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POLYMORPHIC TRANSITIONS OF CARBAMAZEPINE DURING GRINDING AND COMPRESSION

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ABSTRACT

Carbamazepine is a potent anticonvulsivant, but, irregular plasma levels are noticed. The variability of therapeutic efficiency can be attributed to interindividual sensibility, chronobiologic effect, but also to rates of dissolution which can differ when polymorphs are induced by technologic operations.

Several crystalline forms of Carbamazepine have been characterized. As for us, we have studied three crystalline modifications which can be found in commercialized galenic forms : the most usual beta form, the alpha form and the dihydrate.

The aim of this work was to investigate :

- the behaviour of these three crystalline forms during compression,
- the possibility of crystalline structural changes under grinding and tabletting conditions. Indeed, polymorphous transformations may occur during technologic operations such as grinding or compression owing to the increase of internal energy.

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Grinding was performed in a ball mill for 15 and 60 minutes. Compression was carried out using an instrumented single punch machine. The different parameters of compression, and hardness of resulting tablets were investigated.

X Ray diffraction and Differential scanning calorimetry were carried out on the different samples of ground powders and on carefully crushed samples of each batch of tablets.

The results point out at the best compressibility of dihydrate, and the most effective stability of the alpha form. However, the usual beta form remains stable in normal conditions of fabrication and storage.

1 INTRODUCTION

The various polymorphic forms of a drug have the same chemical composition, but different physical structures .The organization of the molecules in space is different from one to another (different crystal lattice parameters) , consequently many physical and mechanical properties are different :

- internal energy levels ; in consequence, the melting points and solubilities may differ .
- the surface free energy of the different faces of the crystalline particles ; the bonding forces between the particles may be modified, and the hardness of resulting tablets, after compression, will eventually be different.
- molecule's distribution along each space direction in the crystal lattice will not be identical, which will result in different mechanical behaviour for instance the transmission of forces according to the directions.

On the other hand, modifications of physical and mechanical behaviour will eventually be brought to light after insertion of water molecules in the crystal lattice : hydrate formation (pseudopolymorphism).

These differences in the physical structure have influence on several properties of crystalline particles, for instance their behaviour under grinding or compression.

Many authors have noticed polymorphic transitions or crystallinity decreases for some drugs under grinding and compression (1) (2) (3).

Other authors have studied the compressibility of different polymorphic forms of one substance (drug or excipient) (4) (5) (6).

As for us, we have studied carbamazepine. The polymorphism of this drug has been investigated by several researchers :

- four polymorphic forms may exist according to Kuhnert - Brandstätter (7),
- six polymorphic forms, according to Pölhmann (8),

On the other hand, carbamazepine forms a dihydrate with water (9) (10) (11).

Industrial raw material "Carbamazepine" is usually the beta form.

This beta form has been characterised in the different tablets which have been found on the European Market, but a small quantity of alpha form can be sometimes found (12).

Yet in aqueous suspensions, carbamazepine exists as the dihydrate (12).

Alpha carbamazepine is easily prepared by heating the beta form at 170°C for two hours. These two forms have been reported by several authors particularly Pöhlman (8),Kuhnert-Brandstätter(7).

Other polymorphic forms have been described but they appear to be very unstable (7) (10).

The dihydrate has been reported by Laine (9), Kahella (11) and Umeda (10).

It seems to be obtained with a better yield by alpha form hydratation (13). After storage at 20°C, in a stoppered glass flask, it loses its crystallization water very slowly.

2 MATERIAL

2 - 1 - Crystalline forms of carbamazepine

- beta form from two origins : carbamazepine a), carbamazepine b).

a) Ciba geigy

b) Sigma

2 - 2 - Properties of these three forms of carbamazepine

TABLE I : Main characteristics of the different forms of carbamazepine studied .

Properties	alpha form	beta form	dihydrate
Behaviour when heated	melting point 190 - 191°C	Transition at 176°C into alpha form	Deshydratation from 30 to 85°C Transition into alpha form
Water content (The Karl Fischer method)	<0,20%	<0,20%	13,2% i.e:34,8g/molecule
Shape of studied particules	narrow needles	ground crystals	needles
Size of studied particules (microscopy)	50 to 60 µm x 5 to 10 µm	a)10 to 30 µm b) <5 µm	20 to 30 µm x 3 à 5 µm

- alpha form prepared by heating the beta form for two hours at 170°C.

- dihydrate prepared by dispersion of the alpha form into distilled water. This suspension was left to settle for 15 days in an oven at 43°C. The needle shaped crystals were filtered by depression and left to dry at a temperature below 20°C in the open air. It is stored in a stoppered bottle.

3 METHODS

3 - 1 - Crystallographic investigation

3 - 1 - 1 - X Ray Diffraction

A powder X Ray diffractometry was carried out using a Philips PW 1720 Generator equiped with a Guinier Hagg Chamber (Cu $K\alpha_1$ radiation, λ = 1,5406 Å)

3 - 1 - 2 - Differential Scanning Calorimetry

A thermal analysis of samples was performed using a differential scanning calorimeter (DSC - 2C, Perkin Elmer) at 10°C/min. and 5 millical./sec. (from 303°K to 473°K).

3 - 1 - 3 - Water content determination

Water content was measured by the Karl Fischer method.

Infra-red spectra analysis did not give more interesting information.

3 - 2 - Compressibility investigation

The carbamazepine samples were compressed with a Frogerais OA single punch tablet machine using 1 cm2 area flat punches. The tablets are produced with the same upper punch displacement, the volume of the compression chamber remaining constant (depth = 1 cm).

For the beta form, we have modified this upper punch displacement for the study of the influence of the compression force on the crystallographic parameters.

Strain gauges are stuck on the upper and lower punches, connected to a computer by means of Wheatstone bridges.

The die of the tablet machine was filled by hand with 550 mg carbamazepine powder.

For each carbamazepine tablet, we can measure, with the help of the instrumented tablet machine :

X = upper punch displacement

Y_1 = upper punch force

Y_2 = lower punch force

The hardness was measured with an Heberlein Durometer.

We can calculate :

Y_2/Y_1 = indicative of force transmission through the powder.

$Y_{1/hardness}$ = indicative of the aptitude of powders to give a hard tablet (14).

3 - 3 - Carbamazepine stability during galenic processes

3 - 3 - 1 - Grinding

Grinding was performed in a planetar ball mill for an appropriate period (15 and 60 minutes).

X Ray diffraction, differential scanning calorimetry and determination of water content were carried out on each sample .

3 - 3 - 2 - Compression

Compression was performed as described above (cf 3-2).

For the most usual beta form, three levels of pressure were investigated. It was very difficult to apply several compression forces to

the alpha form. Anyhow that crystallographic study should be of little interest, the alpha form being in theory the more stable form.

X Ray diffraction study was performed on some powder samples obtained both from the surface and from the center of tablets. Differential scanning calorimetry and determination of water content were caried out on the dihydrate tablet.

4 RESULTS

4 - 1 - Compressibility investigation

Results are collected in tables II and III.

4 - 1 - 1 - Alpha, beta and dihydrate comparison

If we consider the Y_1/hardness ratio,we can see that the dihydrate seems to be the most compressible form of carbamazepine : a higher hardness of tablets is obtained for a lower force upon upper punch.

The usual beta form is the worst.

The intermediate alpha form although presenting a good ratio Y_1/hardness, induces sometimes sticking.

4 - 1 - 2 - Influence of the commercial origin of the carbamazepine (Table II)

Tablets cannot be obtained with the pure beta commercial form of carbamazepine b) : the smaller size of the particle may be the reason.

These results seem to have a consequence on those obtained with the alpha forms prepared from the two beta forms.

4 - 1 - 3 - Influence of the compression force (Table III)

The use of a 10 KN compression force seems to be a limit : a higher force only gives a very small increase of the hardness.

4 - 2 - Carbamazepine stability during galenic process.

4 - 2 - 1 - Grinding

- alpha form : RX Diffraction patterns and DSC curves exhibit no distinctive change either after 15 min. or after 60 minutes of grinding (Figures n° 1 and 2). A decrease in the intensity of the lines of the X Ray films may be attributed to a decrease of the cristallinity : but this phenomenon could be also ascribed to the decrease of the particle size.

- beta form : RX diffraction patterns (Figure n° 1) remain unchanged after 15 as 60 minutes. A slight decrease in the intensity of the lines may be noticed.

Table II : Compression characteristics of alpha, beta carbamazepine and its dihydrate (compression at the same upper punch displacement, but in various conditions of relative humidity in the compression room).

Sample origin	Beta				Alpha prepared from				Dihydrate			
	a)			b)	a)			b)				
Relative humidity	33%	33%	65%	65%	33%	65%	65%	65%	33%	65%	60%	60%
X_1 (mm/100)	578	578,5	572,5	569	577	568	570	570	577	568,5	561,5	568,5
Y_1(KN)	8,1	8,7	10,6	24,6	10,5	16,1	12,4	20,9	12,0	14,6	12,4	11,8
Y_2(KN)	6,8	6,9	9,2	20,6	7,3	12,5	9,5	16,7	8,3	11,5	10,0	9,2
Hardness (N)	31,9	30,4	29,4	no correct tablet "capping"	73,6	95,6	88,3	>157	147,1	156,9	137,3	137,3
Y_2 / Y_1	0,84	0,79	0,87	0,83	0,69	0,77	0,76	0,80	0,69	0,78	0,80	0,78
Y_1/Hardness	254	287	359	meaning-less	143	168	141	133	81	94	91	86

TABLE III : Influence of compression force on compression characteristics of beta carbamazepine a).

X (1/100mm)	578,5	603,5	625,5
Y_1 (KN)	8,74	17,76	31,48
Y_2 (KN)	6,9	13,33	23,99
Hardness (N)	30,4	41,7	without meaning capping
Y_1/Hardness	287,48	425,97	
Y_2/Y_1	0,78	0,75	0,76

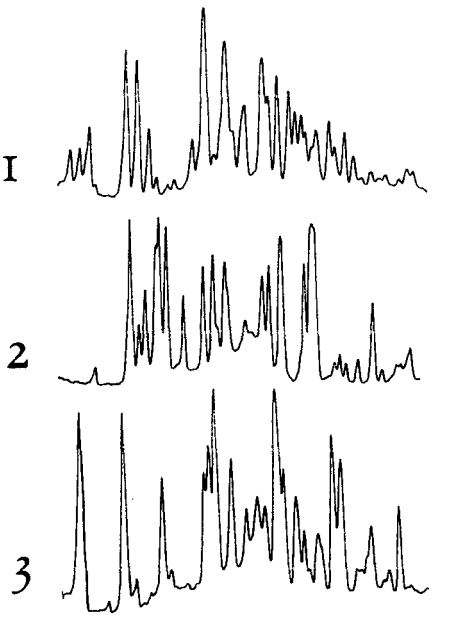

FIGURE n°1 : X Ray diffraction patterns of carbamazepine forms : 1) alpha, 2) beta, 3) dihydrate.

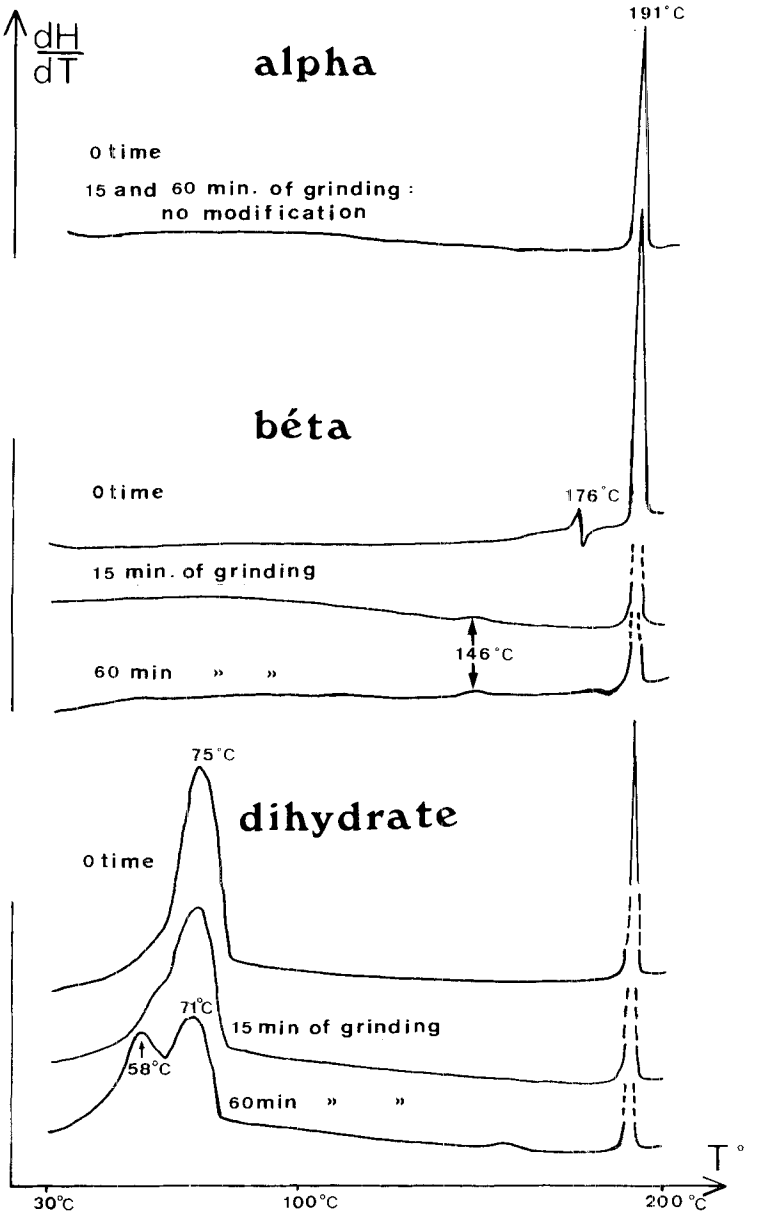

FIGURE n° 2 : Effects of grinding time on the thermal properties of the different forms of carbamazepine (as recorded by DSC at a heating rate of 10°C/min.).

On the other hand, surprisingly, we can see DSC curve modifications (Figure n° 2). * After 15 minutes, we can notice :

. a very small and wide endothermic peak at 146°C.

. the absence of the endotherm corresponding to the transition from beta to alpha at 176°C.

. a sharp endotherm corresponding to the melting of the alpha form at 191°C.

* After 60 minutes, the thermogram is nearly the same as the one observed after 15 minutes but with a very small exotherm at 172 -173°C. We have made an X Ray diffraction spectrum on a sample of beta (grinding 15 minutes) after heating by scanning calorimetry up to 160°C, that is to say just after the small endothermic peak (146°C), we have obtained the spectrum of the pure alpha form.

So it may be possible to say that this endothermic peak at 146°C corresponds to the transition of beta to alpha form.

We have no found another explanation to this discrepancy between RX diffraction patterns and DSC curves . But it may be thought that RX diffractometry gives more reliable informations than the thermoanalysis about physical structure.

- Dihydrate

. RX diffraction patterns (Figure n°1) : the observations are the same as for the two previous forms : no modification.

. DSC curves (Figure n° 2) : if we compare these thermograms to that one of the dihydrate at 0 time, we can see :

* After 15 minutes, a slight displacement of the deshydratation endotherm at 75°C,which begins at a lower temperature. The peak is wider.

* After 60 minutes, the loss of water seems to occur in two stages : two endothermic broad peaks are observed at 58 and 71°C. We have calculated the area under these peaks, and expressed these areas in percentage by mg of drug :

grinding time	Area under the peak of DSC curves of the dihydrate
- 0 time	15,43 %
- 15 minutes	14,10 %
- 60 minutes	13,16 % (1st peak = 7,09 % ; 2nd peak = 6,10 %)

TABLE IV : Water content of dihydrate after grinding.

Grinding time	Water content
0 time	13,6 %
15 minutes	13,3 %
60 minutes	12,4 %

So, it seems that under grinding, the molecules of water are less bonded , and are released at a lower temperature.

The Karl Fischer determinations of water content of these samples show no significant deshydratation (TABLE IV).

By thermogravimetry, we have obtained nearly the same results. By heating the samples at 10°C/minute, with a starting temperature of 24°C, the loss of weight occurs between 34°C and 90°C, the values are :

- 12,9 % for the dihydrate at 0 time,
- 11,8 % for the dihydrate after grinding time of 60 minutes.

The dihydrate after grinding seems to remain a dihydrate, but a modification of particle size and crystal habit can explain the modifications in the kinetics of the loss of water during heating. Several authors have reported quite the same observations : Vromans about lactose monohydrate (15), Takahashi about ampicillin trihydrate (16). Under the microscope, we can see very great habit modifications of the partcles : the small narrow needles are transformed into larger, rounded and blocky shaped crystals. Perhaps, a recristallisation occurs during grinding, as it was described by Hüttenrauch (17) in the case of cellulose.

4 - 2 - 2 - Compression

- Alpha and beta forms :

X Ray diffraction patterns of powdered samples from the surface and from the center of the tablets, do not exhibit any significativ change whatever the compression force may be.

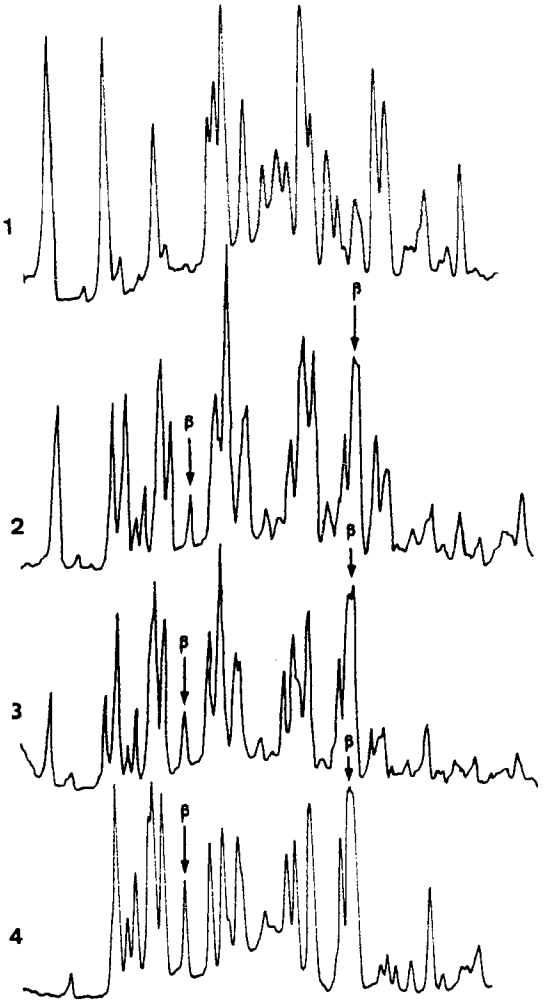

FIGURE n° 3 : X Ray diffraction patterns of dihydrate (1) and beta carbamazepine (4) at 0 time, and dihydrate carbamazepine after compression : powder obtained from the surface of tablets (2), powder obtained from the center of tablets (3).

- Dihydrate :

in our experimental conditions we can observe on the X Ray spectra a transformation of about 50 % of the dihydrate into beta form : it is nearly the same percentage of transformation in the powder samples obtained both from the surface and from the center of tablets (Figure N° 3).

No significant loss of water by the Karl Fischer method was found.

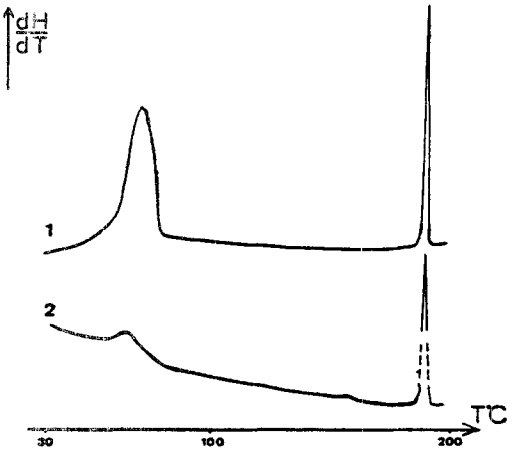

FIGURE n° 4 : Effect of compression on the thermal properties of dihydrate carbamazepine (as recorded by DSC at a heating rate of 10°C/ min.) : 1) before compression, 2) after compression.

But, on the DSC curve (Figure N° 4) we can see that the loss of water must begin before 30°C, because the basis line is raised higher and there is a very wide peak at 66°C which probably corresponds to the dehydratation: the crystal lattice must be deformed so the kinetics of the loss of water is modified (it is not possible to begin the thermal analysis at a lower temperature than 30°C with our differential scanning calorimeter) .

CONCLUSION

The beta form is the usual commercial raw material of carbamazepine. In this work, we have showed that the alpha form and the dihydrate present a better compressibility than the beta form. But, it may be noticed that : - the most compressible form, the dihydrate, is not stable under compression ;

- the alpha form induces sticking ; yet this later defect could be corrected by an appropriate formulation.

We have made surprising and interesting observations concerning dihydrate in theory as well in practice, we are still working on the subject.

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