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Polymorphism of chloroquine diphosphate

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Summary

Chloroquine diphosphate was investigated by differential scanning calorimetry, thermogravimetric analysis, infrared spectroscopy, X-ray powder diffraction and by scanning electron microscopy for the indication of differences between anhydrous and hydrous polymorphs. The experiments clearly showed that the transition of anhydrous chloroquine diphosphate into hydrated compounds is possible by storing the drug at high relative humidity. Compression of the raw material did result in the formation of a new polymorph. This emphasizes the necessity for standardization of the manufacturing process of chloroquine diphosphate as well as a closer characterization of the solid drug as a part of the quality control.

Introduction

The existence of different crystalline modifications and amorphous states of a single compound is called polymorphism (Doherty and York, 1988). The polymorphs will show a difference in thermodynamic parameters (i.e., solubility, melting point, density, crystal shape, optical properties and vapour pressure). The various polymorphic forms of a compound therefore behave as distinct chemical entities. The consequence is that the physicochemical properties and bioavailability of a solid compound in a dosage form is strongly dependant upon the crystalline modification(s) present (Haleblian and McCrone, 1969; Haleblian, 1975; York, 1983; Thoma and Serno, 1984; Lindenbaum et al., 1985; Stoltz et al., 1989; Wadsten and Lindberg, 1989; Miyamae et al., 1990). Two polymorphs can also show different stability towards temperature and relative humidity (Haleblian, 1975). The crystal structure can further affect tablet density and porosity, aggregation and mechanism of disintegration, as well as the plastic and elastic properties of a solid dosage form. Bioavailability will therefore directly or indirectly be influenced by the crystal form used (Haleblian and McCrone, 1969; Haleblian, 1975; Stoltz et al., 1989). It has been suggested that almost every organic compound exist in different polymorphic states (Haliblian and McCrone, 1969; Kanenіwa et al., 1988). Hydrates and solvates also give rise to the same problems as polymorphs because of their different properties in the solid

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state (pseudopolymorhism). Investigating the polymorphic behaviour of drugs and excipients is an important part of the preformulation work because the choice of crystalline modifications might influence the stability and effectiveness of the formulation (Nyquist and Wadsten, 1986).

Various analytical methods can be used in the study of polymorphism. Infrared spectroscopy and X-ray diffraction have provided the tools for the identification of crystal structure. However, thermal analysis techniques are increasingly used for detection, description and analysis of polymorphic forms and mixtures. Thermogravimetric analysis (TG), differential thermal analysis (DTA) or differential scanning calorimetry (DSC) are now used on a routine basis in the preformulation work or in the quality control of drug formulations.

The drug examined in this study, chloroquine diphosphate, is used as an antimalarial. The compound is formulated as injection solutions, syrups or as tablets. The solid dosage form is by far the most frequently used. Previous studies indicate that chloroquine diphosphate excists in two crystal forms with melting points 188 and 207°C, respectively (Hong, 1976; Aerde et al., 1984; Furuseth et al., 1990). A close control of the solid drug is therefore required to prevent batch to batch variations causing alterations in dissolution rate and shelf-life of the tablets. The aim of this study was characterize the various crystal forms of chloroquine diphosphate and to evaluate the parameters responsible for the transformation of one modification into another.

Materials and Methods

Materials

Chloroquine (7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline diphosphate; CQ) was supplied by Rhonè-Poulenc. Indium metal (99.9% purity, melting point 156.6°C, enthalpy of fusion 28.45 J/g) and bismuth metal (99.9% purity, melting point 273.0°C) were used for the calibration of the differential scanning calorimeter.

Methods

Preparation of samples

Influence of temperature: Samples were stored in ampoules under nitrogen at 185°C for 7 days.

Influence of humidity: Samples were stored at 80% relative humidity (RH) at 20°C for 14 days.

Influence of pressure: Samples were compressed to 1 mm thick tablets under a pressure of 10 tonnes/cm^2 for 5 min.

Influence of grinding: Samples were ground in an agate mortar.

Thermal analysis (DCS)

DSC thermograms were obtained using a Perkin Elmer DSC 7 Differential Scanning Calorimeter. Samples (6–7 mg) under a flow of nitrogen were scanned from 100 to 250°C at a rate of 10°C/min. The samples were scanned at least in duplicate. The thermograms were normalized before calculation of melting point (defined as T_{onset}) and enthalpy of fusion (J/g).

Thermogravimetric analysis (TGA)

Thermogravimetric analysis were carried out using a Perkin Elmer TGA7 thermogravimetric system. Samples (10–15 mg) under a flow of nitrogen were heated from 30 to 300°C at 20°C/min.

Infrared (IR) spectroscopy

The IR spectra of the samples in a potassium bromide disc were recorded using a Bruker IFS 88 Infrared Spectrophotometer.

X-ray powder diffraction (XPD)

X-ray powder diffraction data were recorded using a Guinier camera, 25 mA, 35 kV with CrK-radiation.

Scanning electron microscopy (SEM)

The morphology of the crystal forms was investigated by the use of a Joel JSM-35C Scanning Electron Microscope. The samples were coated with a layer of gold in palladium (60:40) prior to being photographed by use of a sputter-coater for 4 min.

Results and Discussion

The DSC recording of an untreated sample of chloroquine diphosphate from Rhonè-Poulenc is shown in Fig. 1. Two endothermic peaks could be detected with onset temperatures at 188.0°C (106.9 J/g) and 216.4°C (48.4 J/g), respectively. This indicates that the sample consists of two crystal modifications of chloroquine phosphate. Based on previous studies (Furuseth et al., 1990) the two peaks were postulated to represent a hydrate and an anhydrous form of chloroquine. A sample of CQ was then stored for 7 days at 185°C under a nitrogen atmosphere. The thermogram is shown in Fig. 2. Only one endothermic peak could now be observed, with onset temperature at 217.9°C (120.8 J/g). This peak corresponds to the highest melting modification in the original thermogram, indicating that the sample is completely transformed to the anhydrous form after heating. This was further confirmed by thermogravimetric analysis. The original sample showed a weight reduction of 1.2% when heated from 30 to 300°C. The ratio of CQ/water was calculated to be 3:1. The postulated anhydrous form of CQ did not show any weight reduction when analysed by thermogravimetry. Grinding the crystals in a mortar made dehydration of CQ more favourable, possibly by decreasing the particle size and increasing the specific surface of the crystals (Fig. 3). The melting point of the hydrate was lowered as a consequence of grinding (T_{onset} 171.7°C, 64.2 J/g). An exothermic peak was detected in the temperature interval from 188 to 210°C. This peak is possibly due to the recrystallization of the original hydrate leading to the anhydrous form.

Both the original sample and the anhydrous sample (formed after heating of CQ) were stored at 81% RH and 20°C for 14 days. The resulting thermograms demonstrate that a change has taken place in both samples (Figs 4 and 5). Both the original hydrate and the anhydrous form of CQ were transformed into a modification with lower melting point (T_{onset} 183.9, 108.2 J/g). This modification showed a weight reduction of 1.6% as determined by thermogravimetric analysis, and a

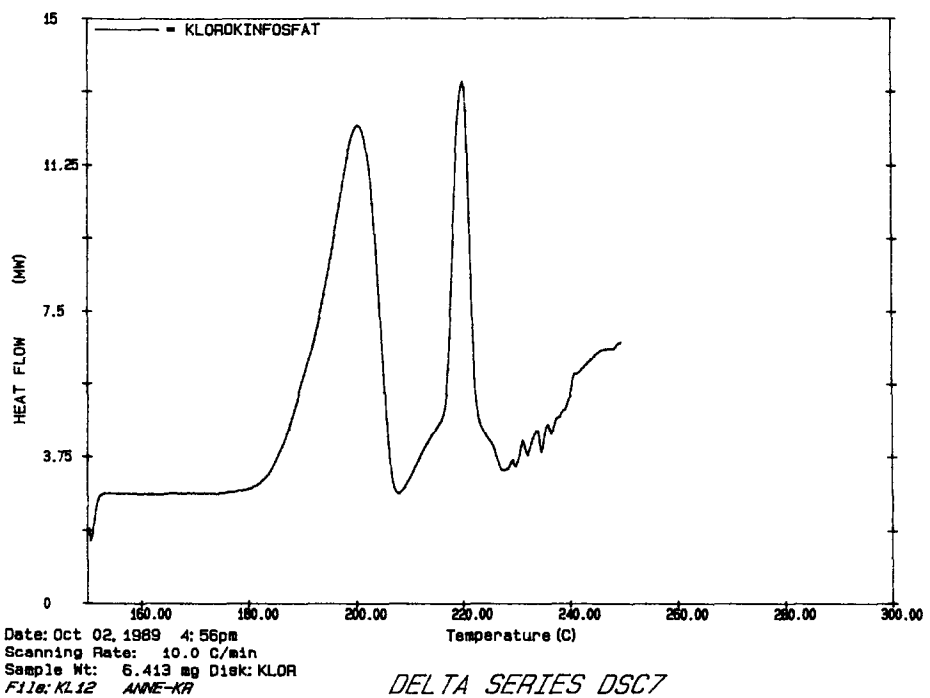

Fig. 1. DSC thermogram of chloroquine diphosphate from Rhonè-Poulenc.

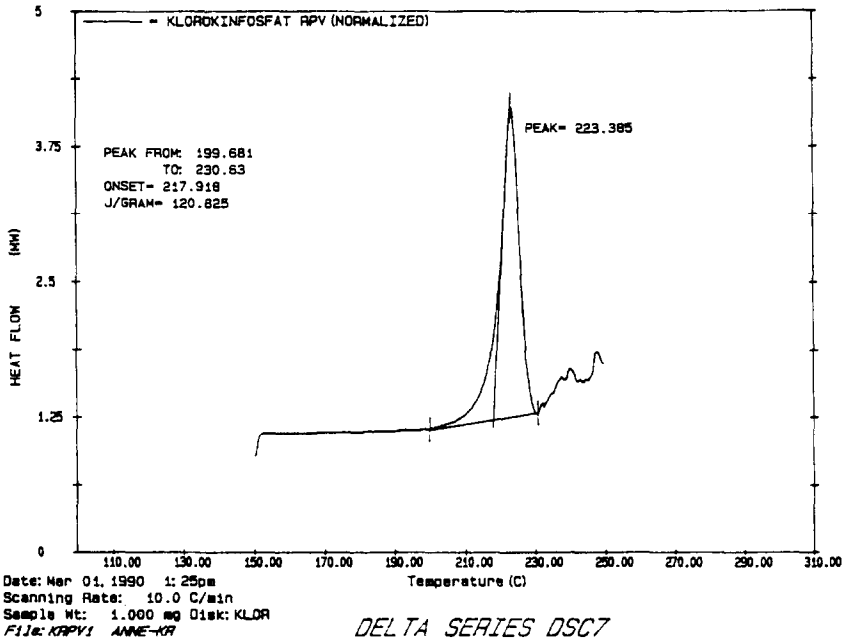

Fig. 2. DSC thermogram of chloroquine diphosphate stored at 185°C for 7 days.

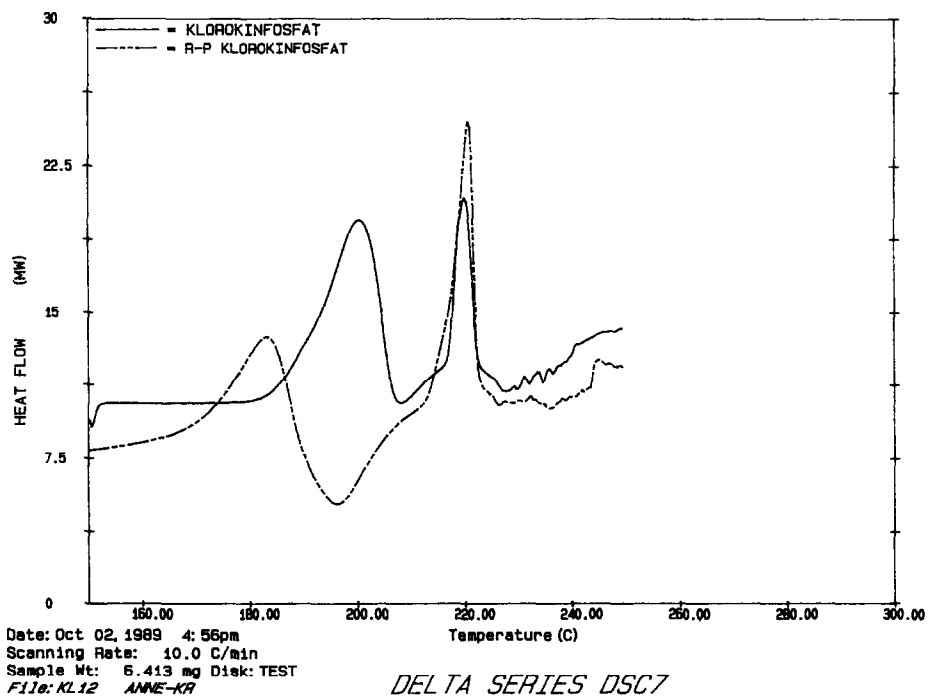

Fig. 3. DSC thermogram of chloroquine diphosphate ground in a mortar. (———) Sample before grinding; (------) sample after grinding.

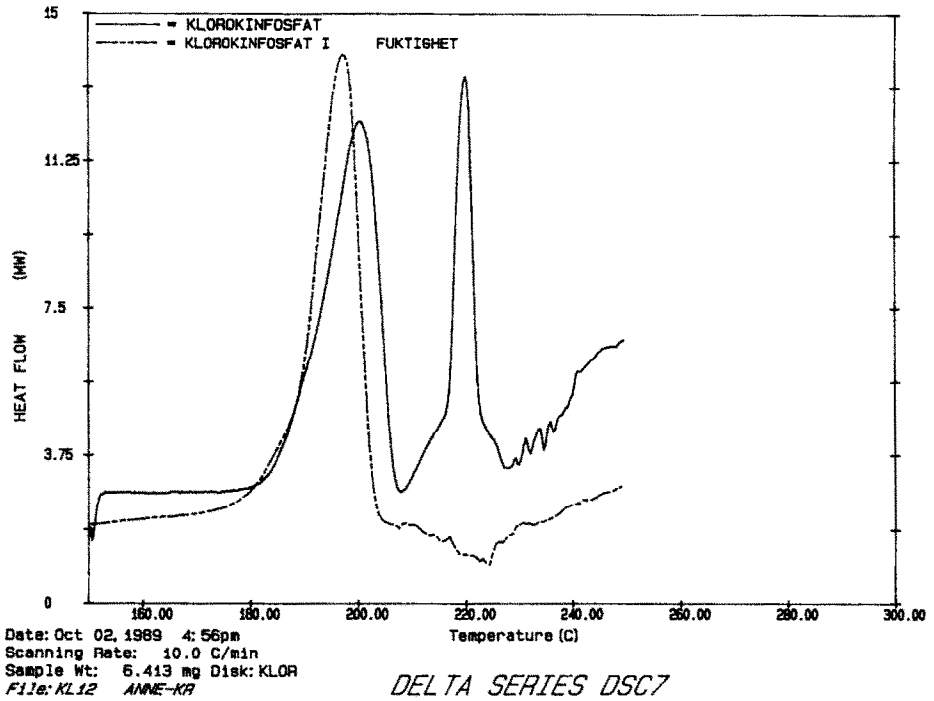

Fig. 4. DSC thermogram of chloroquine diphosphate stored at 81% RH and 20°C for 14 days. (———) Reference; (------) sample after exposure to 81% RH.

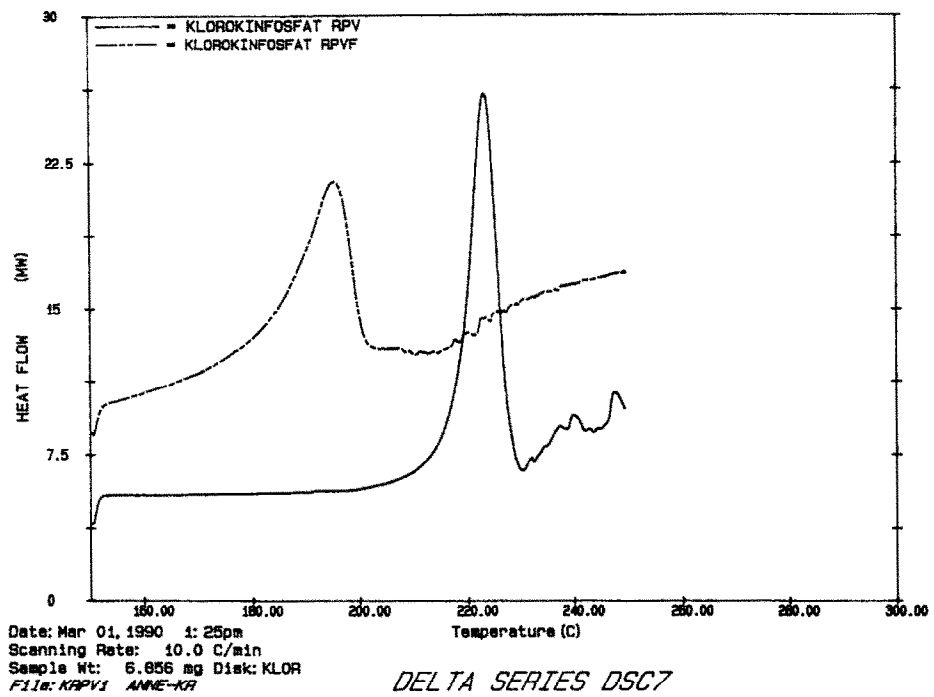

Fig. 5. DSC thermogram of the anhydrous form of chloroquine diphosphate stored at 81% RH and 20°C for 14 days. (———) Reference; (------) sample after exposure to 81% RH.

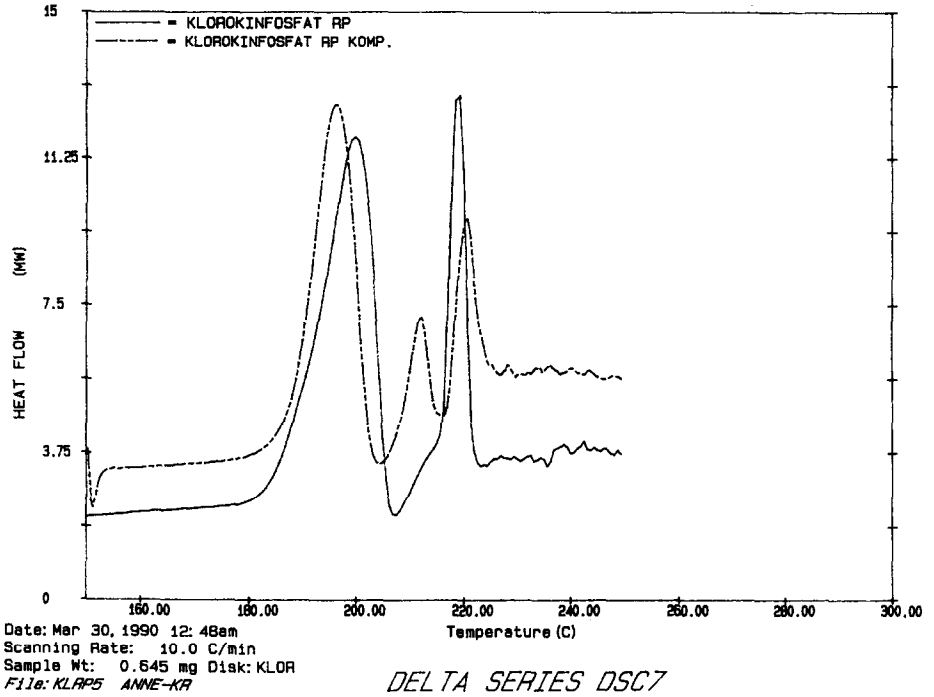

Fig. 6. DSC thermogram of chloroquine diphosphate compressed to a 1 mm thick tablet under a pressure of 10 tonnes/cm^2 for 5 min. (———) Reference; (------) sample after compression.

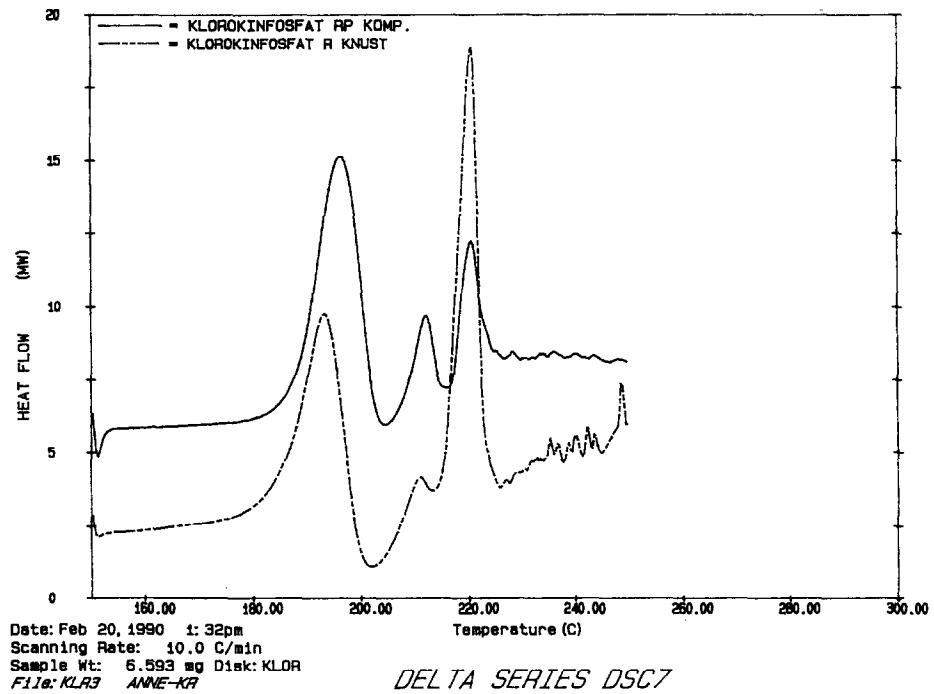

Fig. 7. DSC thermogram of chloroquine diphosphate compressed to a 1 mm thick tablet followed by grinding in a mortar. (———) Compressed sample; (------) compressed sample after grinding.

CQ/water ratio of 2:1 could be calculated. It was not possible to obtain the anhydrous form of CQ by reheating the 2:1 hydrate. The hydrate decomposed at approx. 200°C. The IR spectra and XPD data of the two hydrates were identical. However, a clear difference in crystal form between the samples was observed by use of scanning electron microscopy. The original CQ sample had crystals with clean, even surfaces. The low-melting-point hydrate showed crystals with uneven, porous surfaces which looked clearly different from the starting material.

The original CQ sample was compressed to a 1 mm thick tablet on applying a pressure of 10 tonnes/cm^2 for 5 min. The resulting DSC record showed the formation of a new crystal modification (T_{onset} 207.5°C, 11.2 J/g) (Fig. 6). Only trace amounts of this crystal modification could be detected when the compression was followed by crushing the tablet in a mortar (Fig. 7).

Conclusion

Chloroquine diphosphate can exist in at least four polymorphic forms. The two main polymorphs could be identified as a hydrate and as an anhydrous form of CQ. The anhydrous crystal form could be obtained by storing the hydrate at elevated temperatures. Dehydration was favoured by grinding of the raw material. A change in relative humidity led to the formation of a second hydrate. This pseudopolymorph was higher in water content than the original form and decomposed upon heating without previous dehydration. Compression of the raw material did result in the formation of yet another crystal modification. It is therefore obvious that the procedures used in the preparation of the raw material and in the handling of the samples will influence the number and ratio of polymorphic forms in a batch of chloroquine diphosphate.

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