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SOLID-STATE MICROCALORIMETRY ON DRUG-CYCLODEXTRIN BINARY SYSTEMS

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Differential scanning calorimetry DSC has been applied to the analysis of drug-cyclodextrin binary systems in order to gain experimental evidence of the interaction and determine the stoichiometry of the inclusion compound. Two model systems, paracetamol-betacyclodextrin and vinburnineg-ammacyclodextrin were tested through the comparison of thermal behaviors of interacted and non-interacted mixtures containing excess drug. DSC allowed a confirmation of both interaction and stoichiometry of the inclusion compounds.

Keywords: drug-cyclodextrin, solid-state microcalorimetry

Introduction

Cyclodextrins are cyclic oligosaccharides able to host in their cavity, which is prevailingly hydrophobic, molecules of various kinds, thus affecting the physical and physicochemical properties (e.g. solubility, stability, dissociation constant) of the guest, and ultimately, in the case of drugs, its bioavailability and therapeutic efficiency [1]. The inclusion in the cyclodextrin cavity generally causes the loss of macroscopic properties of the guest such as melting point, boiling point, etc. [2]. Microcalorimetry on solid state is widely used for the characterization of inclusion compounds. The experimental approach is generally limited to a qualitative comparison between physical mixtures and interaction products obtained by common procedures (freeze-drying, coprecipitation, solvent evaporation, kneading). Moreover, a single composition (most frequently the 1/1 mol/mol ratio) is tested and the lack of endothermic effects due to fusion shown by interacted mixtures in the melting region of the crystalline drug is generally taken as an evidence of inclusion.

A major drawback of this assumption lies in the possible amorphization of crystalline drugs during the preparation of inclusion compounds, which would also lead to a similar thermal pattern. Moreover, no attention is generally paid to

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the thermal behavior of drug-cyclodextrin binary systems in toto, that is in a wide range of compositions.

It seems worth to emphasize that the comparison of thermal behaviors of interacted and non interacted mixtures having the same total composition and containing excess drug would allow an estimate of the interaction ratio.

On the basis of these premises, the application of differential scanning calorimetry (DSC) on drug-cyclodextrin binary systems in the solid-state, aiming to gain further experimental evidence of real inclusion and determine the stoichiometry of the inclusion compound, seemed worth of investigation. Results concerning the systems *p*-acetamidophenol (paracetamol, PA)/ betacyclodextrin (beta-CD) and eburnamenin-14(15H)-one (vinburnine, VIN)/ gammacyclodextrin (gammaCD) as model guest/host binary systems, whose interactions in terms of inclusion compound formation and characterization have been already described [3–5], are reported and discussed.

Experimental

Materials and methods

PA (*mp* 169°–170°C) and VIN (*mp* 174°–175°C) (Chiesi Farmaceutici SpA, Parma, Italy), betaCD and gammaCD (Roquette Frères, Lestrem, France) of commercial purity grade were used.

Drug-cyclodextrin physical blends in different mol/mol ratios were prepared by thorough grinding with pestle in a china mortar: interacted mixtures were obtained from physical blends by kneading with small portions of a water/methanol solution (1/1, v/v) for an hour. The creamy products were then dried at 90°C up to constant weight.

Thermal analyses were performed with a Mettler TA-3000 apparatus, equipped with a DSC-20 cell. Samples (3–7 mg, Mettler M3 microbalance) were scanned in pierced Al pans at 5 –10 deg·min^{-1}, under dry nitrogen atmosphere.

Calculations

Let *na* and *nb* be the moles of guest and host in the starting mixture, respectively, and *R* the guest-to-host interaction ratio (in moles). The free moles of guest after interaction (*na**) will be given by:

$$na^* = na - nb \cdot R \tag{1}$$

where $nb \cdot R$ represents the interacted moles of guest. Since the total mole fraction of the guest (TGMF) is represented by

$$\text{TGMF} = na/(na + nb) \tag{2}$$

consequently,

$$na^* = \text{TGMF}\,(na + nb) - nb \cdot R \tag{3}$$

The free mole fraction of the guest (FGMF) is therefore:

$$\text{FGMF} = na^*/(na + nb) = \text{TGMF} - (1 - \text{TGMF})\,R \tag{4}$$

which can be easily rearranged to

$$\text{FGMF} = \text{TGMF}\,(1 + R) - R \tag{5}$$

Equation 5 bears a physical meaning provided that $na/nb \geq R$ and FGMF ≥ 0. By plotting FGMF *vs.* TGMF a straight line with $(1 + R)$ slope and $-R$ intercept must be obtained.

Therefore, let's consider interacted mixtures containing an excess guest with respect to R and for which the endothermic effect can be reasonably related to the melting of excess component. DSC allows the experimental measure from peak area of fusion enthalpy of such excess (FGMF), associated with the endotherm in the melting region of the crystalline guest. Since the total composition of the system (*na* and *nb*) is known, it is possible to derive R by a simple graphic method

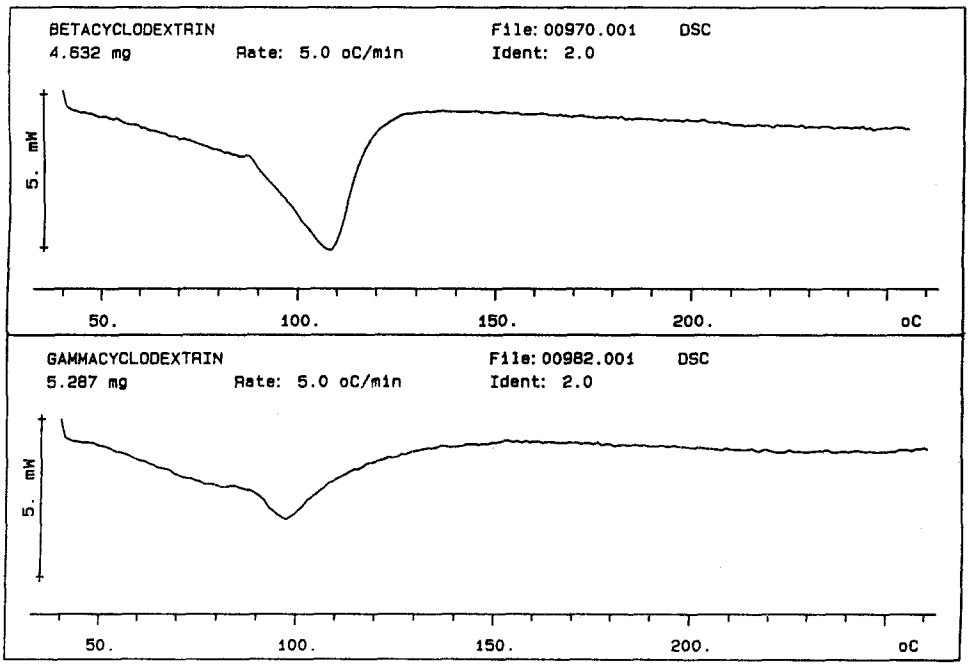

Fig. 1 Thermal profiles of betacyclodextrin and gammacyclodextrin

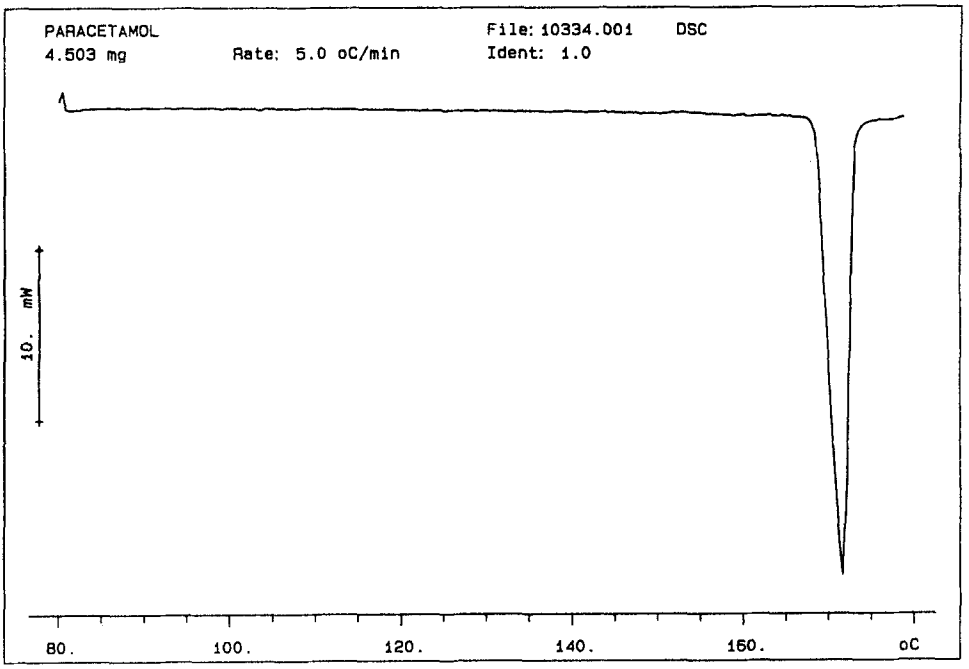

Fig. 2 Thermal profile of paracetamol (PA)

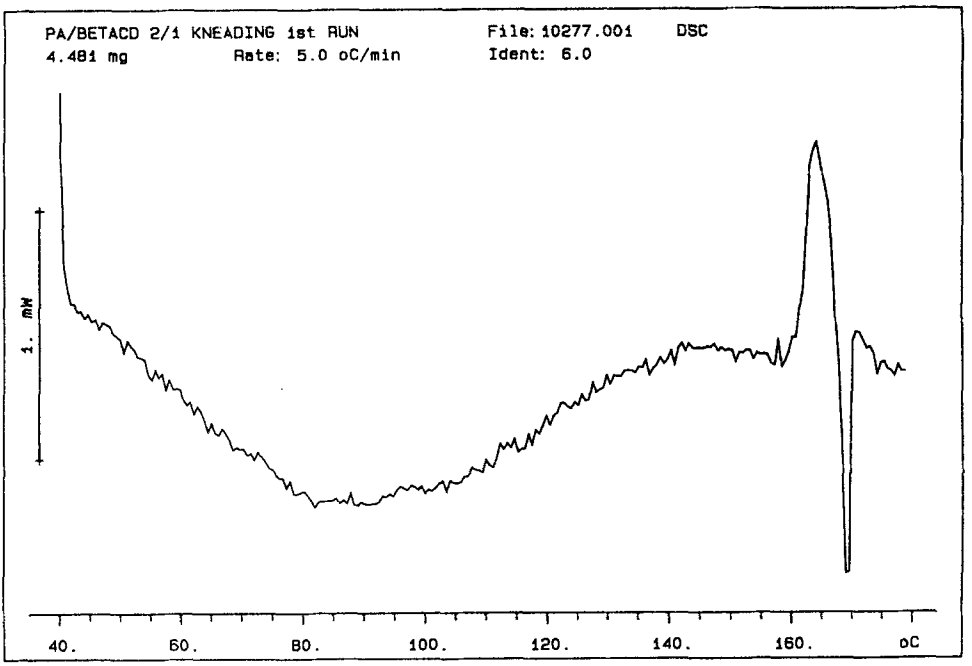

Fig. 3 Thermal profile of PA/betaCD 2/1 kneaded mixture first run (see text)

through the intercept of the straight line, as shown in the following Results and discussion section.

Results and discussion

Thermal profiles of samples of commercial betaCD and gammaCD are reported in Fig. 1. In both cases, a broad endotherm in the 50°–130°C range can be observed, which can be attributed to water loss. Up to the final scanned temperature (300°C) no other significant thermal events were recorded.

Paracetamol-betacyclodextrin binary system

The thermal behavior of commercial PA is shown in Fig. 2. A fusion endotherm can be seen at 169°C. The DSC profile of the 2/1 PA/betaCD kneaded mixture (first run) is reported in Fig. 3. Such a pattern is also characteristic of all kneaded mixtures with a PA/betaCD ratio > 1, and exhibits in the 155°–180°C range a peculiar exo – endo sequence which was ascribed to recrystallization of amorphous PA and subsequent fusion also on the basis of direct observation (hot stage microscopy) [7]. In order to allow the accurate evaluation of endothermic

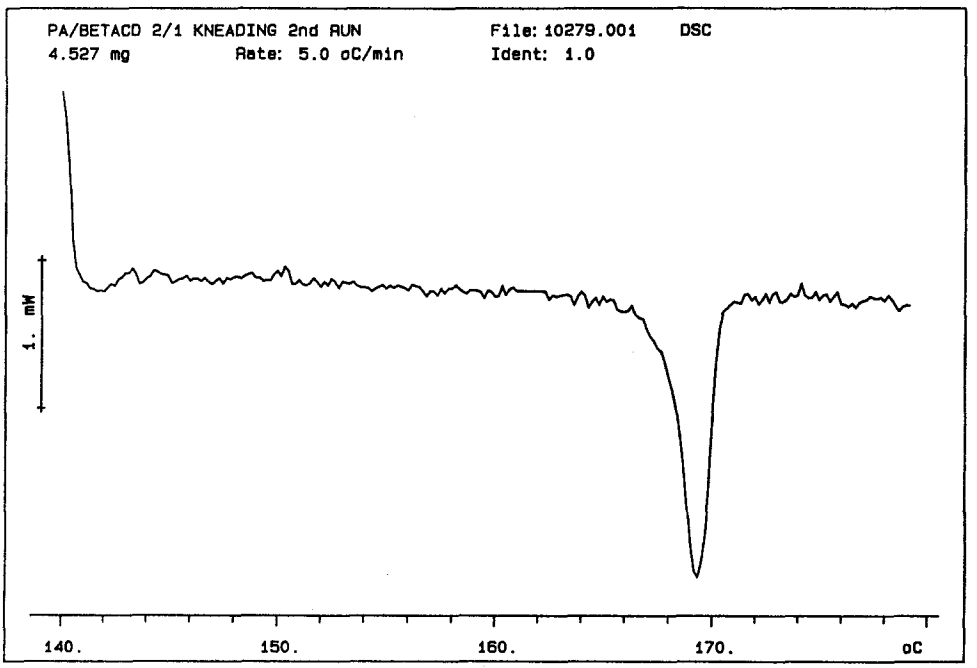

Fig. 4 Thermal profile in the 140°–180°C range of PA/betaCD 2/1 kneaded mixture, final scan of the thermal cycle (see text)

effects, a thermal cycle was therefore set up. The mixture was first heated up to 160°C, kept at this temperature for 5 min, allowed to cool down to 140°C, and finally rescanned up to 180°C (Fig. 4). The same treatment was applied to PA/betaCD kneaded mixtures with various compositions (Fig. 5), in order to obtain thermal traces from which the fusion enthalpies could be easily measured.

Vinburnine-gammacyclodextrin binary system

The thermal profile of VIN is reported in Fig. 6. The fusion endotherm is observed at 175°C. As a general feature, while physical mixtures showed a thermal behavior which was just the sum of those of pure components (Fig. 7*a*), kneaded and co-precipitated products prepared from mixtures with molar ratios < 0.75 (VIN/gammaCD) failed to give the endothermic peak at 175°C. On the other hand the endothermic peak at 175°C appears again when interacted mixtures with molar ratios > 0.75 between components are tested, as shown in Fig. 7*b*.

Determination of the interaction ratio

Figure 8 reports the theoretical curves calculated through Eq. (5) at three different R values together with FGMF values obtained from fusion enthalpies at

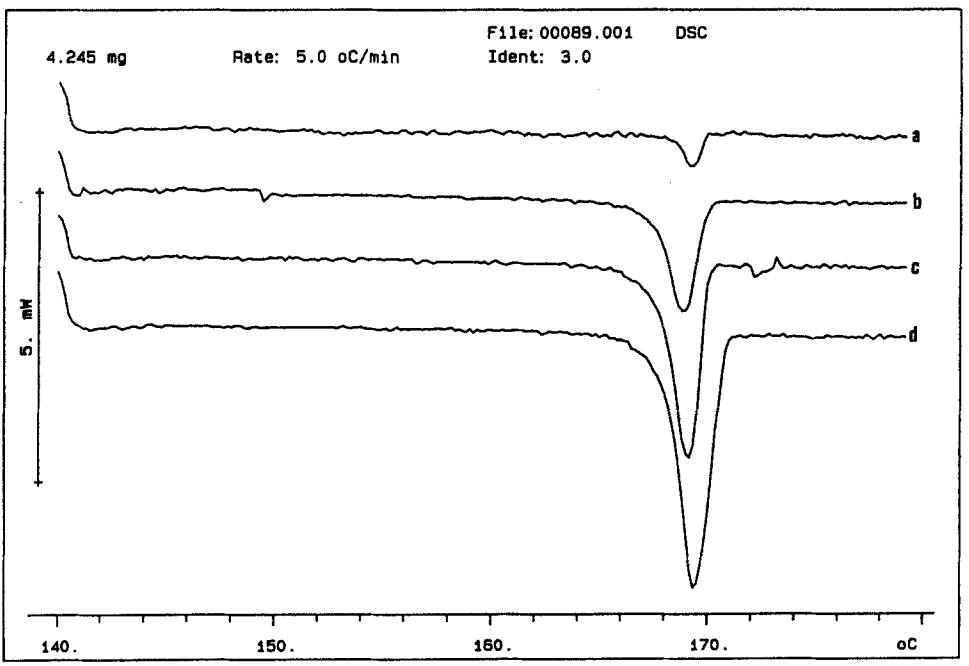

Fig. 5 Thermal profiles in the 140°–180°C range of PA/betaCD kneaded mixtures, second runs (see text): *a*) 3/2; *b*) 2/1; *c*) 2.5/1; *d*) 3/1

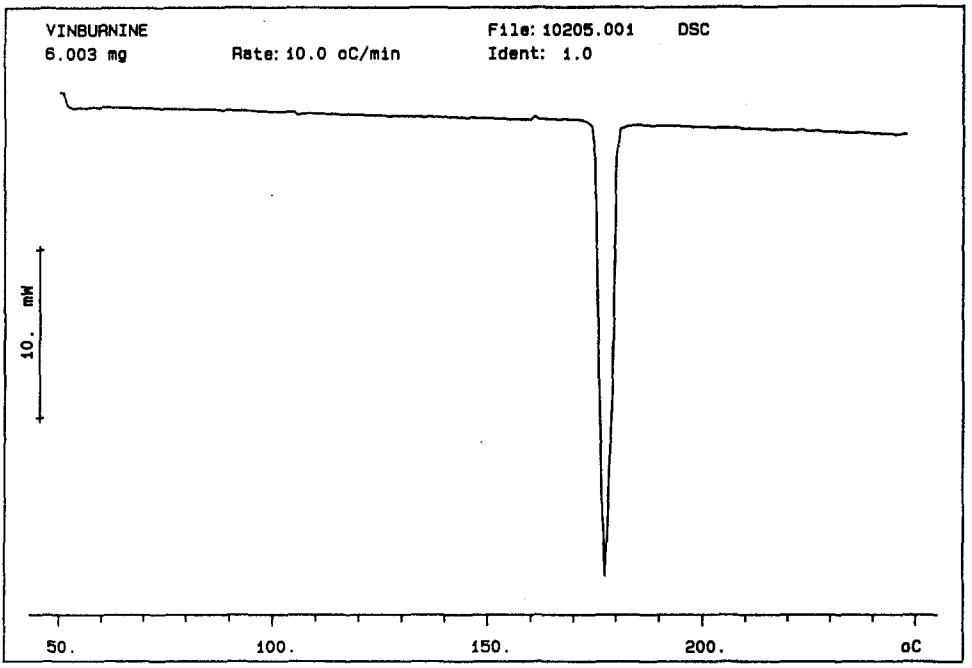

Fig. 6 Thermal profile of vinburnine (VIN)

169°C for PA and 175°C for VIN, respectively. The intercept of each line with the composition axis gives the stoichiometry of the inclusion compound (1/1 for PA/betaCD and 3/4 for VIN/gammaCD). Furthermore it can be observed that the same composition of the inclusion compound is obtained for all interacted mixtures containing excess drug with respect to the interaction ratio.

Conclusions

Microcalorimetry on the solid state (mainly DSC and DTA) is commonly used for the analysis of the interaction between drugs and cyclodextrins. DSC allows a further confirmation of both interaction and stoichiometry of the inclusion compounds between paracetamol and betacyclodextrin and vinburnine and gammacyclodextrin. This is possible also because generally inclusion compounds do not undergo melting within the temperature range where the cyclodextrin lattice is decomposed, although it has been claimed that when guest molecules are incorporated in the cyclodextrin cavity or in the crystal lattice, their melting points usually shift to a higher temperature [2].

The following requirements, in order to apply this method, have to be met:

i) the interaction is easily induced by common procedures such as grinding, coprecipitation or kneading;

ii) the fusion temperature of the guest is lower than the fusion (or decomposition) temperature of the host cyclodextrin;

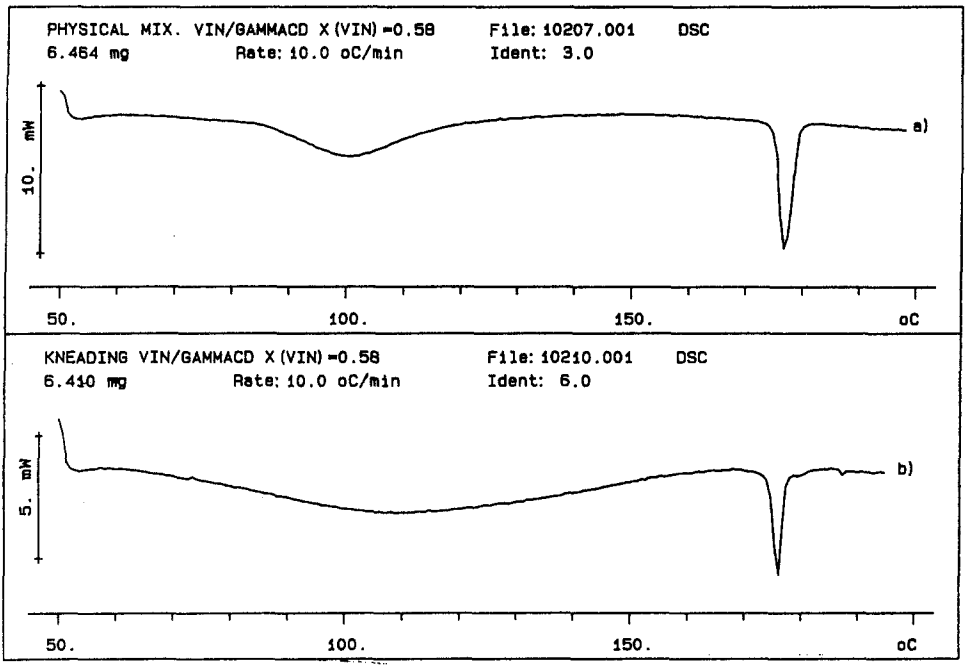

Fig. 7 Thermal profiles of VIN/gammaCD 1.4/1 *a*) physical mixture and *b*) kneaded mixture

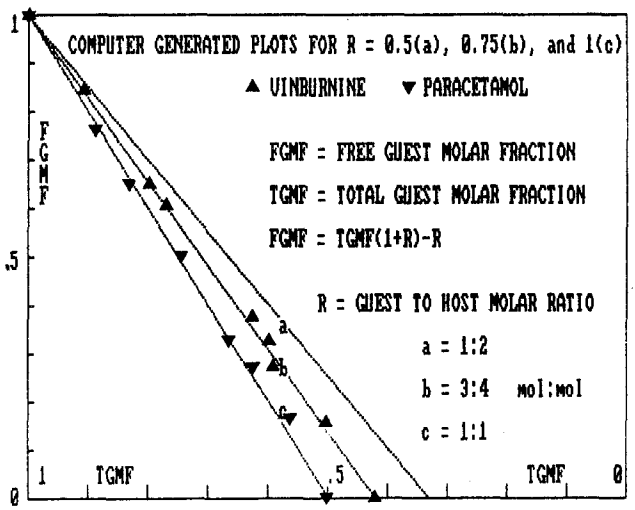

Fig. 8 Computer generated plots according to Eq. (5)

iii) the fusion enthalpy of the drug is not significantly influenced by the presence of the cyclodextrin, in both mechanical and interacted mixtures containing excess guest with respect to the interaction ratio.

The peculiar thermal behavior of PA-betaCD kneaded mixtures (exo-endo sequence) has been observed also in other drug-cyclodextrin systems [6]. Amorphization actually represents a rather common result of cogrinding or freeze-drying drug-cyclodextrins mixtures and it must be considered when flat thermal profiles and X-ray diffraction patterns on powder are invoked as evidences of inclusion [7]. The thermal analysis of drug-cyclodextrin mixtures in a wide range of composition can prove to be useful for a better insight both of inclusion and the stoichiometry of the interaction.*

* * *

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Zusammenfassung — Mittels DSC wurde eine Analyse binärer Medikament-Cyclodextrin Systeme durchgeführt, um eine experimentelle Bestätigung der Wechselwirkung zu erhalten und die Stöchiometrie der Einschlußverbindung zu ermitteln. Über den Vergleich des thermischen Verhaltens von in Wechselwirkung stehenden und nicht in Wechselwirkung stehenden Gemischen mit einem Überschußgehalt an Medikament wurden zwei Modellsysteme getestet: Paracetamol-Betacyclodextrin und Vinburnin-Gammacyclodextrin. DSC erlaubt es, sowohl die Wechselwirkung als auch die Stöchiometrie der Einschlußverbindung zu bestätigen.

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