Journal of Thermal Analysis, Vol. 33 (1988) 1027–1032

INTERPRETATION OF TA-DATA FOR DRUGS: AGEING, REACTIONS ETC.

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The drug systems bacampicillin (S and R epimers) and Alfa-water were investigated by TG–DSC, X-ray diffraction, microscopy, and density measurements. Both systems are mixtures of crystalline and amorphous materials; the interpretation of their effects and properties indicates that the solid samples in the mixture react with each other, even at room temperature. Consequently these results indicate that complex mixtures are present and that ageing is going on.

During production of drug substances our experience is that solid materials normally come out as mixtures. Pure samples are obtained less frequently but that number can be increased if special precautions are taken.

When there is a mixture, one of the components normally is X-ray amorphous which is the most difficult solid to characterize. However, thermal analysis is one way indirectly to obtain useful chemical information i.e. simply to prove its existence and further its melting, degradation etc. When dealing with solid mixtures one has also to take into account the solid-solid interaction which may take place at room temperature already i.e. at storage [1].

We shall present some observations and conclusions from two systems: I bacampicillin hydrochloride (1) and II the research drug Alfa.

I Bacampicillin hydrochloride is precipitated in a mixture of ethyl and *n*-butyl acetate. All batches so far analysed are mixtures and contain crystalline S-epimer and amorphous R-epimer in different proportions. The residual content of these solvents is generally not more than 5% by weight but both the total amount and the ratio between the two solvents can vary (Fig. 1). These onset temperatures as well as the characteristic temperatures for the DSC-signals (Fig. 2) are put together giving Figure 3. The relationship thus derived suggests some connection between chemical composition and certain physical properties.

According to the TG experiments the first two DSC peaks are not associated with a weight change whereas the third is connected with the decomposition of the material. As can be seen in Fig 3 the linear correspondence of weight change is almost congruent to the DSC-signals.

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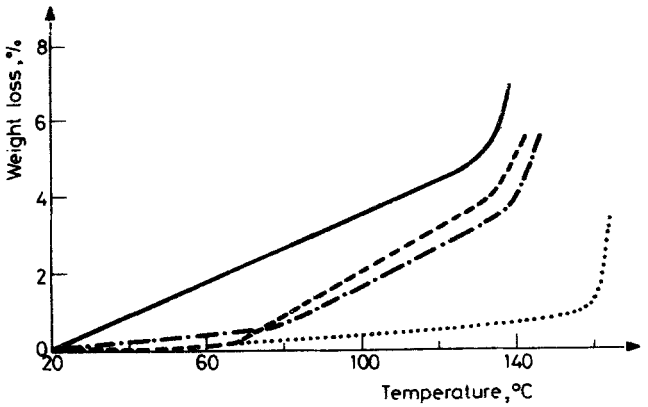

Fig. 1 Weight loss diagrams for four samples of bacampicillin hydrochloride from the thermogravimetrical determinations.
I R/S-epimer ratio 90/10 (———)
II R/S-epimer ratio 46/54 (– – – –)
III R/S-epimer ratio 21/79 (– . – . –)
IV R/S-epimer ratio 9/91 (– – – –)

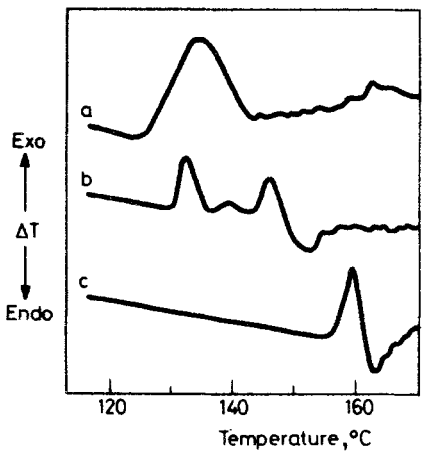

Fig. 2 DSC curves of the three samples of bacampicillin hydrochlorid, with different R/S-epimer ratios. $a = 90/10$, $b = 39/61$, $c = 10/90$.

In an attempt to find and understand the nature of these effects, some mixtures of solvent-free R- and S-epimers, both of 90% purity, were gently ground together. This resulted in DSC-diagrams with onset temperatures similar to the starting materials, i.e. if mechanically mixed they do not interfere with each other.

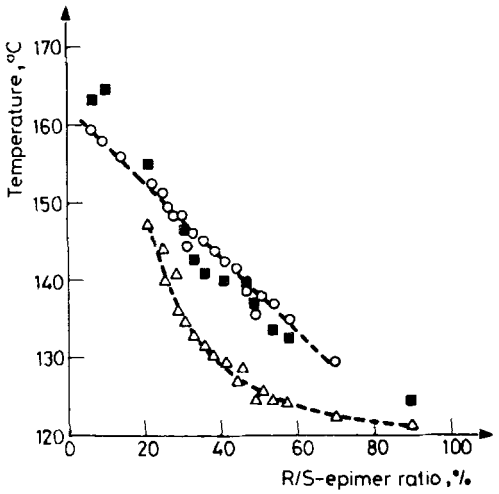

Fig. 3 Characteristic onset temperatures for exothermic DSC signals I (△) and III (○) and corresponding TG-signals (■) for different batches of bacampicillin hydrochlorid.

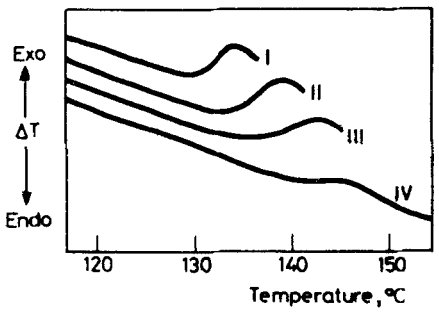

Fig. 4 Consecutive reheating of a sample of bacampicillin hydrochlorid showing the change in DSC-signal I.

If the amorphous R-epimer is heated just to its "transition" temperature in a consecutive series without weight loss, the first exotherm can be destroyed, as shown in Fig 4. The resulting sample, which without weight change becomes yellow and brittle, is not crystalline and is practically insoluble in water. By performing HPLC analysis on this product, a complex mixture is identified which can be regarded as resulting from a polymerization process including part of the solvents which have not disappeared during the preceding heat treatment.

The data in Fig 3 show the relation for temperature *vs.* composition of a mixture of crystalline and amorphous epimer. It is important to know that the curve is valid for the first run only because of the slow polymerization. The results imply, however, that these materials do interfere with each other although it has been proven that a mixture of the two solvent-free end members actually behave as a mixture. If we consider the proposed model with the R-epimer solidified on the surface of the S-epimer, it might be assumed that the first DSC-signal is associated with the decomposition of the R-epimer. The second small peak is probably connected to a solid-solid interaction.

In order to explain the third DSC-effect we must take into account a strong influence of the solvents, ethyl and especially butyl acetate, and the way these molecules are associated with the solids. Apart from a usual solubility in the amorphous phase, the results suggest some type of hydrogen bonded composition between the solvents and the crystalline S-epimer. The site for the solvent is probably in the wide tunnels and the increase in temperature (Fig. 3) may thus correspond to a higher amount of hydrogen-bound complexes towards the crystalline side. The dimension of one molecule butyl acetate is quite close to the tunnel dimension in one unit cell and this would give rise to an addition compound of one molecule butyl acetate and three molecules bacampicillin hydrochloride.

II. Concerning the drug *Alfa* the story is quite different. It was found almost impossible to obtain reproducible results even when the analysis were performed with samples from the same batch. From time to time pots or containers had a thin brittle surface coating and other were slightly sticky. Two combined TA-analysis with 10 deg/min from the same container look like: the coating (Fig. 5) and from the inside (Fig. 6).

Our interpretation is the following: in the temperature region 80–100° a monohydrate decomposes forming an anhydrate which melts at about 175° just before its degradation. A pure monohydrate would lose 4.4% water by weight. The endothermic peak around 160° comes from an amorphous anhydrate which seems always to be present in different amounts. This effect can be registered between 155° and 170°, lower temperatures for young samples and higher values for old materials. The highest temperature is registered for a batch more than two years old indicating some kind of ageing phenomenon.

A large area for the intermediate peak corresponds to a sticky sample with a high amorphous content. The brittle surface material is crystalline monohydrate rather fast formed if an understoichiometric, with respect to monohydrate, powder is exposed to normal air. This thin layer is an almost complete seal for further diffusion of water wapour.

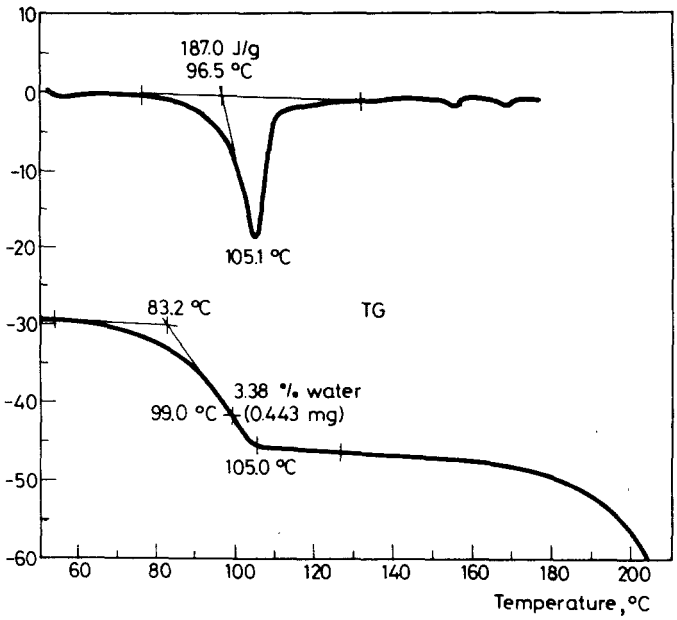

Fig. 5 TG and DSC of a sample from the thin brittle surface of Alfa.

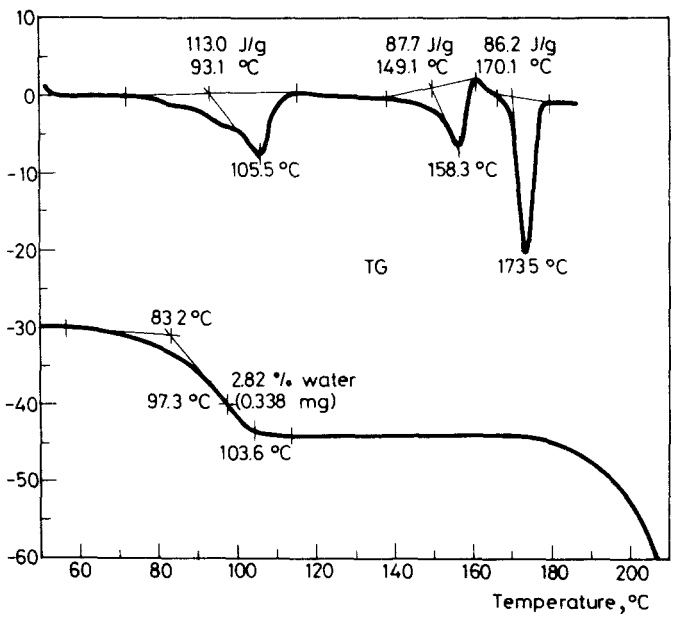

Fig. 6 TG and DSC of a sample from the same batch as Fig. 5 but from the inside.

At this stage we thought that the main behaviour of the system was understood. However, when some samples were analysed at slower heating rates completely different DSC-diagrams were obtained. This means that many different reactions, solid-solid, solid-liquid etc, may occur in the mixture due to prolonged heating of systems with slow reactions rates.

References

1 H. Nyqvist and T. Wadsten, Acta Pharm. Suec., 22 (1985) 215-228.

Zusammenfassung – Die Wirkstoff-Systeme Bacampillicin (S- und R-Epimer) und Alfa-Wasser wurden mittels TG und DSC, Röntgenbeugung, Mikroskopie und Dichtemessungen untersucht. Beide Systeme stellen Mischungen kristalliner und amorpher Stoffe dar; eine Deutung ihrer Effekte und Eigenschaften zeigt, dass die festen Stoffe in der Mischung miteinander reagieren, sogar bei Raumtemperatur. Die Ergebnisse beweisen das Vorliegen komplexer Mischungen und das Ablaufen von Alterungsvorgängen.

РЕЗЮМЕ — Два наркотических препарата бэкампициллин (S и R — эпимеры) и Альфа-вотер были изучены методом ТГ-ДСК, рентгенодиффракционным методом, микроскопией и измерением плотности. Обе системы являются смесью кристаллического и аморфного вещества. Приведенная интерпретация проявляемых эффектов указывает на то, что твердые образцы в смеси реагируют друг с другом даже при комнатной температуре, что свидетельствует о наличии сложных смесей, подвергающихся старению.