatment may take place to a great extent in a short time.

Many pharmaceutically important compounds exist in more than one crystalline form (e.g., Borka, 1991). The choice of the right modification may be important because of their different physical properties. Metastable polymorphs usually have higher solubilities and dissolution rates compared with stable forms. Also, the tableting behavior of a powder may depend on the polymorphic form used (Burger, 1982).

The transformation from one polymorphic form into another during mechanical treatment may adversely change the properties of the powder. After grinding or tableting the result may be a composition of two or more different forms. Also, the spontaneous transformation from a metastable form into a stable form may occur causing a stability problem.

The aim of this paper is to study the polymorphic transformation of anhydrous caffeine during mechanical treatment. The degree of transformation has been determined as a function of grinding time and as a function of tableting pressure. The tableting tests have been carried out by using a mixture of anhydrous caffeine and maltodextrin because of the poor tableting of pure anhydrous caffeine. This should be borne in mind, since some excipients may change the degree or rate of the polymorphic transformation (Chan, 1986).

Materials and Methods

Materials

Anhydrous caffeine (1,3,7-trimethyl-2,6-dioxipurine) exists in two polymorphic forms (Cesàro and Starec, 1979). The transformation temperature between the low-temperature II and the high-temperature I modification is about 141°C. Form II was prepared as follows. Commercially obtained anhydrous caffeine (Sigma Chemical Co. U.S.A.) was recrystallized twice from distilled water. The wet crystals were dried for 8 days at 30°C and thereafter for 4 h at 80°C by using silica gels. Form I was prepared by heating form II at 180°C for 10 h. Maltodextrin (Maltrin M510) was obtained from Grain Processing Corp., U.S.A.

Methods

The grinding of anhydrous caffeine was carried out with a Retsch K9 MM ball mill (Retsch Mühle, West-Germany) with speed of 70 rpm. The tablets were made of a mixture of anhydrous caffeine and maltodextrin. The mixing was performed with a Turbula T2C-mixer (WA Bachofen, Switzerland) at a speed of 20 rpm for 5 min. The tablets were pressed with a Korsch EK-0 DMS (Korsch Maschinenfabrik, Germany) tablet press at a running speed of 33 rpm by using flat-faced punches (10 mm diameter).

X-ray powder diffraction measurements were made with a Philips PW1820 diffractometer. The diffractograms were recorded under the following conditions: Ni filtered CuK_α radiation (λ = 0.15418 nm), voltage 50 kV, current 40 mA, automatic divergence slit (irradiated sample length 12.5 mm), receiving slit 0.1 mm, scatter slit 4°, step scan (step size 0.01 or 0.015°, sample time 1 s), proportional detector.

Data were collected and analyzed by using the Philips APD1700 program. The background corrected integrated intensities of reflections were determined from measured diffractograms with the PW 1869 profile fitting program. Fig. 1 shows an example of this determination. The mass absorption coefficients of different polymorphic forms are the same. For this reason the integrated intensity of the characteristic reflection of the form is linearly proportional to the amount of that form in the sample. The degree of transformation can be determined by comparing the background corrected intensities with the corresponding intensity of a reference sample which contains only the form in question.

Results and Discussion

The characteristic diffractograms of both forms (II and I) of anhydrous caffeine between $5° \leq 2\theta \leq 35°$ are presented in Fig. 2. The diffractograms are clearly different. The 2θ values of the most significant reflections and the correponding rela-

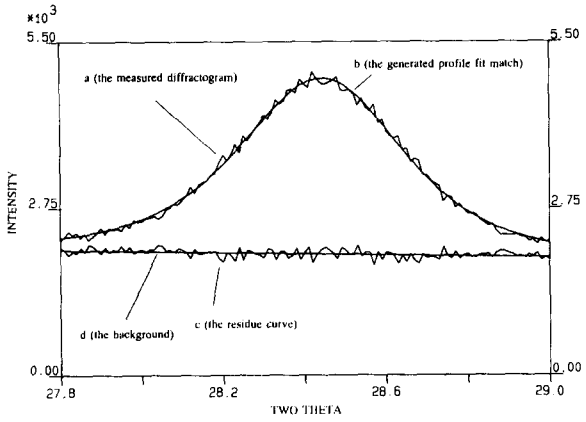

Fig. 1. Determination of the integrated intensities with the PW1869 profile fitting program. For a good fit the measured diffractogram (a) and the generated profile fit (b) match. In this case the residue-curve (c) is almost straight and matches with the background (d). If the profile fit is good the integrated intensity of reflection is same as the area of the profile-curve.

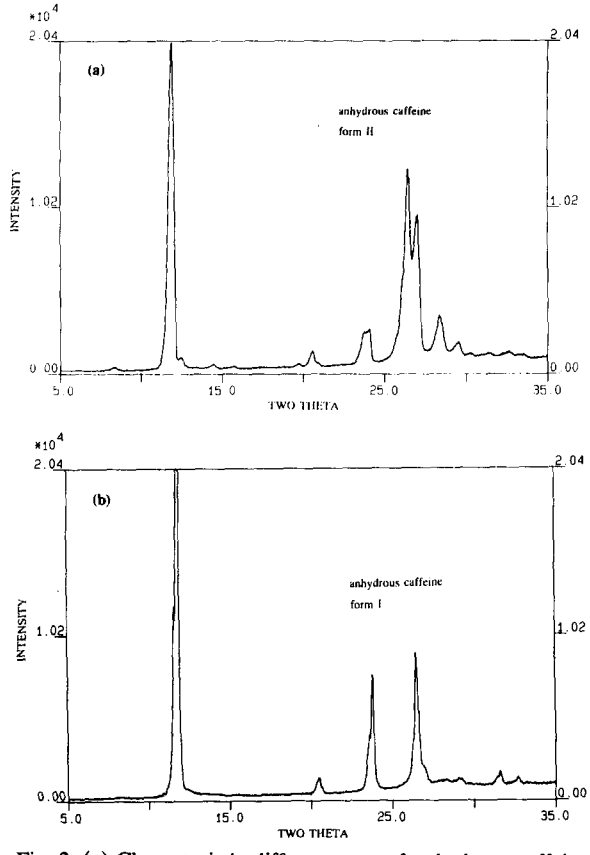

Fig. 2. (a) Characteristic diffractogram of anhydrous caffeine form II and (b) form I. The reflection at a 2θ value of about 28.4° (characteristic for form II) is most suitable for quantitative analysis.

tive intensities are summarized in Tables 1 and 2. The reflection at the 2θ value of about 28.4° is most suitable for quantitative analysis. This reflection is characteristic for form II and does not overlap with the other reflections.

Fig. 3 shows the diffractograms of Maltrin M510 powder, Maltrin M510 tablet (28 kN) and anhydrous caffeine form II. Maltrin M510 is clearly amorphous without any sharp reflections and compression has no effect on the diffractogram. The diffractogram of the mixture of caffeine and Maltrin shows reflections characteristic for caffeine solely.

The polymorphic transformation as a function of grinding time

The polymorphic transformation of caffeine from form I into form II has been studied as a function of grinding time. Fig. 4 shows the diffractograms after 1, 3, 10, 30 and 60 min of grinding. The extent of transformation is determined by comparing the background corrected intensities with the corresponding reflection of the pure form II. The results of quantitative analysis are listed in Table 3. These results show that transformation takes place rapidly; after 1

TABLE 1

The most significant reflections of anhydrous caffeine form I

Peak no.	Angle (2θ) (°)	I/I_{max} (%)
1	11.56	20
2	11.84	100
3	20.51	2
4	20.67	1
5	23.54	6
6	23.79	14
7	26.44	15
8	27.01	2
9	29.04	1
10	31.55	2
11	32.63	1

TABLE 2

The most significant reflections of anhydrous caffeine form II

Peak no.	Angle (2θ) (°)	I/I_{max} (%)
1	8.34	1
2	11.81	100
3	12.02	73
4	12.54	3
5	14.42	1
6	15.73	1
7	19.69	1
8	20.55	5
9	20.92	1
10	23.73	9
11	24.05	11
12	26.42	60
13	27.03	44
14	28.42	9
15	29.55	2
16	30.30	0.1
17	31.43	1
18	32.61	1
19	33.53	0.3

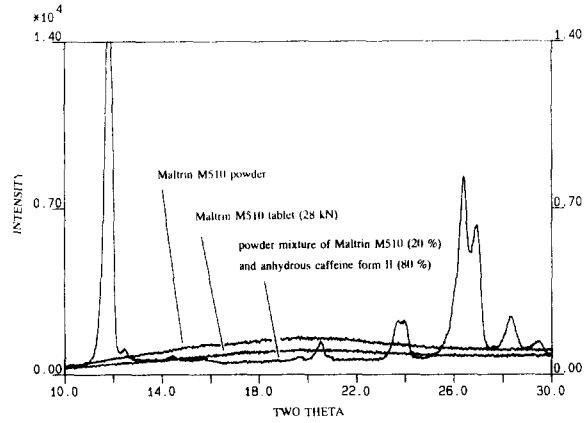

Fig. 3. Characteristic diffractograms of Maltrin M510 powder, Maltrin M510 tablet (measured from the surface) and a mixture of Maltrin M510 (20%) and anhydrous caffeine form II (80%). The diffractogram of the powder mixture shows the reflection characteristic for caffeine form II only.

min the relative amount of form II is about 74% and after 3 min the sample is almost totally transformed into form II.

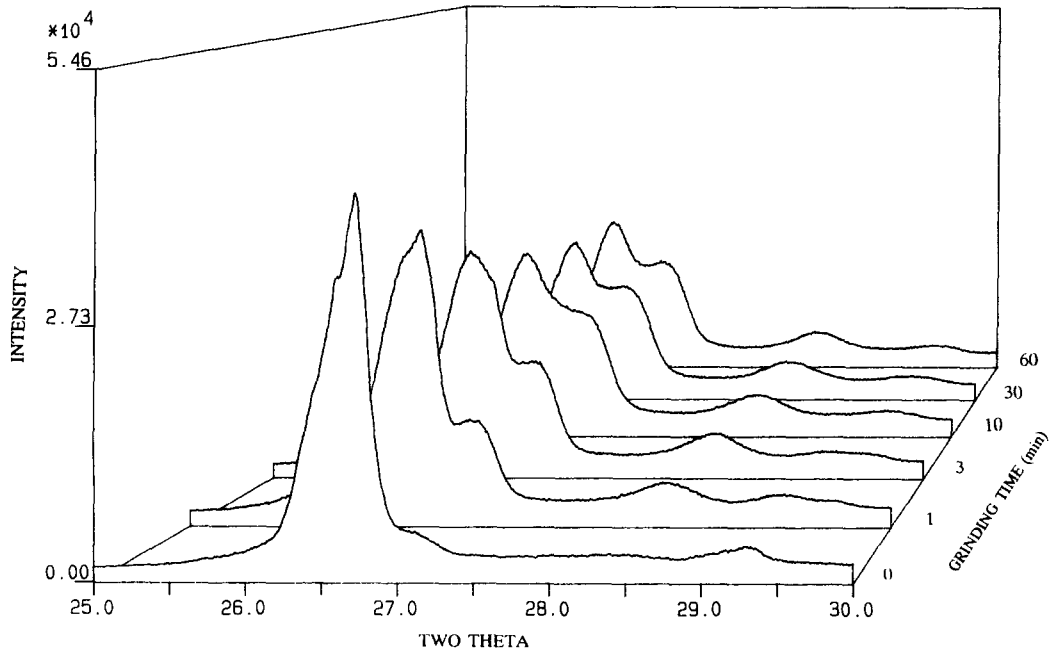

Fig. 4. Transition from form I to form II as a function of grinding time. Grinding periods: (a) 0, (b) 1, (c) 3, (d) 10, (e) 30 and (f) 60 min.

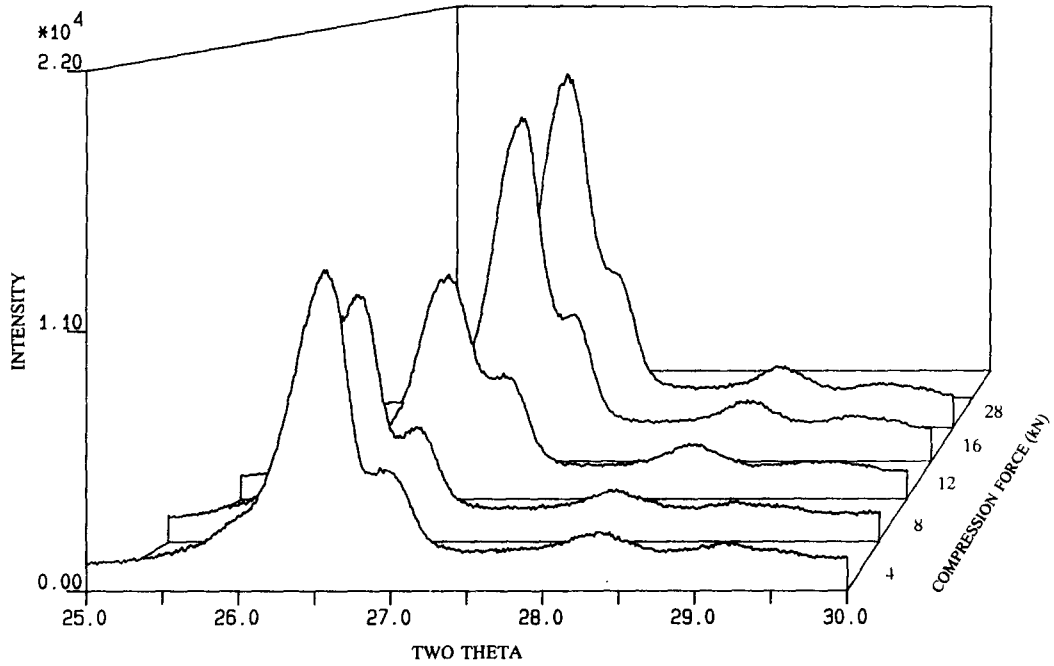

Fig. 5. Diffractograms measured from the surface of the tablets. Compression forces: (a) 4, (b) 8, (c) 12, (d) 16, and (e) 28 kN.

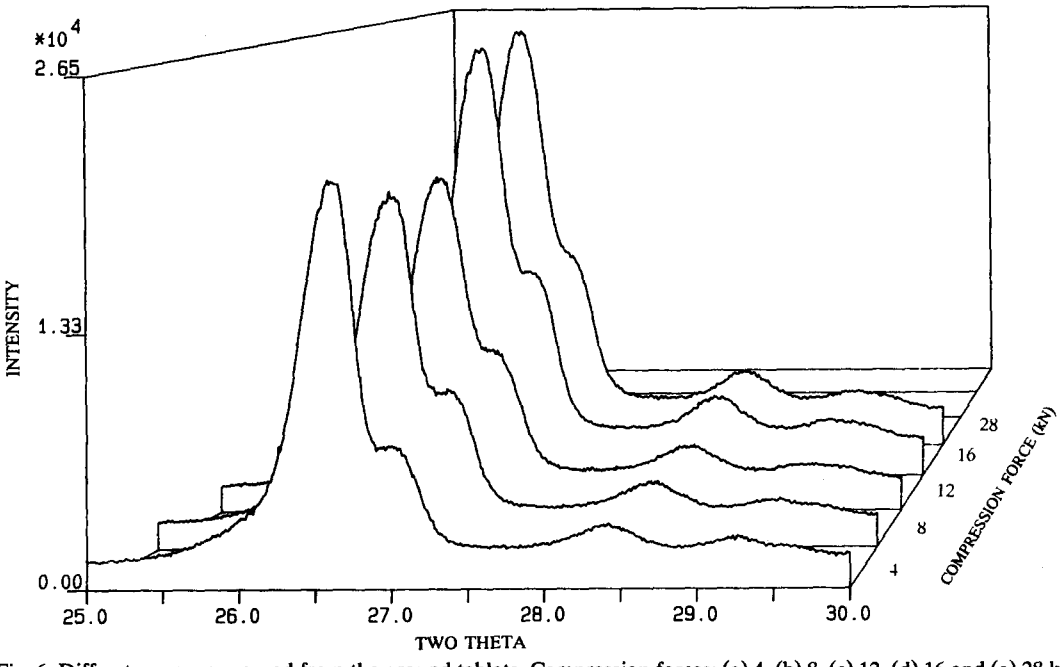

Fig. 6. Diffractograms measured from the ground tablets. Compression forces: (a) 4, (b) 8, (c) 12, (d) 16 and (e) 28 kN.

TABLE 3

The degree of polymorphic transformation as a function of grinding time

Grinding time (s)	Amount of form II in the sample (%)
0	0
1	74
3	98
10	97
30	96
60	95

The polymorphic transformation as a function of compression pressure

Because of the poor tableting properties of caffeine, tablets were made of a mixture of anhydrous caffeine form I (80%) and maltodextrin (20%). The tablets were pressed using compression forces of 4, 8, 12, 16 and 28 kN, corresponding to pressures of 51, 102, 153, 204 and 357 MPa, respectively. At each compression force five tablets were made. The relative amount of form II after compression was determined from the surface of the tablets. Subsequently, the tablets were ground gently in a mortar and the degree of transformation was determined from the powder samples representing the entire tablet. Fig. 5 shows examples of diffractograms measured from the surface of the tablets and Fig. 6 from the powder samples.

The results of quantitative analysis are expressed in Fig. 7. The degree of transformation measured from the surface is high even at low pressures. The compression force of 4 kN leads to a degree of transformation of about 70%. At higher values of the force, the degree of transformation is almost constant, about 80%. The corresponding values measured from the ground tablets are a little lower (between 50 and 60%). This suggests that the transition occurs mainly near the surface of the tablet. When the compression force is raised the volume of the transformed area increases causing linear growth of the degree of transformation measured from the ground tablets.

Both the grinding and tableting experiments show that polymorphic transformation readily takes place. This might also be the case with other polymorphic drug substances. For this reason, it is essential to examine the effect of mechanical treatment upon polymorphic transformation when the metastable form is chosen.

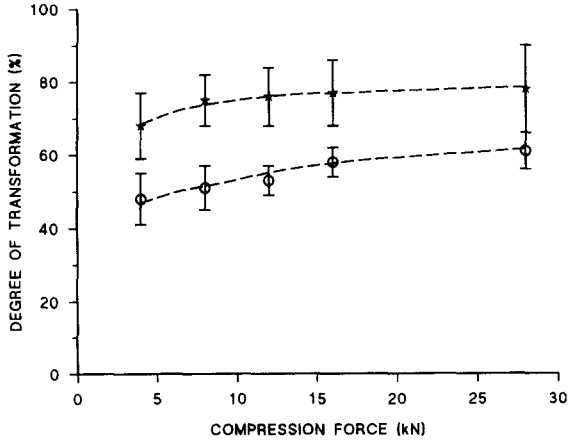

Fig. 7. Results of quantitative analysis for the transformation of form I to form II as a function of compression force. The degree of transformation was measured from the surface of the tablets (★; 10 measurements) and from the ground tablets (○; 5 measurements).

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