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Polymorphic behaviour of chloroquine diphosphate

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The crystalline structure of two different batches of chloroquine diphosphate was studied. Differential thermal analysis showed the existence of two polymorphic modifications in one of the batches, whilst spectral analysis did not reveal any differences. This discrepancy is attributed to the fact that the second modification is formed during the transition phase when analysed by differential thermal analysis. This recrystallization process is initiated by the presence of seed material. The ratio of transition heat of both modifications is dependent on particle size and heating rate during analysis.

During preformulation studies of chloroquine diphosphate, a crystallographic characterization of two batches of the drug, purchased from two different suppliers, was carried out. Chloroquine diphosphate is reported to exist in two different polymorphic forms (Merck Index 1976; Paulini 1953). To identify the polymorphic type of the batches under investigation, we used differential thermal analysis (DTA), X-ray diffraction, Raman spectroscopy and ir spectroscopy.

Because polymorphic behaviour was only supported by the results of DTA, further investigation was made to evaluate these findings.

Materials and methods

Chloroquine diphosphate was purchased from Rhône-Poulenc, France (CDP1) and Sigma, U.S.A. (CDP2).

X-ray diffraction patterns were obtained with a Philips PA 25, equipped with a copper anticathode (25 mA, 40 KV).

Raman spectroscopy was performed using a SPEX 1401 spectrometer, equipped with an Ar^+ laser (ν = 19 430 cm^{-1}). Ir spectra were recorded on a Beckman IR spectrometer type 7, using KBr discs. Fluorescence analysis was with a Philips fluorescence spectrometer equipped with an Au anticathode (40 mA, 60 KV.). Spectra of light elements were recorded using a pentaerythritol crystal (002) with gasflow detection. A LiF crystal (200) with a scintillation counter was used for the determination of heavy elements.

DTA was carried out with a Mettler TA 2000 analyser. Samples of 7 mg were heated in open aluminium crucibles. The sensitivity range was 200 μV.

The powders were sized on test sieves (Haver and Boecker) with an air-jet sifter (Alpine).

Results and discussion

DTA of CDP1 shows two endothermic peaks respectively at 196 °C and 216 °C while the DTA trace of CDP2 reveals only one endotherm at 196 °C (Fig. 1). These results indicate the existence of a mixture of two polymorphic modifications in CDP1.

To confirm the difference in crystalline structure between both products, X-ray powder diffraction was carried out. The resulting values of d, 2θ and I/I_{max} are reported in Table 1. Neither pattern could be differentiated from the other. An attempt was made to gain additional information by vibrational spectroscopy. Analysis of the ir absorption spectra did not reveal any complementary data from overlapping of the broad phosphate bands. The Raman spectra specifications are shown in Table 2. Again no difference between CDP1 and CDP2 could be detected.

To elucidate the observed discrepancy between the thermal and spectral analyses, further DTA-data were obtained. Fluorescence analysis was performed on both products to exclude erroneous conclusions due to sample impurity. No other elements besides phosphorus and chlorine could be detected.

Because electron scanning microscopy revealed a difference in crystal habit only between the bigger

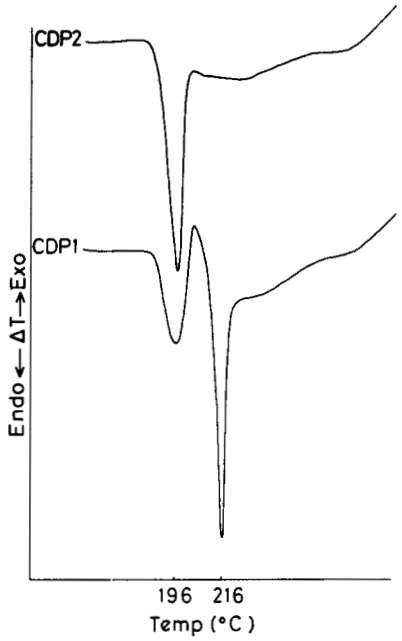

FIG. 1. Differential thermograms of CDP1 and CDP2. Heating rate: 5 °C min^{-1}.

* Correspondence.

Table 1. X-Ray diffraction pattern of chloroquine diphosphate.

2θ	d	I/I_{max}	2θ	d	I/I_{max}
7·8	11·10	21	28·2	3·14	11
9·4	9·40	24	29·5	3·00	17
11·2	8·10	18	31·8	2·80	13
11·8	7·48	30	32·6	2·73	12
13·4	6·62	8	33·8	2·64	7
14·0	6·30	12	34·6	2·58	7
16·0	5·50	8	33·6	2·51	8
16·8	5·25	39	36	2·48	9
18·6	4·78	26	37·2	2·41	8
19·4	4·55	96	38·4	2·33	9
21·1	4·20	100	39·8	2·25	7
23·0	3·87	33	40·8	2·21	5
23·5	3·75	12	41·8	2·15	9
24·5	3·59	68	42·8	2·10	8
25·2	3·51	14	44·8	2·01	7
26	3·41	22	47·2	1·92	9
27	3·28	96			

particles of both powders, we presumed CDP1 to be a mixture of crystals originating from two different crystallization processes. Therefore we wondered if there was any connection between particle size and polymorphic behaviour so the following sieve fractions of CDP1 were prepared: 32–63, 63–100, 100–125, 125–180 and 180–250 μm. The DTA of these fractions showed a clear decrease of the transition heat quantity (ΔQ) of the second modification with increasing particle size, while no change was noticed in the ΔQ of the first modification. When the 150–250 μm fraction was crumbled with pestle and mortar and sieved again in fractions as described above, an identical relation was obtained. These results indicate that the influence of particle size on the ΔQ of both endotherms cannot be caused by a difference in crystalline structure between the fractions.

Again X-ray patterns were identical in all cases.

With a heating microscope, it was possible to study visually the melting behaviour of both powders. For

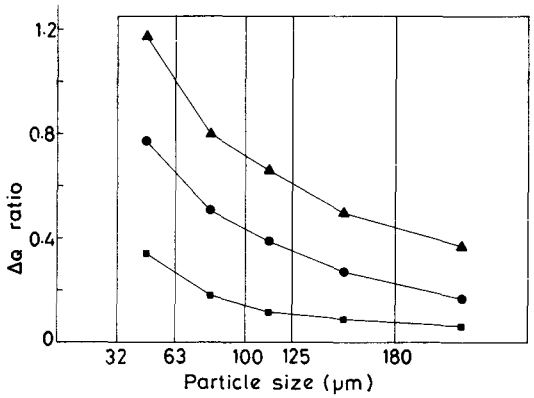

FIG. 2. The effect of particle size and heating rate on the ratio of transition heat of the second modification towards the first during DTA of CDP1. Heating rate °C min^{-1}: ▲ = 2.5; ● = 5; ■ = 10.

Table 2. Raman spectroscopy of chloroquine diphosphate.

ν (cm^{-1})	ν (cm^{-1})
600 w	1460 w
770 mw	1550 s
900 w	1600 w
1070 w	1650 w
1100 ms	2875 w
1170 w	2925 w
1200 w	2975 w
1250 w	3050 w
1380, 1410 dblt	

w = weak; mw = medium weak; ms = medium strong; s = strong; dblt = doublet

CDP2 this process was completed at 200 °C, above which no further changes were observed. But for CDP1 between 200–210 °C the formation of small regular crystals occurred and these melted at 216 °C, which corresponds with the second peak in its thermogram.

It is postulated that, during the first transition phase of CDP1, the second modification is formed by partial recrystallization, characterized by the exothermic peak occurring between both endotherms and initiated by the presence of seed material. Indeed, when equal amounts of CDP1 and CDP2 were mixed and analysed by DTA, no decrease of the ΔQ of the second modification was noticed. Moreover, removal of potential seed material by recrystallization of CDP1 from water–methanol, led to the disappearance of the second endothermic peak.

If it is assumed that the second modification results from a conversion of the first modification during the melting process, the transition kinetics should be dependent not only on the particle size as demonstrated, but also on the available transition time between both endotherms. In fact, increasing the heating rate had no effect on the ΔQ of the first modification whilst a distinct decrease of ΔQ of the second modification was observed.

The combined effect of both parameters is visualized in Fig. 2. As expected, the influence on the heating rate increases with smaller particles, whilst the effect of particle size is the most pronounced at the lowest heating rate. The enthalpy change of the first modification is 14·9 cal g^{-1} (63 J g^{-1}). Because the actual amount of the second form depends upon how much has crystallized from the first melting process, the enthalpy change could not be calculated.

As the observed polymorphic behaviour is only established during the melting process, it is obvious that this cannot be detected by spectral analysis at ambient temperature.

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