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Short Communication

TRANSITIONS OF CHLORAMPHENICOL PALMITATE
A rebuttal

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This short communication is a comment on the paper 'Transformation of Chloramphenicol Palmitate from Therapeutically inactive Polymorph A to active Polymorph B' by Csakurda-Harmathy and Konkoly Thege [1]. In this article it is stated that they were able to transform the stable form A of Chloramphenicol Palmitate to the metastable form B by what they called 'cyclic treatment'. We cite: 'Cyclic treatment was applied, i.e. the sample was heated to above its melting point and cooled at different cooling rates'. According to them, this would mean that the two polymorphs A and B would have an enantiotropic relation, because it is known that at lower temperatures B converts to A [2–3]. This enantiotropic relation between the two polymorphs was also suggested by Aguiar and Zelmer and by Wadke and Reier [4–5], but was contradicted by Burger [6–7].

In their comment on the conclusion of Burger that the two polymorphs have a monotropic relation Csakurda-Harmathy and Thege stated: 'However he made no effort to prove this.' They claim that with the so-called 'cyclic treatment' the opposite has been proved and write: 'Thus, we succeeded in transforming the stable inactive modification A to the 'metastable', but pharmaceutical effective modification B.' Here we will show that the arguments of Burger do not need extra experimental evidence, that the 'proof' of Csakurda-Harmathy and Konkoly Thege is wrong and based on a misunderstanding of crystal growth and finally we will suggest some experiments that might give extra, superfluous proof for a monotropic relation between the two polymorphs A and B.

In Table 1 the data from the literature is listed. Unfortunately Csakurda and Konkoly Thege do not supply the heats of fusion from their DSC curves, however we have measured 1/2 W h from their curves and given the corresponding values

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in mm^2. The calculated heats of fusion by Burger agree with the measured values of Borka and have the same ratio as the measured values of Csakurda and Thege. All the values of the heats of transition (form B → A) agree on the fact that this should be an exothermic transition.

In case of two polymorphic forms four relations are possible. i) form A is the most stable and monotropic related to form B; ii) form B is the most stable and monotropic related to form A; iii) below T_{tr} form A is the most stable one and enantiotropic related to form B; iv) below T_{tr} form B is the most stable and enantiotropic related to form A. Case ii) can be ruled out, because literature lists that form B transforms to form A at several different conditions [2–3]. Figure 1 shows the energy diagrams according to Burger and Ramsberger [7] for the remaining possibilities.

Table 1 Temperatures and heats of fusion and transition of the two polymorphs A and B. An asterisk indicates that the values are calculated and the heats of fusion of Csakurda-Harmathy and Konkoly Thege have been calculated using their graphs (in mm^2)

	$T_{m,A}$/ °C	$T_{m,B}$/ °C	$\Delta H_{m,A}$/ kcal mol^{-1}	$\Delta H_{m,B}$/ kcal mol^{-1}	$\Delta H_{B\rightarrow A}$/ kcal mol^{-1}
Csakurda [1]	95	89	30 mm^2	21 mm^2	–
Aguiar [4]	–	–	–	–	–6.4
Wadke [5]	–	–	–	–	–5.3
Burger [6]	95	89	15.3*	10.0*	–5.3
Borka [8]	–	–	15.3	10.4	–

In Fig. 1A the energy diagram is given of an enantiotropic system with form B as the most stable low temperature form. From this it is clear that for this system $T_{m,A} > T_{m,B}$, $\Delta H_{m,A} < \Delta H_{m,B}$ and $\Delta H_{B\rightarrow A} > 0$ (endotherm). Thus, polymorph A has always the highest melting temperature together with the lowest heat of fusion. A transition from polymorph B to polymorph A is only possible at temperatures equal or above T_{tr} and will be endothermic. Table 1 , however, shows that for Chloramphenicol palmitate form B has the lower heat of fusion and that the transition from polymorph B to polymorph A is exothermic. From this we can conclude that the polymorphic system described by Fig. 1A can not be applied to forms A and B of Chloramphenicol Palmitate.

Figure 1B shows the energy diagram of an enantiotropic system with as low temperature form polymorph A. This immediately shows that in such a system $T_{m,A} < T_{m,B}$, $\Delta H_{m,A} > \Delta H_{m,B}$ and $\Delta H_{B\rightarrow A} < 0$ (exothermic). In this case polymorph A would have the lowest melting point and the highest heat of fusion, a transition from polymorph B to A is only possible at temperatures below the transition point and will be exothermic. In spite of what one would conclude on basis of the heats of fusion and heat of transition this can not be the case for the two poly-

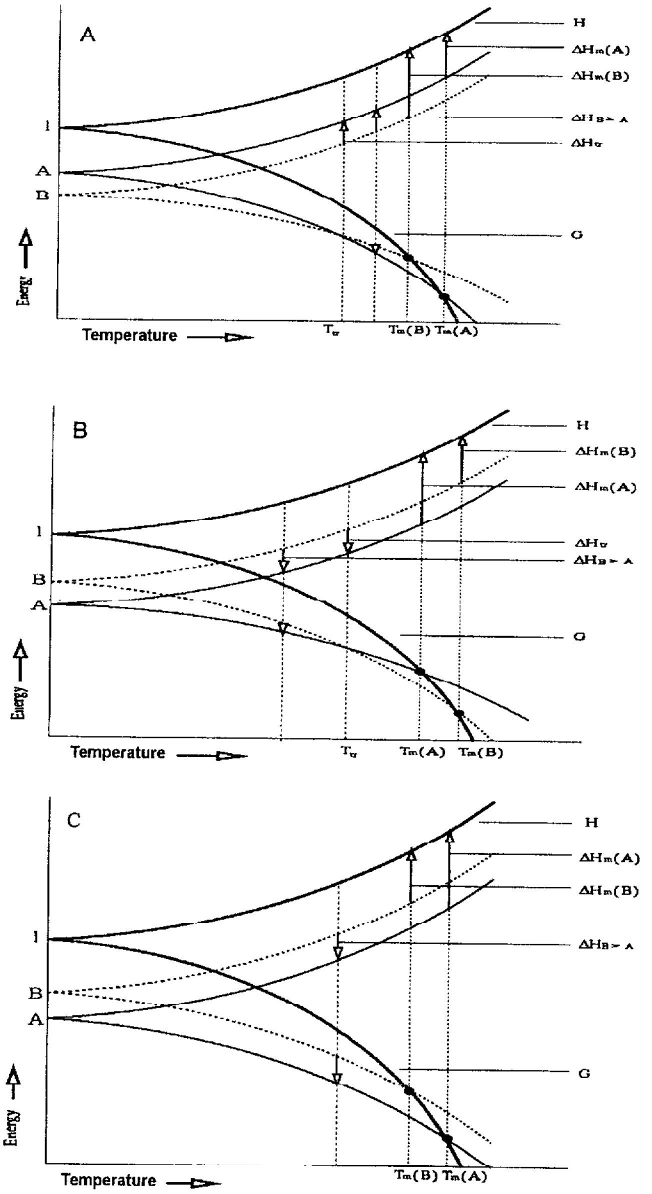

Fig. 1 Energy *vs.* temperature diagrams of two enantiotropic systems a) and b) and a monotropic system c). In these figures the upper three curves are the enthalpy curves and the lower three the Gibbs free energy of A=form A, B=form B and l=liquid. The transition point, i.e. were the Gibbs free energy of the two forms is equal, is indicated with 'tr' and the transition from polymorph B to polymorph A at an arbitrary temperature with B → A

morphs A and B of Chloramphenicol Palmitate, because form A clearly has a higher melting point than form B. These comparisons lead beyond any doubt to the conclusion that the forms A and B of Chloramphenicol Palmitate are not enantiotropic related, but monotropic.

Finally, the energy diagram of a monotropic system, as listed in Fig. 1C, fully agree with the data of polymorphs A and B (Table 1). For this system the form A has both the highest melting temperature and heat of fusion ($T_{m,A} > T_{m,B}$ and $\Delta H_{m,A} > \Delta H_{m,B}$) and the exothermic transition from polymorph B to A can occur at every temperature below the melting point of form B.

We note here that an enantiotropic behaviour as described by the energy diagram in Fig. 1B has been reported both by Aguiar and Zelmer [4] and by Wadke and Reier [5]. From solubility data they calculated the transition temperature T_{tr}, which were 88 and 84°C respectively. However, to do so they extrapolated the solubility curves over more than 40°C, which gives together with the error of the measurements a large deviation in T_{tr}. Moreover, their calculated T_{tr}'s are quite close to the melting points of the two polymorphic forms (89 and 95°C) and if the transition temperature (T_{tr}) is higher than the highest melting point ($T_{m,A}$) a monotropic system, like in Fig. 1C, would be obtained.

We believe that these arguments are enough to conclude that the system is monotropic. However Csakurda-Harmathy and Konkoly Thege performed some experiments, which to their belief gives evidence to the fact that the system is enantiotropic. To do so they heated the sample above its melting point and crystallised it again. This was repeated several times and called 'cyclic treatment'. They write in their article: 'Cyclic treatment was applied, i.e. the sample was heated to above its melting point and then cooled at different cooling rates' and 'After polymorph A had melted, the sample was cooled slowly'. After cooling the sample they find polymorph B and believe that they have transformed form A to form B: 'Accordingly, during the cooling process, form A was transformed to form B'. However, the only thing they have done during their experiment is that they melted form A and subsequent crystallised form B from the melt, which is no evidence for an enantiotropic system or even a phase transition! It is not surprising that a metastable form is crystallised upon cooling a melt. According to Ostwalds rule of stages upon crystallisation first the metastable phase will be formed and even Burger [6] himself stated that form B could be formed this way: 'For this study form B was obtained from the melt' (translated by the authors).

The only way to experimentally prove that form A and B are not monotropic related is to observe at some point a phase transition from polymorph A to B or by measuring the stability at all temperatures till the melting point. This can be tried by heating form A at different temperatures, but always lower than its melting point! Sometimes these phase transitions can be sped up by adding an amount of the desired polymorph B and/or by 'wetting', but not solving, the sample with a solvent. However, we believe that the arguments that lead to a monotropic system are more than satisfactory and therefore the above mentioned experiments are superfluous.

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