Journal of Thermal Analysis, Vol. 32 (1987) 1139–1143

DSC OF SUN-EXPOSED CHLOROQUINE PHOSPHATE

G. Mulokozi, I. Edafiogho, A. M. Mulokozi*
and *S. Diete-Spiff*

DEPARTMENT OF CHEMISTRY AND DEPARTMENT OF PHARMACOLOGY,
UNIVERSITY OF SOKOTO, NIGERIA

(Received October 2, 1986)

Pharmaceutical intended for use in the tropics are required to maintain their stability under the most severe storage conditions. Chloroquine phosphate, a common antimalarial formulation, was exposed to the sun of the roof top under the extreme heat of the Saharan climate during the hot and dry season (February to June) at an average day temperature of 43°. The heat of melting ΔH determined by differential scanning calorimetry decreased from 60.1 J/g to 33.2 J/g after exposure for 73 days, corresponding to 49% decomposition. Differential scanning calorimetry is shown by this work to be a rapid and reliable technique for the routine quality control of chloroquine phosphate powders and tablet formulations.

Since pharmaceuticals are often organic compounds with well-defined melting points, differnential scanning calorimetry can be used for their easy, rapid and reliable quality control.

This technique has been found to be quite appropriate for determination of the deterioration of chloroquine phosphate on exposure to the sun under the severe Saharan climatic conditions obtaining in Sokoto during the dry season (January to May). This study is particularly relevant, because antimalarial formulations including chloroquine phosphate (dominant on the market) are sold locally by traders who in the majority of cases are ignorant of the ideal storage requirements. It is therefore possible that millions of users in the tropics receive the antimalarials after they have been subjected to considerable exposure to the sun.

Pure chloroquine phosphate shows a main endothermic peak at 196.5°, followed by a small one at 210.3°. These peaks are associated with the melting of its two crystalline forms. The heats of melting derived from the integrated peak areas on a DSC scan were used to determine the content of chloroquine phosphate in the sun-exposed samples. The technique was also used to determine the content of chloroquine phosphate in pharmaceutical formulations.

* New address of author to whom correspondence should be referred: University of Dar-es-Salaam, Tanzania.

John Wiley & Sons, Limited, Chichester
Akadémiai Kiadó, Budapest

Experimental

Tablets of chloroquine phosphate were obtained from the University Health Clinic, as supplied by Avion Pharmaceutical, Hamburg, W. Germany. The average weight of the tablets, as derived from the weight of 100 tablets randomly picked from a sample batch, was 250 mg. Pure chloroquine phosphate, a white crystalline compound melting at 194–196°, was obtained by dissolving the tablets in distilled water, and filtering to remove the insoluble matter, followed by evaporation and two additional recrystallizations of the product from solutions in distilled water. The product was washed with a little acetone and then air-dried. The product was predominantly in the form melting at 193–196°. The product gave the analytical data 8.05% N (Kjeldahl estimation) and 18.26% PO_4 (gravimetric as $Mg_2P_2O_7$), based on the content of the aqueous extract after the base had been liberated with sodium hydroxide solution and extracted with ether. The theoretical values based on the molecular weight 515.39 for $C_{16}H_{26}ClN_3 \cdot 2H_3PO_4$ are 8.15% N and 18.43% PO_4.

Exposure experiments

A 250 mg sample was finely ground and placed in a 25 ml beaker, and the beaker was sealed with cellophane to avoid contamination by dust and other airborne particles. The beaker was placed on the roof top. The temperature in the immediate surroundings of the sample was monitored daily with a thermometer. The average day temperature was 44°. Once every week the sample was ground to expose a fresh surface, and 5–10 mg was taken for DSC studies. In a sample control experiment designed to explore the effect of heat, a 200 mg of chloroquine phosphate was continuously heated in the oven at 100°.

Differential scanning calorimetry

A Mettler 3000 thermoanalysis system consisting of a DSC cell, a thermobalance, a microprocessor and a printer/plotter was used. 5–10 mg of the sample, accurately weighed on the thermobalance, was sealed in an aluminium crucible; the lid was perforated with a pin in order to avoid pressure building up during heating. A heating rate of 10 deg/min was employed.

Results and discussion

The thermal curve of a freshly crystallized sample of chloroquine phosphate is shown in Fig. 1(a). From room temperature up to the temperature of melting, the curve does not show any other process. Accordingly, the air-dried sample is anhydrous. This was confirmed by thermogravimetric analysis. The peak temperatures were 196.5° and 210.3°. For the automatic integration and evaluation of the peak areas an appropriate program was utilized. Figures 2(a) and (b) show the peak integration, from which ΔH = 60.1 and 5.0 J/g were derived, respectively,

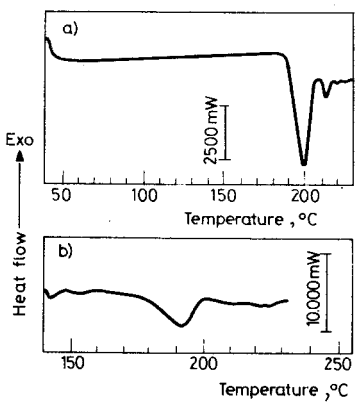

Fig. 1 (a) Thermal curves of (a) Freshly crystallized chloroquine phosphate (7.155 mg, heating rate 5 deg/min); (b) Sun exposed sample (73 days, 4.520 mg, heating rate 5 deg/min)

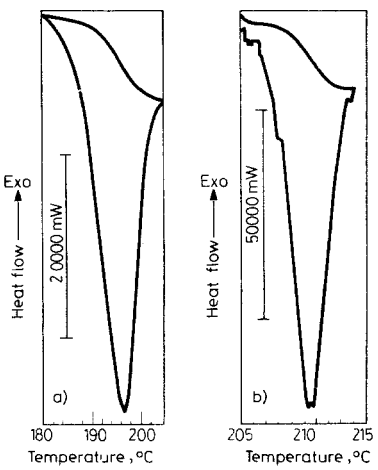

Fig. 2 The peak integration for freshly crystallized chloroquine phosphate. (a) First peak at 196.5 °C, ΔH = 60.1 J/g. (b) Second peak ΔH = 5.0 J/g

for the peaks at 196.5° and 210.3°. Exposure of the sample to the sun for 23 days reduces the size of the peaks appreciably. The first gives $\Delta H = 40.58$ J/g and the second $\Delta H = 3.4$ J/g. For quantitative interpretation of the data, the assumption is made that the two crystalline forms of chloroquine phosphate do not differ appreciably in their lattice energies, as otherwise only one form, the stable one, would be obtained. The error inherent in this assumption is low, because the second form is present in small proportion. Hence, the two enthalpies of melting can be added together to give the overall enthalpy of melting. The ratio of the two forms in the pure sample is $60.1 : 5.0 = 12 : 1$.

Exposure of the sample to the sun for 23 days reduced the chloroquine phosphate content from 100 to 67.5%. Exposure for 73 days reduced the content to 51% and the second peak was no longer visible in the curve (Fig. 1(b)), i.e. 49% of the chloroquine phosphate was decomposed.

It is interesting to investigate the effect of heat. The sample kept in the oven at 100° for 39 days in a control experiment had $\Delta H = 55.86$ and 4.65 J/g for the first and second peaks, respectively. This corresponds to a 92.9% content of chloroquine phosphate and a decomposition of only 7.1%. This is in sharp contrast to the result after exposure to the sun for 23 days, when the content of chloroquine phosphate was reduced to 67.5%. This control experiment suggests that the solar radiation, and most probably the UV component, is the predominant cause of the decomposition of chloroquine phosphate.

For the quantitative determination of chloroquine phosphate in tablets, Resochin tablets, a product of Bayer formulated in Nigeria, were used in preference to the formulation of Avion Pharmaceutical used in the preparation of pure chloroquine phosphate. This was because the latter showed peaks around the melting thermal effect, which presumably originated from additives to the tablets. The thermal curve of a finely-ground sample (7.9 mg) from the Resochin tablet is measured. The melting process gave $\Delta H = 45.5$ J/g and 3.6 J/g for the first and the second peaks, respectively. The chloroquine phosphate content of a Resochin tablet is therefore 75.4%, equivalent to 176.2 mg of the free base. The recommended full dose (10 tablets) is 1.5 g equivalent of base [1] and the average full dose of Resochin found in this investigation is 1.7 g equivalent of base. The increase in the dosage (17.3%) is an acceptable compensation for the increased resistance of the parasites.

Conclusions

The present study demonstrates the suitability of DSC in the routine quality control of chloroquine phosphate formulations. It is also shown that light seriously affects the stability of chloroquine phosphate.

The effect of heat is of less significance. Extensive deterioration is possible when finely-ground samples are exposed to the sun and when samples are continually ground in order to expose the maximum surface. This danger is minimized by pressing tablets which are marketed in brown bottles or in packets of tin foils, as in the case of Resochin formulated in Nigeria.

References

1 W. Martindale, The Extra Pharmacopoeia, 27th Ed., The Pharmaceutical Press, London 1977, p. 343.

Zusammenfassung — Für die Verwendung in den Tropen vorgesehene Arzneimittel müssen unter extremen Bedingungen lagerfähig sein. Chloroquin-Phosphat, ein bekanntes Mittel gegen Malaria, wurde auf einem Dach der Sonne unter der extremen Wärme des Sahara-Klimas während der Hitze- und Trockenperiode (Februar bis Juni) bei einer durchschnittlichen Tagestemperatur von 43 °C ausgesetzt. Die durch DSC bestimmte Schmelzwärme ΔH nahm von 60.1 J/g nach 73 tägiger Hitzeeinwirkung auf 33,2 J/g ab, was einem Zersetzungsgrad von 49% entspricht. DSC erwies sich als eine schnelle und zuverlässige Technik zur routinemäßigen Qualitätskontrolle von Chloroquin-Phosphat in Pulver- oder Tablettenform.

Резюме — К фармацевтическим препаратам, предназначенным для использования в тропиках, предъявляются требования сохранности их устойчивости при сильно изменяющихся условиях хранения. Обычный антималярийный препарат хлорокин фосфат был выдержан на солнце в условиях чрезвычайно жаркого климата Сахары во время горячего и сухого сезонов (февраль–июнь) при средней дневной температуре 43°. Определенная методом ДСК теплота плавления (ΔH) препаратов, выдержанных в течении 73 дней, уменьшалась от 60,1 дж/г до 33,2 дж/г, что соответствовало 49% разложению вещества. Следовательно, дифференциальная сканирующая калориметрия может служить быстрым и надежным методом качественного контроля порошков и таблеток хлорокин фосфата.