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Studies on the Characteristics of Carbochromen Hydrochloride Crystals. II.[1] Polymorphism and Cracking in the Tablets

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The cause of cracking of tablets containing carbochromen hydrochloride was further investigated in the light of the crystal modifications described in the previous paper. In tablets, form II′ crystals were transformed into dihydrates (form II) upon water absorption and this led to the occurrence of capping-like cracking of the tablet. However, tablets made of form I′ crystals did not crack under the same conditions.

The volume expansion of form II′ tablets on exposure to moisture was larger than that of form I′ tablets. Apparent density variation in the tablets was measured by the drilling load method, and it was found to be uniform in form I′ tablets whereas a face of discontinuity was observed in the form II′ tablets. A possible explanation of these results is that form I′ crystals break down on phase transformation and the tension is dispersed in all directions. In contrast, form II′ crystals expand along one of their crystal axes and create distortion in the tablet.

Keywords——carbochromen hydrochloride; cracking of tablet; water of crystallization; crystal modifications; apparent density variation; drilling load method; expansion of tablets

Research on preparing carbochromen hydrochloride (Carb·HCl) tablets by the wet granulation method showed that some lots of tablets were apt to crack at the core during storage. The cracked tablets have been found to contain much of the modified form II crystals, while the uncracked ones consisted mostly of form I crystals.[1] Cracking of the core and coated tablets has been the subject of a number of reports.[2–7] In most cases, the coated part of the tablet cracked due to expansion of the core with moisture absorped generally through the pores between particles.[2–6] With respect to cracking at the core, only one article by Utsumi *et al.*[7] was found. In their study, the tablet core broke into pieces unlike the case of Carb·HCl tablets, which cracked in a particular dirrection in a manner resembling the capping phenomenon that occurs just after tablet compression. None of these reports discuss the relationships between cracking phenomena and polymorphism of the crystals in the tablets.

In the previous paper,[1] we clarified the polymorphism of Carb·HCl and the physical changes accompanying the interconversions among the five crystal forms. In that study, we tried to obtained basic data on the changes of Carb·HCl crystals during granulation, drying, compression and storage of tablets under standard conditions. Now we report a detailed examination of the properties of tablets prepared from two different crystal modifications of Carb·HCl, forms I′, and II′, and describe the relation of form to the cracking phenomena.

Experimental

1) **Material**——Forms I and II were prepared by keeping bulk Carb·HCl (Cassela Co., Ltd.) under 75% relative humidity (RH) for one week at 25 and 40°C, respectively. These processes completed the transformation of various crystal forms to forms I and II, respectively. The crystal forms of the final products were ascertained from their X-ray powder diffraction patterns and infrared (IR) spectra. Forms I′ and II′ were prepared from forms I and II, respectively, by vacuum-drying at 5 mmHg, and 40°C for 16 h. The sizes of both forms of crystals thus prepared were similar to each other, ranging between about 5 and 15 μm.

2) **Examination of the Change in Crystal Form produced by Compression**——Forms I′ and II′ were compressed under the conditions described below using a single punch machine (Autograph, Shimadzu Co., Ltd.);

Amount of sample: approximately 500 mg
Die and punch: 11 mmϕ, flat (the die was lightly dusted with magnesium stearate)
Compression pressure: 0.3, 0.6, 1.0, 1.5 or 2.0 ton/cm^2
Compression speed: 2.5 mm/min (kept constant during the following procedures)
Ejection speed: 5.0 mm/min (the same as above)

X-Ray diffractions of the surfaces and some cross sections of the tablets were measured. Form II′ was very hygroscopic, so handling was conducted as rapidly as possible and, when necessary, its crystals or tablets were stored in a desiccator with P_2O_5.

3) **Investigation of the Properties of Tablets**——Using 100 mg of Carb·HCl crystals, form I′ or II′, flat tablets of 7 mm diameter were made by applying a pressure of 0.3, 0.8, 1.5, 2.5 or 4.0 ton/cm^2. Moisture absorption and cracking of the tablets were examined after storage at 25°C and RH 11 to 93%. As a reference, tablets of form II were prepared in the same manner and stored at 25°C and RH 75%. The moisture absorption rate was determined at 25°C and RH 75% with a Cahn electrobalance (Ventron Lnstruments Co.), and the final crystal form of tablets was examined by X-ray diffraction.

4) **Measurement of Stress Distribution in Tablets**——For this purpose, tablets (11 mmϕ, flat, containing 500 mg of Carb·HCl) were prepared by applying 1.5 ton/cm^2 of pressure. Stress distribution was measured for freshly prepared tablets with a drilling-load apparatus (Yamato Kagaku Co.)[8] equipped with a 2 mm end mill. The center of the surface of a tablet and two middle points on a certain radius were drilled at a speed of 1 mm/min. Measurement was done for both faces of the tablet.

TABLE I. Cracking of Tablets containing Carbochromen Hydrochloride

(1) Effect of Relative Humidity on the Cracking of the Form II′ Tablet at 25°C

Relative humidity (%)	11	22	33	44	57	68	75	85	93
Period for cracking appearance	Not cracked (2 weeks)		77 h	←		21 h	→	← 6 h →	
Moisture absorption	Not observed		←			Observed		→	

Compression pressure: 1.5 ton/cm^2.

(2) Effect of Compression Pressure on Period required for Cracking of Form II′ Tablet at 25°C and RH 75%

Pressure (ton/cm^2)	0.3	0.8	1.5	2.5	4.0
Period for cracking appearance (h)	2	3.5	7.5	7.5	22

(3) Expansion and Cracking of Tablets containing Various Ratios of Carbochromen Hydrochloride, Form I′ and II′, after Storage at 25°C, RH 75% for One Month

Form II′ (%)		0	10	30	50	70	80	90	100
Form I′ (%)		100	90	70	50	30	20	10	0
Expansion ratio[a] (%)	Diameter	1.9	2·2	4.0	7.0	6.6			
	Thickness	4.1	4.7	8.9	10.9	16.5			
Cracking of tablet		←		Not observed		→	←	Observed	→

a) Expansion ratio (%) with respect to initial diameter and thickness.

5) **Cracking and Expansion of Tablets as a Function of Form II′ Content**——Various ratios [Table I-(3)] of form I and form II crystals were mixed thoroughly by gentle grinding in a mortar and by sieving. These mixtures were dried *in vacuo* to produce a mixture of form I′ and form II′. Using about 500 mg of these mixtures, tablets (8 mmϕ, flat) were prepared at 1.0 ton/cm^2 of pressure. Each tablet was stored at 25°C and RH 75% for one month. Cracking of tablets was examined, and the diameter and thickness of the non-cracked tablets were measured periodically with a dial gauge during one month.

6) **Conditioning of Relative Humidities**——The conditioning was performed as described in the previous paper.[1]

Results

1. Cracking of Form II′ Tablets

The examination of the crystal form before and after compression showed that phase transformation had not occurred during the compression process at pressures between 0.3 and 2.0 ton/cm^2. As an example, the result with 1.5 ton/cm^2 is shown in Fig. 1. Moisture absorp-

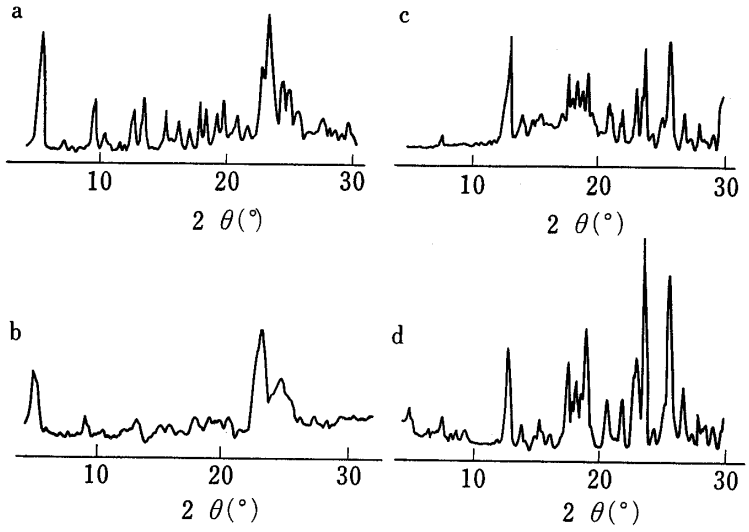

Fig. 1. X-Ray Powder Diffraction Patterns before and after Compression of Carbochromen Hydrochloride

a) form I′ powder, b) form I′ tablet surface (1.5 ton/cm²), c) form II′ powder, d) form II′ tablet surface (1.5 ton/cm²).

tion rates of tablets consisting of form I′ or II′ are graphically shown in Fig. 2, while the relationships of relative humidity and compression pressure with cracking of form II′ tablets are shown in Tables I-(1) and I-(2), respectively. The moisture absorption rate of the form II′ tablets was much greater than that of the form I′ tablets, as expected from the study reported previously.[1] Table I-(3) shows the relationship between cracking or the expansion ratio and the content of forms I′ and II′ in the tablets. In Fig. 3, the expansion ratios are plotted against the content of form II′. As is clear from the figure, a linear relationship was obtained for 0 to 70% content of form II′. Using this relationship, the expansion ratio of tablets containing 100% of form II′, which could not be measured due to cracking, was estimated by extrapolation to be about 10% in diameter and 20% in thickness in comparison with the initial values. Fig. 4 shows an example of cracking of a form II′ tablet kept at 25°C and RH 75% for 8 h.

Cracking in a cup-shaped pattern occurred, while a form I′ tablet showed no sign of cracking even after two-month storage Fig. 5. X-Ray examinations showed that in the cracked tablet, form II′ was transformed into form II. A tablet prepared by using form II crystals

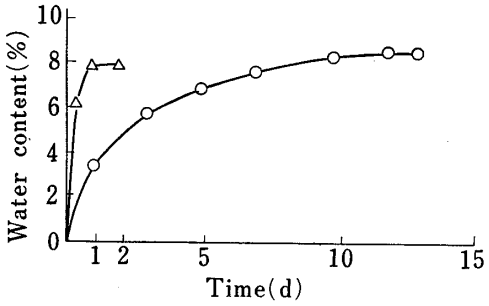

Fig. 2. Moisture Absorption of Rate Carbochromen Hydrochloride Tablets consisting of Form I′ or Form II′ Crystals at 25°C RH 75% (measured with a CAHN Electrobalance)

○: form I′, △: form II′.

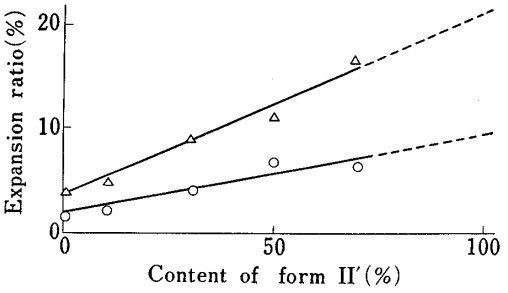

Fig. 3. Expansion Ratio of the Tablet consisting of Carbochromen Hydrochloride of Form I′ and II′

△: thickness, ○: diameter.

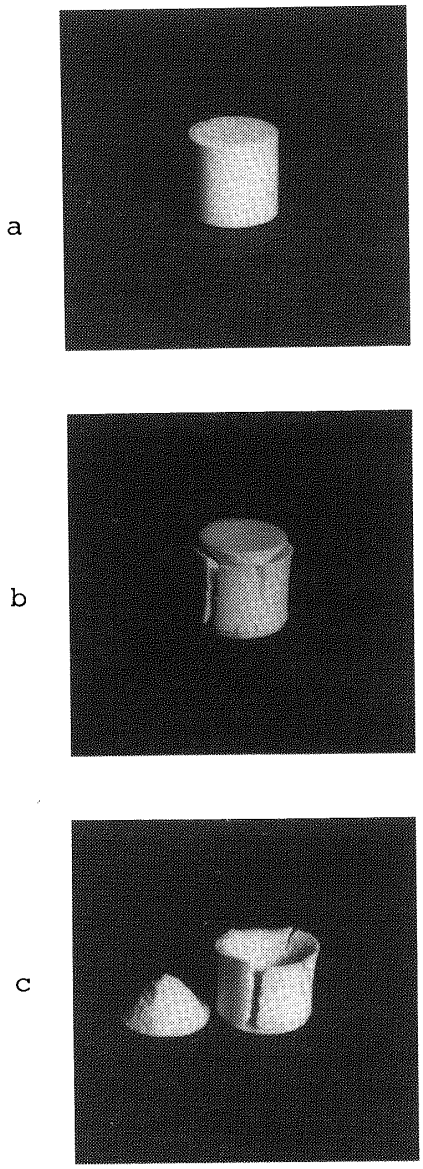

Fig. 4. Cracked Tablets with Transformation of Form II′ into Form II

a) original form II′ tablet, b), c) cracked form II tablet after storage at 25°C, RH 75% for 8 h.

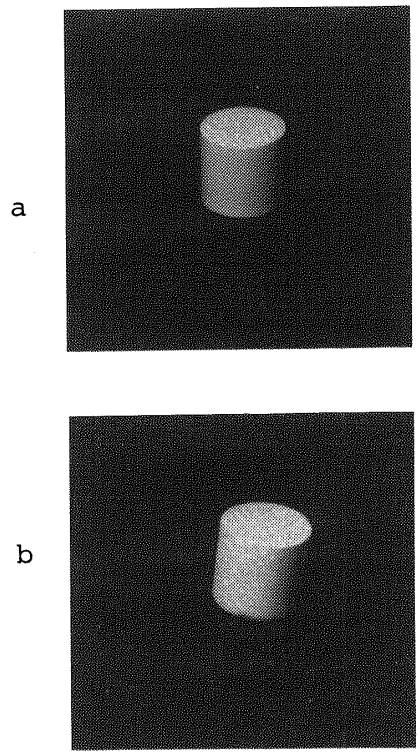

Fig. 5. Tablets with Transformation of Form I′ into Form I

a) original form I′ tablet, b) form I tablet after storage for 2 months at 25°C, RH 75%.

from the beginning did not absorb any water under similar conditions and kept its original appearance during storage.

2. Stress Distribution of Tablets

Fig. 6 presents the results of the stress distribution study. The drilling positions are shown in Fig. 6-a. The results obtained from the side of the upper punch are shown in Fig. 6-b. The stress distribution patterns of the form I′ tablet were nearly the same in the three positions (A, B, C) of measurement and, therefore, only the pattern (form I′ B) obtained at B is shown. The figure shows that the stress was uniformly distributed along the measured direction. In contrast, the Form II′ tablet showed a sudden increase in load. The position of this increase was deeper at B than at A and C. The patterns at A and C were similar. The results of measurement of the lower punch were not significantly different from those of the upper punch.

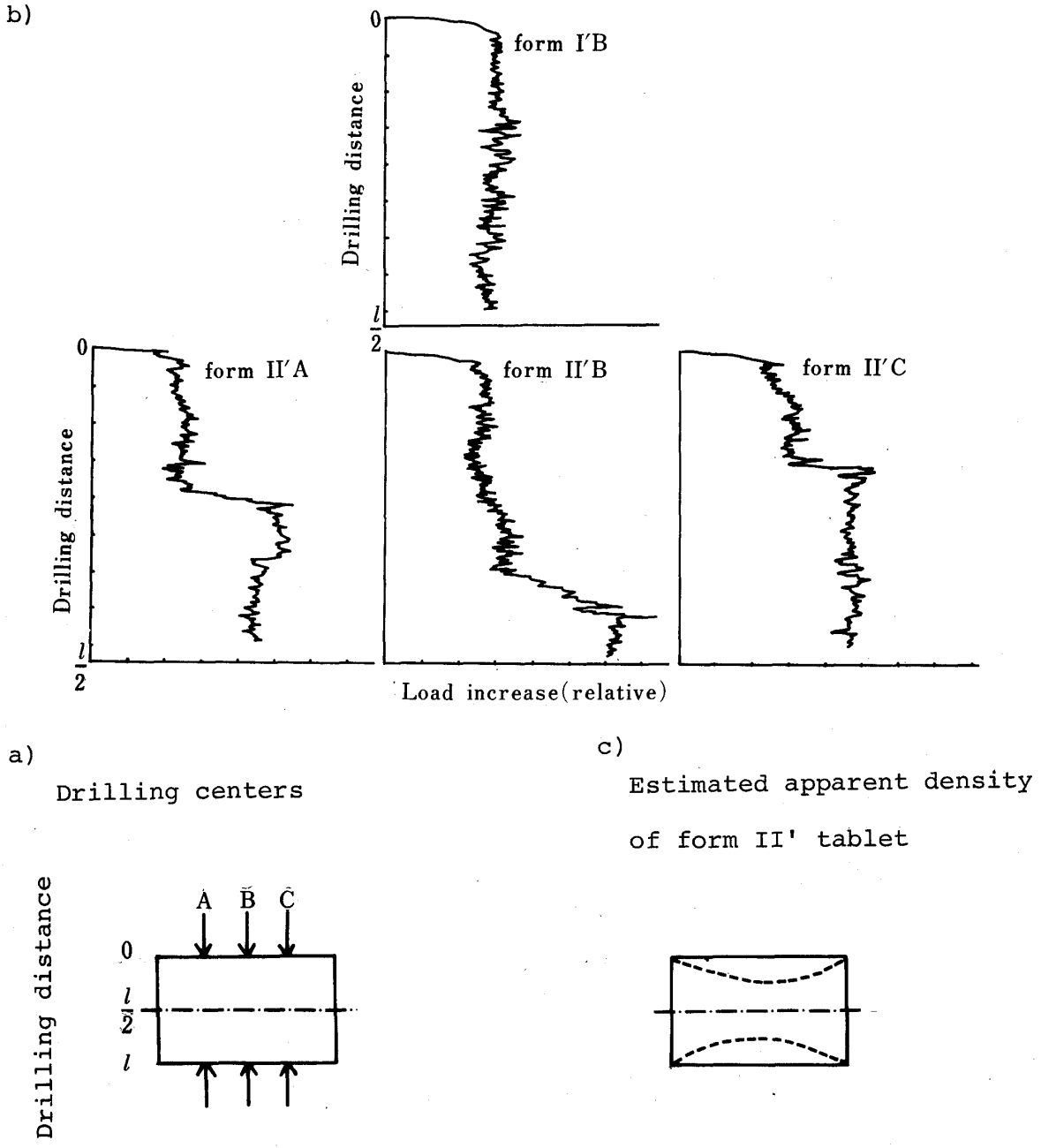

Fig. 6. Measurements of the Drilling-load Distribution of Tablets of Carbochromen Hydrochloride
a) drilling centers, b) drilling load distributions, c) estimated apparent density variation of form II' tablet.

Discussion

According to the usual wet granulation method, Carb·HCl and additives were mixed with a suitable amount of water and formed into granules. During this process, Carb·HCl in form I' or form III will be converted into form I or, above 40°C, into form II as is clear from the previous paper.[1] If the granules are exposed to suitable amounts of heat and moisture, some of the form I crystals may be transformed into form II, which produces form II' on further drying. The granules were then dried and compressed into tablets. With these processes, forms I and II will afford forms I' and II', respectively. This implies that the contents of form I' and form II' crystals in the tablets thus prepared vary considerably depending on the manufacturing conditions. The experiments described here on tablets prepared without using any additives revealed the following relationships.

(1) The higher the RH is, the earlier the cracking starts.

(2) At RH values where Carb·HCl crystals in the tablet do not absorb moisture, no cracking occurs even in tablets made of form II′ crystals.

(3) Cracking is retarded in tablets prepared at a higher compression pressure.

The first two relationships imply that moisture absorption has an important role in the cracking phenomenon. The third one may be explained by the decrease in the rate of moisture absorption caused by the decrease in porosity of tablets prepared at a higher compression pressure.[3]

From the linear relationship between the expansion ratio and the form II′ content in the tablet, the tablet consiting solely of form II′ crystals was calculated to expand 10% in diameter and 20% in thickness on exposure to moisture. In contrast, the tablet consisting of form I′ expands only 2% in diameter and 4% in thickness under the same conditions.

Curiously, the tablet of form I′, which absorbs more water (*ca.* 12%), expands less than that of form II′, which absorbs less water (*ca.* 8%) on exposure to moisture. The reason may be found in the observations described in the previous paper.[1] On absorption of water, form I′ crystals break into pieces and the expansion force is attenuated and equalized in all directions. In the case of the form II′ tablet, however, the absorption of water into a type of clathrate will cause the crystal to expand in one specific direction (in this case along the a-axis), making voids in the tablet. The stress distribution study in the present work showed that the apparent density of the form I′ tablet is uniform throughout, whereas an apparent density gap exists in the form II′ tablet. The location of the gap is schematically illustrated in Fig. 6-c. That is, areas falling outside the dotted line are relatively soft and those inside are hard. This gap suggests that the long axes of form II′ crystals in tablets may be oriented in parallel to the cracking face. On expansion of the crystals following the moisture absorption, the gap results in cracking.

Identifying the cause of the apparent density variation in the form II′ tablet is not easy. However, the X-ray diffraction lines of form I′ were broader in the tablet, whereas those of form II′ were the same for the crystals and the tablet (Fig. 1). Thus, the shear stress during tabletting may cause dislocation of form I′ crystals, whereas form II′ crystals resist the shearing, leading to crystal orientation or uneven apparent density variation. The pattern of cracking in the form II′ tablet resembles the so-called "capping" which often occurs on tablet formation. The capping phenomenon has been intensively studied by many researchers and various theories have been proposed.[9,10] The observed cup-type stress gap in the form II′ tablet may be explainable in terms of some of these theories. For example, capping is said to occur on the surface of stress concentrations which are formed in tablets during compression and ejection.[10] In the case of Carb·HCl tablets, the cracking may be triggered by moisture absorption.

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