Journal of Thermal Analysis, Vol. 50 (1997) 867-871

TRANSFORMATION OF CHLORAMPHENICOL PALMITATE FROM THERAPEUTICALLY INACTIVE POLYMORPH A TO ACTIVE POLYMORPH B
Identification and determination of modification A in modification B by DSC

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(Received March 2, 1996; received form December 8, 1996)

Abstract

The bioeffectivity of the therapeutically stable modification A of chloramphenicol palmitate is essentially less than that of the metastable modification B. The literature data indicate that the transformation of modification B to modification A is always monotropic. However, by means of cyclic heat treatment, the stable, inactive modification A has now been successfully transformed to the 'metastable', but pharmaceutically effective modification B. For identification and determination of the inactive polymorph A (as impurity) in the active polymorph B, DSC affords rapid and well-reproducible results on small samples. This method may be recommended for inclusion in pharmacopoeias.

Keywords: chloramphenicol palmitate polymorphs, cyclic heat treatment, polymorph impurity

Introduction

The polymorphism of chloramphenicol palmitate has been well known for some decades. This problem is important primarily for chemists and analytical chemists, because the therapeutically active B(II) form is thermodynamically metastable, whereas the stable A(I) form is inactive [5–7]. In this paper we discussed (1) the transformations of modification A and B into one another; and (2) the simultaneous identification of polymorphs A and B, i.e. the identification and determination of polymorph A as impurity in polymorph B.

Transformations of one polymorph into the other

In this article entitled 'New experimental results on the polymorphous of chloramphenicol palmitate' [1], in 1977 Burger published a literature review

0368–4466/97/ $ 5.00

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supplemented with his own experience. It has been shown that three polymorphs of chloramphenicol palmitate exist: the A(I), B(II) and C(III) forms. The A(I) form is stable at room temperature, and has a melting point of 95°C, but as a drug it is practically ineffective. Active form B(II) is metastable, with a melting point of 89°C. Modification C(III) is very unstable and difficult to observe. Burger described his own DSC measurements with different mixtures of chloramphenicol palmitate polymorphs A and B. In the DSC curves, the melting endotherms of the two modifications appear simultaneously.

The transition of form B to A is an exothermic process. From this starting point, Burger concluded that the transformation of polymorph B to polymorph A is an irreversible, monotropic process. However, he made no effort to prove this. In his subsequent review, he cited his former article [2], and later authors accepted his conclusion as a fact that the transition of form B to form A is monotropic. Accordingly, they investigated only the conditions and the course of the transformation and failed to study the reverse process [3, 4].

Examination of polymorph impurity

For the identification of modification A of chloramphenicol palmitate in modification B, the IR method is recommended in the American [5], British [6] and Hungarian [7] pharmacopoeias alike. In 1974, Ferioli *et al.* [8] advocated the advantages of the DSC method. They identified 0.1–7% form A in mixtures of polymorphs A and B at a heating rate of 16°C min^{-1}.

Experimental and results

Transformation of one polymorph into the other

Chloramphenicol palmitate (National Institute of Pharmacy) samples containing both modification A and modification B (sample 1) or only modification A (sample 2) were used.

The experiments were carried out with a DuPont 990 Thermal Analyzer fitted with a DSC module. Samples (9–4 mg) were placed in an aluminium crucible. The heating rate was 5°C min^{-1} or 2°C min^{-1}. Cyclic treatment was applied i.e. the sample was heated to above its melting point, and then cooled at different cooling rates. In some cases, the cyclic heat treatment was repeated two or three times.

During the heating of sample 1, the melting points of both modifications appeared in the DSC curve (form B, 89°C; form A, 95°C). The sample contained only a small amount of polymorph B; it is readily seen in Fig. 1 that the unstable polymorph B crystallizes to the stable polymorph A at 91°C, the exothermic peak indicating the crystallization. These findings are in good agreement with the conclusion of Burger. After polymorph A had melted, the sample was cooled slowly, and the cooling curve exhibited a sharp exothermic peak at about 70°C. During

repeated heating, only one melting endotherm appeared in the DSC curve, at the temperature characteristic of the melting point of polymorph B. Accordingly, during the cooling process, form A was transformed to form B. Thus, we succeeded in transforming the stable, inactive modification A to the 'metastable', but pharmaceutically effective modification B.

For sample 2, the melting point of form A was seen in the first heating curve. However, when the melt was cooled and reheated only the characteristic melting

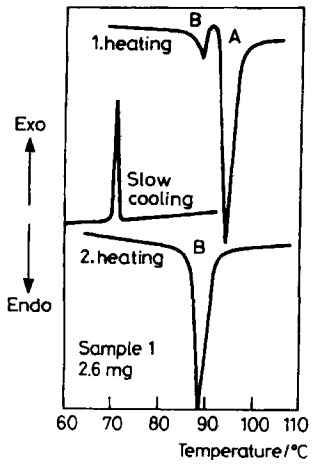

Fig. 1 First heating: chloramphenicol palmitate polymorphs A+B. Second heating: chloramphenicol palmitate polymorph B

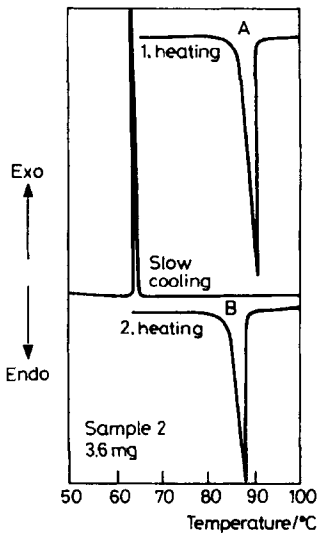

Fig. 2 Chloramphenicol palmitate. The transition process of form A to B

endotherm of modification B appeared, indicating that form A was transformed to form B during the cyclic process (Fig. 2). When heating was stopped immediately after the melting endotherm had returned to the baseline of the DSC curve, subsequent heating revealed that the formation of polymorph B from polymorph A was sometimes not quantitative: besides the melting point of form B, the melting point of form A also appeared (presumably a few nuclei of modification A remained in the melt). The areas of the melting endotherms of the polymorphs provide an indication of the contents of modifications A and B. After the third heating, the sample contained only chloramphenicol palmitate B for a quantitative process, the temperature of heating should be at least 10°C above the melting point of form A, and the cooling process should be very slow.

The freshly prepared modification B was found to be stable for at least 3 months at room temperature.

Examination of polymorph impurity

Mixtures containing 97.95% or 90.00% polymorph B, and 3.05 or 10.00% polymorph A, respectively, were prepared. The sample mass was about 3 mg, and the heating rate was 2°C min^{-1}. Figure 3 shows the melting endotherms of forms A and B separately; from the areas of the peaks, the ratio of the polymorphs can be estimated.

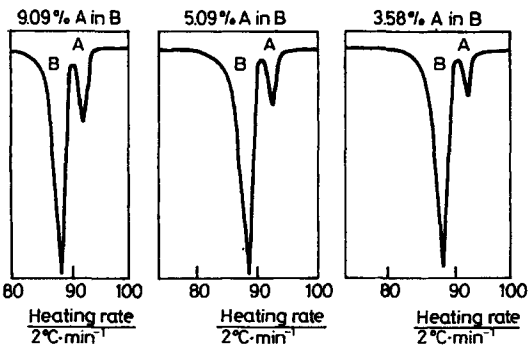

Fig. 3 Identification of polymorph A – as impurity – in B

Discussion

The literature suggests that the transformation of the metastable, but biologically active modification B to the stable, but biologically inactive modification A is always monotropic. However, we have proved that by cyclic heat treatment the process can be reversed and we have succeeded in transforming the inactive form A to the biologically effective form B. We found that at room temperature the freshly prepared polymorph B is stable for at least 3 months.

For the identification of modification A as impurity in modification B, the very complicated IR method is recommended in practice and also in pharmacopoeias, although Ferioli *et al.* [8] described the advantages of the DSC method in 1974. Our own measurements tend to confirm the view of Ferioli *et al.*

In spite of the fact that we applied a heating rate of $2^{\circ}C\ min^{-1}$, whereas theirs was $16^{\circ}C$ min min^{-1}, the results were similar.

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