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Formation of dihydrate from carbamazepine anhydrate in aqueous conditions

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Summary

According to our observations, carbamazepine dihydrate crystals grow by the whisker mechanism (or mechanisms). The habit, the dimensions of the crystals and their rapid growth indicate this. Also the strong orientation in the X-ray diffractogram is in harmony with the whisker theory. The whisker growth explains also the rapid transition from the anhydrous form to the dihydrate one in water.

Dihydrate whiskers which are loosely in the solution as well as ones fastened to the surface of the anhydrous mother crystal has been observed. The oriented crystal structure of carbamazepine dihydrate may be at least one important factor in the growth mechanism of carbamazepine dihydrate whiskers.

Introduction

Carbamazepine is an anti-epileptic drug and it has been used since the early 1960s. The polymorphic (Pohlman et al., 1975; Villafuerte-Robles, 1982) and dissolution behaviour (Kahela et al., 1983) have been recently under discussion.

Anhydrous carbamazepine is supposed to be practically insoluble in water (BP 1980). It is difficult to determine the solubility of the anhydrous form because of its rapid transition to dihydrate crystals in water. As a consequence, the crystals grow rapidly and this is a reason, why the dihydrate form of carbamazepine seems to dissolve in water faster than the more energetic anhydrous form under certain circumstances (Kahela et al., 1983). Dihydrate crystals can also grow on the tablets, which are kept in the humid conditions (Stahl, 1980).

In the following chapters there is a review of the growth process of carbamazepine dihydrate which has tried to find an answer for why it is such a sensitive and rapid process in certain conditions.

Materials and Methods

Carbamazepine anhydrate was obtained from Farmos Group Ltd. The anhydrous crystals have been recrystallized from methanol or ethanol. Carbamazepine dihydrate crystals were prepared from the anhydrous form allowing fine anhydrous powder or an anhydrous crystal to be in water or in relative humidity of 100%. Another possibility is to crystallize dihydrate crystals from the solution of water and ethanol.

Using the optical microscope (Reichert MeF), the change in water or in relative humidity of 100% of anhydrate to dihydrate has been followed.

Using the scanning electron microscope (JSM-U3), the authors have examined the shape and details of the outer structure of dihydrate crystals. On the surface of the specimens it has been vaporized to a thin gold film. The inner structure of the specimens do not correspond with the dihydrate structure after the handling in vacuum. However, the outer structure remains the same (which has been observed qualitatively by the optical microscope).

Powder X-ray diffraction has been used to characterize the different forms of carbamazepine. The diffractograms have been made by CuKα-radiation (16 mA, 40 kV).

Results and Discussion

(1) Growth in the solution

The structure of carbamazepine anhydrate — recrystallized from methanol or ethanol — can be seen in Fig. 1A. If the anhydrous form of carbamazepine is mixed in water, tiny needle-like crystals soon appear which then begin to grow in a few minutes (Fig. 2). These needle-like crystals are carbamazepine dihydrate, and their X-ray spectrum shows strong orientation (Fig. 1B). In the earliest stage of growth, which can be seen with the optical microscope, they are about 1 μm thick, flexible fibers, which then thicken and straighten out, being now 10 μm or less by diameter (Fig. 3). These long whisker crystals (see Appendix) fasten together lengthways, and this is the main reason for thickening and stiffening. The fastening happens along the long sides, and it happens at every stage of the growth. SEM-photographs of the whisker crystals of various sizes show that from the ends of the crystals protrude ends of still thinner crystals (Fig. 4).

The cross-section of a single needle or platelet of different sizes is rectangular (Fig. 5). The needles and the platelets have inside cavities, which can be a result from crystals growing together.

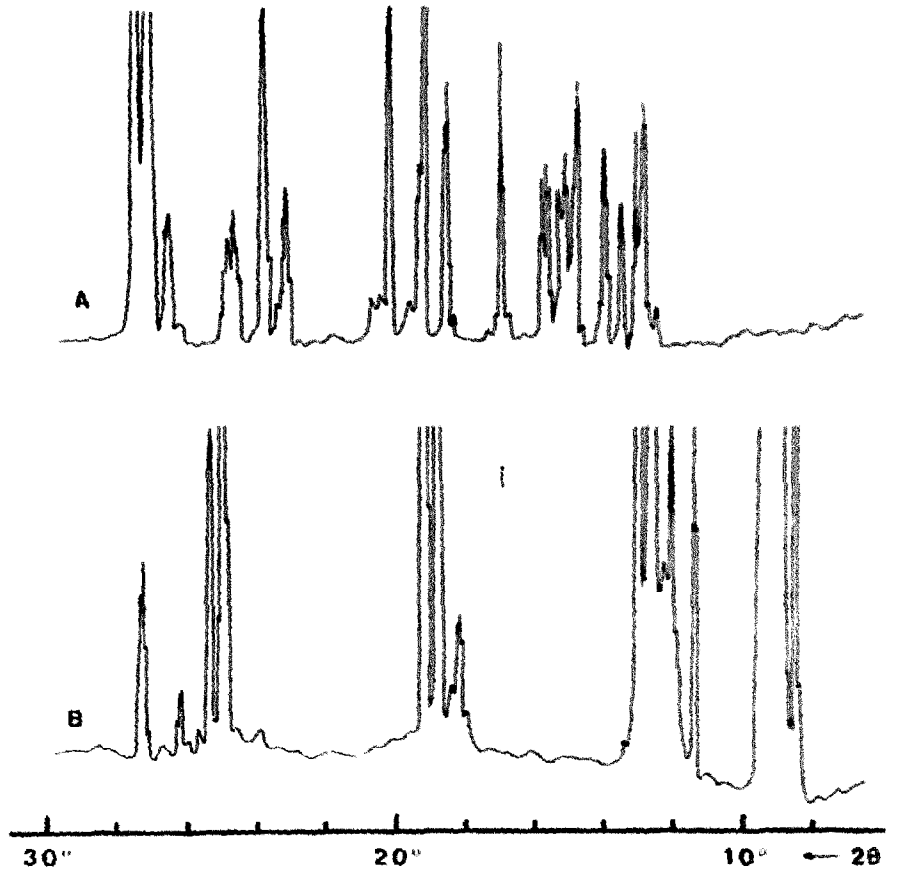

Fig. 1. A: X-ray diffractogram of a freshly crystallized anhydrous form of carbamazepine. B: X-ray diffractogram of dihydrate form of carbamazepine. The strong reflections in spectrum refer to preferred orientation of crystals.

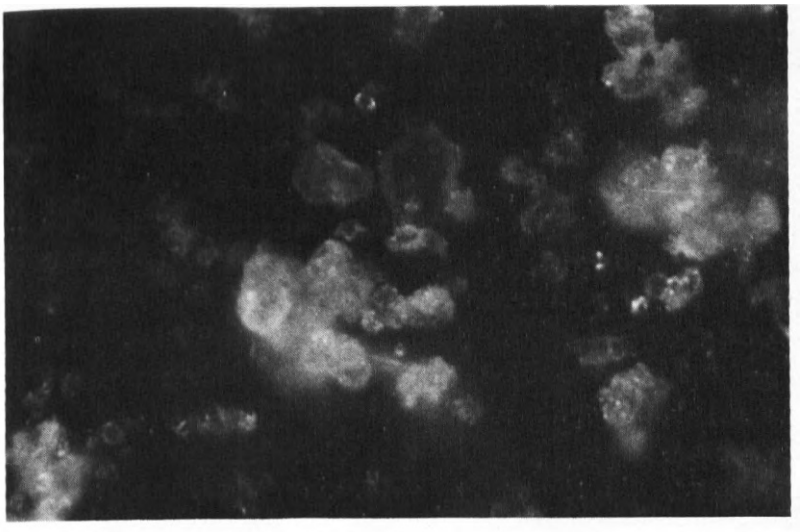

Fig. 2. Anhydrous form of carbamazepine. (1 mm ≈ 3 μm).

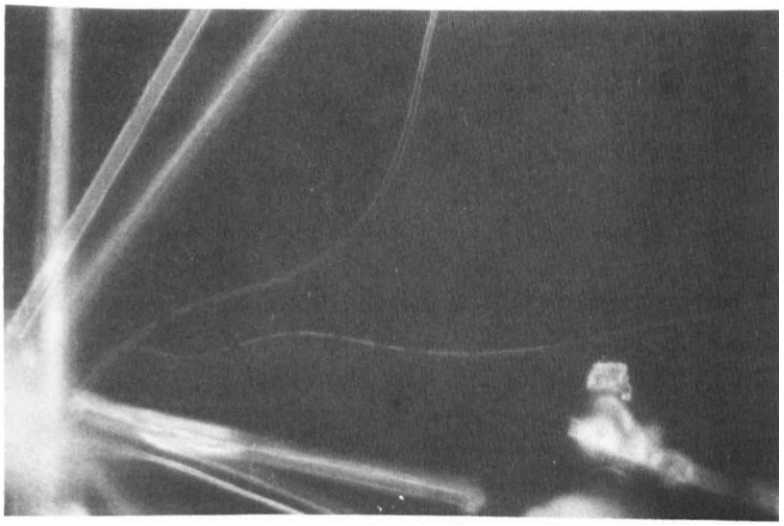

Fig. 3. Carbamazepine dihydrate whiskers in different stages of growth. Observe the thin flexible whiskers. (1 mm ≈ 2 μm.)

Anhydrous carbamazepine dissolves a little in water (unpublished results). The concentration of the solution is, however, sufficient to maintain the one-dimensional growth of the dihydrate whiskers. The insoluble anhydrous particles act as the nucleation centers of the whiskers.

(2) The changes in the mother crystal

If one larger anhydrous crystal ($\phi = 2 \ldots 4$ mm) is put in water, soon there can be observed both separate as well as whiskers fastened to the mother crystal. Often

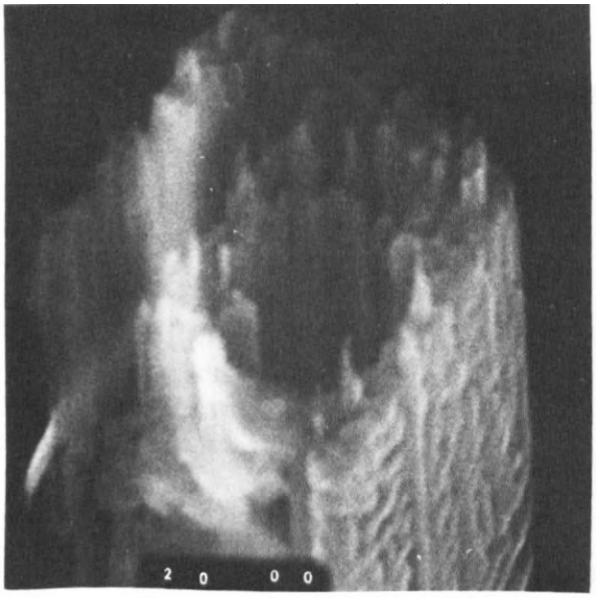

Fig. 4. The thin whiskers joined to constitute larger rigid crystals. (1 mm ≈ 0.3 μm.)

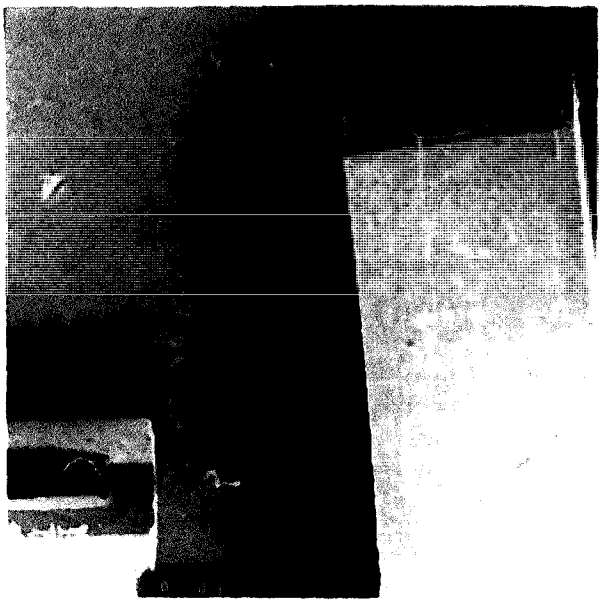

Fig. 5. The end of two platelet crystals. The cross-section of the crystals are rectangular and they have inside a cavity. (1 mm ≈ 16 μm.)

there are clusters of whiskers on the surface of the anhydrous mother crystal. That is, the whiskers grow from one point in many different directions (Fig. 6). They grow either on the plane of the surface or at a small angle with respect to the plane, which depends on the crystallography of the mother crystal. If a whisker grows out from the surface but it is fastened to it, there can be observed a thickened base at the fastening point, or the fastening point is in a hollow (Fig. 7A and B). The whisker growing along the surface seems to erode a path around itself (Fig. 7C).

Fig. 6. Cluster of whiskers on the surface of anhydrous crystal. (1 mm ≈ 15 μm.)

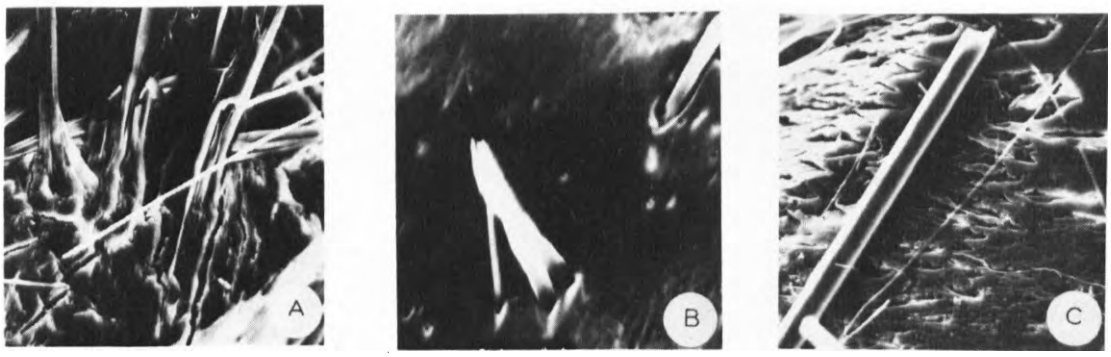

Fig. 7. A: the whisker fastened to the surface with a thickened base. (1 mm ≈ 7 μm.) B: whiskers growing out from the hollows on the surface. (1 mm ≈ 0.7 μm.) C: the whiskers growing along the surface of mother crystal. (1 mm ≈ 7 μm.)

In the case of Fig. 7A, it is possible that molecules drift from the base of a whisker by diffusion to the top, where the growing point exists. The fastened whiskers may have a different growth mechanism than those whiskers growing in the solution. But it does not necessarily have to be so, because also in this case the solution surrounds the mother crystal. On the surface of the mother crystal there may exist proper nucleation sites, e.g. impurities or structural defects, as protruding screw dislocations such as the hollows in Fig. 7B. This could refer to the whisker growth by the screw dislocation mechanism. The eroded area around the whisker in Fig. 7C is, at least partly, used up for the formation of the whisker. In the solution,

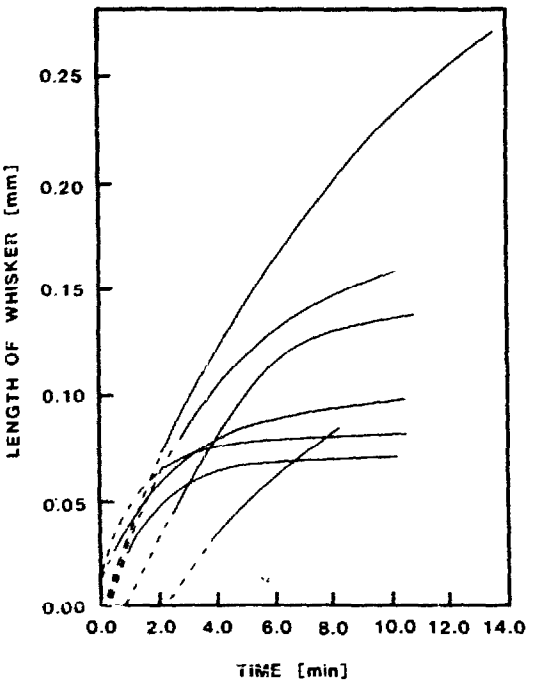

Fig. 8. The whisker growth as a function of time at room temperature. The observations were carried out by optical microscope.

growing whiskers as well as ones fastened to the mother crystal are similar in form, that is, their cross-section is rectangular.

(3) About the growth mechanism and the growth rate

The whisker growth by screw dislocation is the most common and also in the case of carbamazepine dihydrate the most probable growth mechanism. Fig. 7A could point to the diffusion mechanism, as it was found above. But it must be noted, that Fig. 7A and 7B are of different situations, that is, the whisker in Fig. 7A represents the growth stage, which has proceeded for much longer than the whiskers in Fig. 7B. It may be possible that also the structural anisotropy (see Appendix) has a meaning in the growth of carbamazepine dihydrate whiskers.

In Fig. 8 there is given the length of some whiskers in water as a function of the growth time. The slopes of the initial curves give the estimate of the growth rate as 1×10^{-6} m/s. There exists also a much more rapid growth, but such a growth rate is inconvenient to measure. After some minutes the growth becomes clearly slower. Furthermore, it can be seen from Fig. 8, that some whiskers grow longer than some others.

Appendix

Whiskers

A whisker is a needle-like single crystal, whose ratio length/diameter is at least 5, but is very often even 1000 or more. Diameters vary between 20 nm and 100 μm. The shape of the cross-section is not the same in different whiskers. Both the inner and outer structure of the whiskers is nearly perfect, because their small size and oriented shape cannot contain very many structural defects. That is why they are also mechanically stronger than the corresponding conventional crystals. Also the vapour pressure of the whiskers is abnormally low, thus these crystals are relatively stable. This is caused by the long sides of the whiskers. These sides are usually low-index planes and so their energy is very low.

The whiskers grow in one direction much faster than in the other. Their growth rate is quite fast, $10^{-6} \ldots 10^{-4}$ m/s, which postulates a particular growth mechanism. Many growth mechanism models have been presented with which one has tried to explain the different situations in practice. It has been observed that even the same substance has whiskers, which have grown by different ways. However, from different growth mechanisms the following stages can be separated.

(1) Nucleation.
(2) The proper whisker growth stage, during which the long thread or needle-like crystals grow up.
(3) The thin crystals thicken. (This stage can also be lacking.)
(4) The growth becomes slower or stops wholly.

Because the whisker growth is one-dimensional in nature, the concentration of the solution in growth conditions must stay under a certain critical level, so that no nucleation would happen on the long sides of a whisker. The most important growth mechanisms are the growth by the axial screw dislocations (growth from solution or

vapour) and so called VLS-mechanism (vapour–liquid–solid mechanism; growth from vapour). There are also many other mechanisms, such as those which are based on structural anisotropy, impurities or diffusion (Evans, 1972).

The structural anisotropy has obviously a noticeable meaning for organic whiskers. The most organic substances have a more or less anisotropic structure. So the different surfaces of a crystal have different surface energy depending on intermolecular bondings and on the packing of molecules on the surface. Substances, which have a structure with strong orientation, can have these surface energy differences large enough to induce whisker growth. There is no detailed theory about this, mainly because of the lack of exact surface energy data. This effect helps, however, the whisker growth of non-cubic materials. It also explains the whisker growth of many organic substances. This kind of substance is e.g. metaldehyde, phtallic anhydride and hydroquinone (Evans, 1972).

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