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DIFFERENTIAL SCANNING CALORIMETRY OF CHLOROQUINE SULPHATE EXPOSED TO SUN, HEAT AND ULTRAVIOLET RADIATION

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Chloroquine sulphate, like the phosphate, is an antimalarial formulation widely used in the tropics. The stability of such formulations is therefore of interest in the combat against malaria. A DSC study has been made of the effects of exposure to the sun, heat and UV radiation on the stability of chloroquine sulphate, similarly as performed earlier for chloroquine phosphate. When freshly recrystallized from a water-acetone mixture, chloroquine sulphate exhibits two endothermic peaks, at 169.4° and 204.7°, for the expulsion of crystal water (one molecule) and for the melting process, respectively. The exposure of chloroquine sulphate to the sun, heat and UV radiation leads to splitting of the peak for melting.

We reported previously the decomposition of chloroquine phosphate during exposure to the sun on the roof top at the extreme Saharan temperatures obtaining in Sokoto during the dry season [1]. A similar study has now been undertaken on chloroquine sulphate, which, like chloroquine phosphate, is widely used in the tropics for the treatment of malaria.

Freshly recrystallized chloroquine phosphate is usually obtained as a mixture of two crystalline forms, giving melting peak temperatures of 196.5° and 210.3°, due to amine-imine tautomerism [2]. Our studies on freshly recrystallized chloroquine sulphate, on the other hand, revealed one simple peak for melting, indicating the existence of one form only (the amine). The exposure of chloroquine sulphate to the sun, heat in an oven at 100°, and UV light (λ = 254 nm) was observed to cause the splitting of the melting peak at 204.7° into two: one at 200° and the other at 211.6°. The exposure of chloroquine sulphate to the sun, heat and UV light apparently activates the amine proton in favour of formation of the imine crystalline form. The increase in the imine form as a function of the exposure time was investigated by differential scanning calorimetry (DSC).

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Experimental

Pure chloroquine sulphate was obtained from chloroquine tablets marketed by May and Baker, England, under the trade name "Nivaquine". Ten tablets of 250 mg each were finely powdered and the powder was added to 100 ml of distilled water. The mixture was heated on a water-bath under stirring for 30 minutes and the solution was slowly evaporated until the beginning of crystallization. On cooling, 1.8 g of white crystals was isolated. Further recrystallization from water—acetone gave pure chloroquine sulphate (mp. 205–208°).

DSC on the freshly recrystallized, sun and heat-exposed samples was carried out with a Mettler 3000 thermal analysis system. The working principle has been well described elsewhere [3], except for an improvement of the accuracy due to the use of a microprocessor for continuous thermal analytical data storage and automatic peak integration.

For the exposure of chloroquine sulphate, three equal portions of 400 mg each were finely ground; one portion was placed in a 50 ml beaker which was sealed with cellophane film and placed in the sun on the roof top; the second portion was placed in an oven set at 100°; and the third portion was placed on a watch-glass and irradiated with UV light ($\lambda = 254$ nm). Once every week, the samples were finely ground to expose a fresh surface before the next exposure, after 5–8 mg portions had been taken for DSC.

Results and discussion

The DSC curves of the freshly recrystallized sample are shown in Fig. 1. There are two peaks, one at 169.4° for the expulsion of crystal water and another at 204.7° for the melting process. The water content of 1 molecule per formula unit was confirmed by thermogravimetry (Fig. 2). The absence of a second peak for the melting process (as observed in the case of chloroquine phosphate [1]) indicates that freshly recrystallized chloroquine sulphate exists in one crystalline form. The existence of two crystalline forms of chloroquine phosphate was explained by the amine-imine tautomerism [2]. On exposure of chloroquine sulphate to the sun, the original peak for the melting process at 204.7° is split into two, one at 200° and another at 211.6°, as shown in Figs 3a and b.

The enthalpy ΔH of melting of the freshly recrystallized chloroquine sulphate was computed from peak integration to be 69.1 J/g or 30.1 kJ/mol (Fig. 4). For sun-exposed samples, the enthalpy of melting is the sum $\Delta H_1 + \Delta H_2$ for the two peaks. The maximum exposure time of 34 days gave a curve as in Fig. 5, for which $\Delta H_1 = 33.72$ J/g and $\Delta H_2 = 32.02$ J/g, yielding an overall melting enthalpy

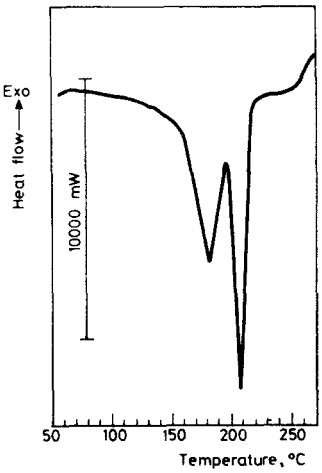

Fig. 1 DSC curve of freshly prepared chloroquine sulphate

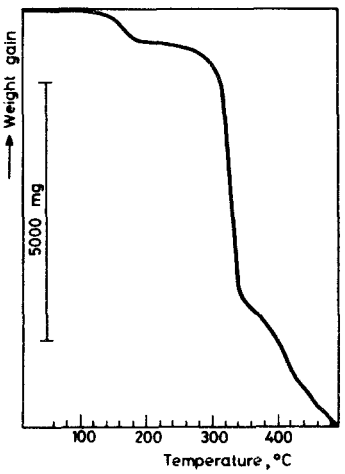

Fig. 2 TG curve of freshly prepared chloroquine sulphate

$\Delta H = 65.74$ J/g. It is interesting to note that the peak temperatures remain unchanged during the period of exposure (34 days), that is 200° and 211.6° for the first and second peaks of the melting process. On the other hand, the exposure of chloroquine phosphate to the sun for 30 days shifts the first and predominant peak for the melting process from 196.5° (freshly recrystallized) to 193.4°. The shifting of the melting peak temperature for sun-exposed chloroquine phosphate and sulphate with progressing exposure time is shown in Table 1. These data show clearly that

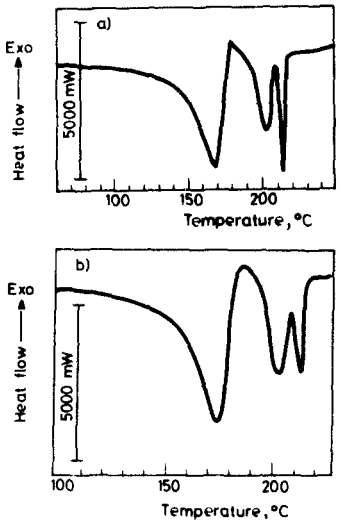

Fig. 3 DSC curve of chloroquine sulphate. (a) exposed to the sun for 12 days; (b) exposed to the sun for 20 days

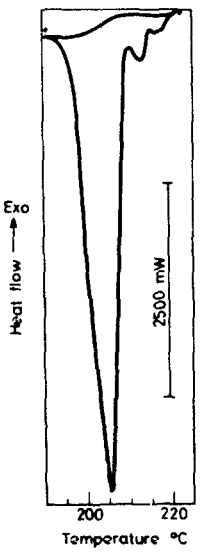

Fig. 4 DSC peak integration of melting peak for freshly prepared sample (ΔH = 69.1 J/g)

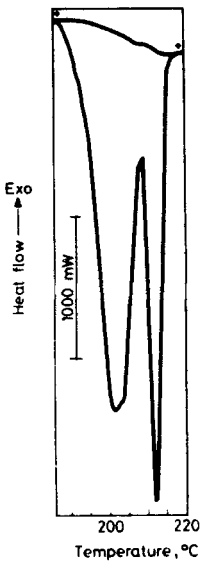

Fig. 5 DSC peak integration for the melting peaks after exposure of chloroquine sulphate to the sun for 34 days (ΔH = 65.74 J/g)

Table 1 Variation of peak temperatures T_1 and T_2^* for sun-exposed chloroquine phosphate and sulphate with progressing exposure time

		Exposure time, days					
		12	15	20	23	30	34
Phosphate	T_1, °C	—	195.0	—	194.4	193,0	—
Sulphate	T_1, °C	199.9	—	200.0	—	—	200.2
	T_2, °C	211.6	—	211.5	—	—	211.6

*T_2 for the phosphate becomes increasingly difficult to determine accurately, because of the low concentration of the imine form.

chloroquine sulphate is less sensitive than chloroquine phosphate to sun exposure. The lowering of the peak temperature for chloroquine phosphate is caused by an increasing quantity of decomposition products with progressing exposure of the sample. Further support for this interpretation of the observations is provided by a comparison of ΔH, the enthalpies of melting. If the energy barrier between the two crystalline forms is assumed to be small, the sum $\Delta H = \Delta H_1 + \Delta H_2$ can be considered to be proportional to the sum of the concentrations of the two crystalline forms in the sun-exposed samples. For chloroquine phosphate, ΔH

decreased from 60.1 to 40.3 J/g during 30 days of exposure, corresponding to 33% decomposition. However, in the present investigation, the corresponding melting enthalpy of chloroquine sulphate decreased from 69.1 to 65.7 J/g during 34 days of exposure to the sun. This corresponds to 4.9% decomposition.

The exposure of chloroquine sulphate to heat (100° in the oven) also splits the endothermic peak for the melting process. In this case, however, a longer exposure time is required to develop the second peak (Fig. 6). Again, the temperature

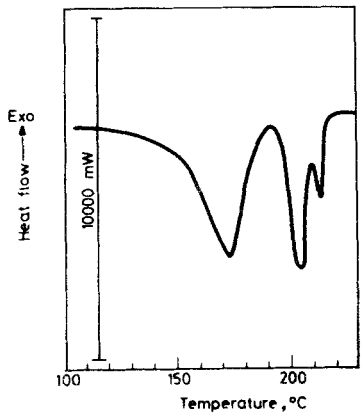

Fig. 6 DSC curve of heat-exposed chloroquine sulphate (33 days at 100°), showing the development of the second peak

difference between the peaks T_1 = 202.7° (average) and T_2 = 203.1° is smaller as compared to the situation for sun-exposed chloroquine sulphate. Heating at 100° does not decompose chloroquine sulphate as much as the effect of sun exposure.

The exposure of chloroquine sulphate to UV light (λ = 254 nm) also caused splitting of the melting peak. However, the development of the second peak was slower as compared to the effect of sun exposure. The DSC curve of chloroquine sulphate after exposure to UV light for 21 days is shown in Fig. 7.

Conclusion

The exposure of freshly prepared chloroquine sulphate to the sun, heat or UV light splits the peak for the melting process. The effect is very pronounced for sun-exposed samples. In addition, our results revealed that pure chloroquine sulphate exists in one crystalline form, in contrast to pure chloroquine phosphate, for which amine and imine forms are known [2]. However, the exposure of chloroquine sulphate to the sun, heat or UV light splits the melting peak into two, suggesting the

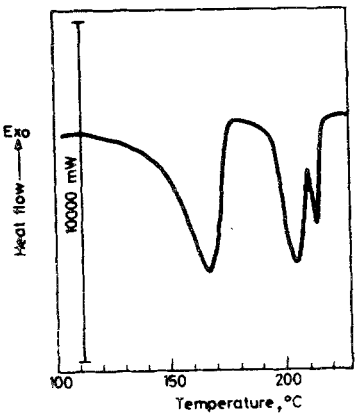

Fig. 7 DSC curve of chloroquine sulphate after exposure to UV radiation (254 nm) for 21 days

existence of two tautomers, as is the case with chloroquine phosphate. Measurement of the enthalpy of melting for sun, heat and UV light-exposed chloroquine sulphate shows this formulation to be more stable than chloroquine phosphate. Chloroquine sulphate would therefore have a longer shelf-life than chloroquine phosphate under poor storage conditions.

References

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Zusammenfassung — Chloroquine-Sulfat ist ebenso wie das entsprechende Phosphatderivat ein in den Tropen weitverbreitet angewandtes Antimalaria-Präparat. Die Stabilität dieses Präparates hat damit Bedeutung für die Malariabekämpfung. Die vorliegende Arbeit ist eine Erweiterung einer Untersuchung über den Effekt der Einwirkung von Sonne, Hitze und UV-Strahlen auf die Stabilität von Chloroquine-Phosphat auf Chloroquine-Sulfat. Aus Wasser-Aceton-Mischungen frisch kristallisiertes Chloroquine-Sulfat zeigt zwei endotherme Peaks bei 169,4 und 204,7 °C, die durch Abgabe von Kristallwasser (ein Molekül) bzw. durch den Schmelzvorgang bedingt sind. Wird Chloroquine-Sulfat der Sonne, Wärme oder UV-Licht ausgesetzt, so wird der dem Schmelzvorgang zuzuscheibende Peak aufgespalten.

Резюме — Хлорокин сульфат, подобно фосфат-производному, является антималярийным препаратом, широко используемым в тропиках. Для успешной борьбы с малярией требуется знание устойчивости таких препаратов. В работе изучено влияние солнца, тепла и УФ облучения на устойчивость хлорокин сульфата. Хлорокин сульфат, свеже перекристаллизованный из водноацетоновой смеси, показал два эндотермических пика при 169,4 и 204,7°, вызванных, соответственно, выделением одной молекулы воды и процессом плавления. Действие на хлорокин сульфат солнечного света, тепла и УФ облучения вызывает расщепление пика плавления.