Journal of Thermal Analysis and Calorimetry, Vol. 73 (2003) 671–686

THERMAL STUDIES ON MIXTURES OF BENZOIC AND SALICYLIC ACIDS WITH CYCLODEXTRINS

M. K. Rotich[1], *M. E. Brown*[1*] *and B. D. Glass*[2]

[1]Chemistry Department, Rhodes University, Grahamstown 6140, South Africa
[2]School of Pharmacy, James Cook University, Townsville, Queensland 4811, Australia

Abstract

The thermal behaviour of benzoic and salicylic acids is compared with the behaviour of 1:1 molar ratio physical and kneaded mixtures of these acids with each of three different cyclodextrins (β-, hydroxypropyl-β-, and γ-cyclodextrin). Differential scanning calorimetry and thermogravimetry coupled with evolved gas analysis by Fourier transform infrared spectroscopy were used for the thermal studies and X-ray powder diffraction and infrared spectroscopy provided complementary information.

Thermal studies of benzoic acid with the cyclodextrins showed significant interactions in both physical and kneaded mixtures of benzoic acid/β-cyclodextrin and benzoic acid/hydroxypropyl-β-cyclodextrin. Interactions in the kneaded benzoic acid/γ-cyclodextrin mixtures were the most extensive as might be expected for the cyclodextrin with the largest molecular cavity. The results for the salicylic acid/β-cyclodextrin and salicylic acid/hydroxypropyl-β-cyclodextrin mixtures were similar to those for benzoic acid/β-cyclodextrin and benzoic acid/hydroxypropyl-β-cyclodextrin. Again, the kneaded salicylic acid/γ-cyclodextrin mixture showed the most interaction.

Keywords: benzoic acid, cyclodextrins, DSC, IR, salicylic acid, TG, XRD

Introduction

There have been studies of the possible inclusion of a variety of carboxylic acids in the molecular cavities of a variety of cyclodextrins [1]. Benzoic acid (BA) is the obvious choice of the simplest aromatic acid and there is great scope for comparison of its behaviour with less-polar molecules, including benzene itself, and with variously substituted benzoic acids. BA can also be used as the reference guest for comparison of the hosting abilities of different cyclodextrins. α-, β- and γ-cyclodextrins (ACD, BCD and GCD) have been suggested as complexing agents for the resolution of isomers of substituted benzoic acids [2].

Siimer and Kurvits [3] have done a calorimetric study of the formation of complexes of BCD with BA and with sodium benzoate in aqueous solution. Controversy exists over whether the carboxyl group or carboxylate ion enters the BCD cavity ahead of the benzene ring. Their results indicate that BA and BCD form a strong complex in water with a significant enthalpy change, but negligible entropy change. The

---

[*] Author for correspondence: E-mail: m.brown@ru.ac.za

1388–6150/2003/ $ 20.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

dissociation constant of the sodium benzoate–BCD complex is 37 times greater than for the BA–BCD complex and a significant entropy change accompanies complex formation. It is proposed that there is a greater interaction between the interior of the BCD cavity and the benzoate ion than the BA molecule.

The crystal structure of an inclusion complex formed by BCD and BA [4] from a water-ethanol solution showed that the asymmetric unit consisted of 2BCD, 2BA, 0.7 ethanol and 20.65 water molecules. Both BA molecules occupy the central cavities of the BCD molecules with the COOH group directed towards, and protruding through, the narrower rim of the cone. Water molecules stabilize this structure through hydrogen bonding.

Semi-empirical MO calculations [5] were done for ACD and BCD with BA and phenol in the 'head-first' and 'tail-first' positions. Results showed that both ACD complexes and the BCD–BA complex were more stable with the guest in the 'head-first' position. The BCD–phenol complex with the 'tail-first' configuration was the more stable.

Nakai *et al*. [6] studied the interactions of BA and SA (amongst other drugs) after considerable grinding with microcrystalline cellulose and with BCD. They proposed that 1:1 molar ratio inclusion compounds were formed between BA and BCD and between SA and BCD. The study was extended [7] to interactions with tri-O-methyl-β-cyclodextrin (TMCD). 1:1 molar physical mixtures were compared with co-precipitated compounds. The XRD pattern of a physical mixture of BA–TMCD was a superimposition of individual patterns, while the co-precipitated compound had a different crystalline pattern. The DSC curves showed melting of pure BA at 122°C and melting of pure TMCD at 156°C. The co-precipitated compound showed a melting endotherm at 165°C. The inclusion compound was shown to be able to be formed during the heating procedure. Grinding of the physical mixture also had a marked effect on its DSC curve and on its XRD pattern. In a later paper, Nakai *et al*. [8] prepared an inclusion compound of heptakis-(2,6-di-O-methyl)-β-cyclodextrin (DMBCD) with BA by both grinding and heat treatment in sealed tubes. The detailed conditions required are described in [9].

Tsukushi *et al*. [10] used DSC, XRD and IR spectroscopy to study a 1:1 molar ratio physical mixture of BA and tri-O-methyl-β-cyclodextrin (TMCD) (cavity diameter approximately 0.70 nm). A combination of lengthy shaking and grinding resulted in an amorphous BA–TMCD inclusion compound with a glass transition between 58 and 64°C. Crystallization to a metastable phase occurred at about 80°C. There was an irreversible endothermic transition at about 100°C to a stable phase which melted at 174°C.

There is thus no doubt that BA and SA can form inclusion compounds with suitable cyclodextrins. The conditions required for complex formation are more difficult to define, particularly in the solid-state. A detailed study of the thermal behaviour of the substituted aminobenzoic acids: 3-aminobenzoic acid (ABA), 4-aminobenzoic acid, 3-aminosalicylic acid (ASA), 4-aminosalicylic acid and 5-aminosalicylic acid, as well as of the 'parent' benzoic and salicylic acids for reference purposes, has been reported [11]. In this study, three different cyclodextrins (β-, hydroxypropyl-β-, and γ-cyclodextrin, abbreviated in this paper to BCD, HPBCD and GCD, respectively) with different size molecular cavities (see below) were used to prepare 1:1 molar ratio physical and kneaded mixtures with benzoic and salicylic acids. The results of such a study were necessary for comparison with a further study [12] of the thermal behaviour of similarly prepared mixtures of the same three cyclodextrins with isomers of aminosalicylic acid.

The disappearance of the melting endotherm of the potential guest in the DSC curves of the mixture is often used as an indication of host-guest interaction [13]. Measurements of the enthalpy of melting can also be an indication of the amount of guest that has not interacted. Inclusion of a guest in a CD cavity may displace water, so changes in the dehydration endotherms of the CDs may be an additional indication of inclusion [14]. All such indirect indications however, need to be supported by other evidence, such as infrared spectroscopy and X-ray diffraction measurements.

Experimental

Materials

Details of the samples of benzoic acid (BA), salicylic acid (SA) used are given in [11]. Three different cyclodextrins (β-, hydroxypropyl-β-, and γ-cyclodextrins), with the water content, molar masses and molecular cavity sizes given in Table 1, were obtained from Wacker-Chemie GmbH (Munich, Germany). The water content in the cyclodextrin samples was determined by Karl Fischer titration (Mettler DL 18 Karl Fischer Titrator, Mettler-Toledo, Switzerland).

Table 1 Details of the cyclodextrin samples used in this study

Cyclodextrin	Abbreviation	Molar mass/ g mol^{-1}	Water content/ %	Cavity diameter/ Å
β-	BCD	1135	14.9	6.0–6.5
γ-	GCD	1297	11.2	7.5–8.3
Hydroxypropyl-β	HPBCD	1414	9.0	*

* Degree of substitution (DS) is 4.81

Preparation of the cyclodextrin mixtures

1:1 molar ratio physical mixtures were made by mixing the calculated amounts of the dry powder ‘host’ (CD) and ‘guest’ (BA or SA) compounds by shaking and stirring in a test-tube. Grinding was avoided. Kneaded mixtures were prepared using a suitable solvent, in this case, ethanol. The compounds were weighed and transferred into a suitable container, where they were kneaded with sufficient ethanol to make a paste. The mixtures were then placed in an oven at 40 to 50°C overnight to dry, followed by gentle grinding.

Equipment

Thermal analyses were carried out on a Perkin Elmer Series 7 TG and DSC. The TG could be linked to a Perkin Elmer 2000 FTIR via a heated interface and a gas cell (both supplied by Perkin Elmer) and was calibrated in using magnetic standards. Unless otherwise stated, sample masses were between 2 and 5 mg, in an open platinum pan, and the atmosphere was flowing nitrogen. The heating rate used was usually 10 K min^{-1}. DSC experiments were carried out in standard aluminium pans with lids, but uncrimped. Calibration was done using the melting point and enthalpy of melting of indium.

X-ray powder diffraction patterns (using copper K_α radiation) were recorded (for 2θ values from 5 to 60 degrees) for the pure materials and the mixtures with cyclodextrins. IR spectra were also recorded, using a Perkin-Elmer FTIR Spectrum 2000 instrument, for samples compressed in KBr discs.

Results and discussion

Thermal behaviour of benzoic and salicylic acids

The thermal behaviour of the pure acids [11] is summarised in Table 2.

Table 2 Thermal behaviour of benzoic and salicylic acids [11]

Acid	DSC			TG	
	T_{onset}/°C	ΔH/J g^{-1}	ΔH/kJ mol^{-1}	T_{onset}/°C	Mass loss/%
BA	115	131	16	85	98
SA	167	167	23	130	96

Thermal behaviour of the cyclodextrins

When heated in the DSC in nitrogen at 10°C min^{-1} from 50 to 250°C, each of the cyclodextrins (Fig. 1) showed a broad endotherm with the onset temperatures and enthalpy changes given in Table 3. The corresponding TG curves are shown in Fig. 2.

Table 3 Thermal behaviour of the cyclodextrins (see also Table 1)

Cyclodextrin	DSC			TG	
	T_{onset}/°C	ΔH/J g^{-1}	ΔH/kJ mol^{-1}	T_{range}/°C	Mass loss/%
BCD	75	234	266	40–125	11.4
HPBCD	58	58	64	40–120	6.0
GCD	67	56	73	40–120	9.0

Mixtures with cyclodextrins

DSC and TG runs were done on 1:1 molar ratio physical and kneaded mixtures (see section Experimental for preparation) of BA and SA with BCD, HPBCD and GCD. Results for the mixtures were compared with those for the pure constituents recorded under similar conditions.

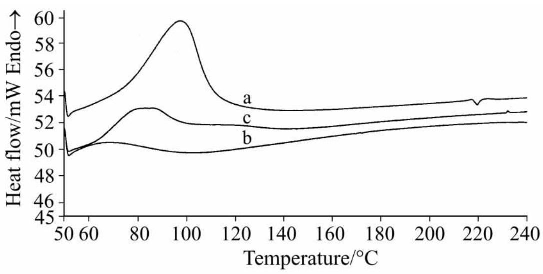

Fig. 1 DSC curves for the cyclodextrins: a – BCD; b – HPBCD and c – GCD (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

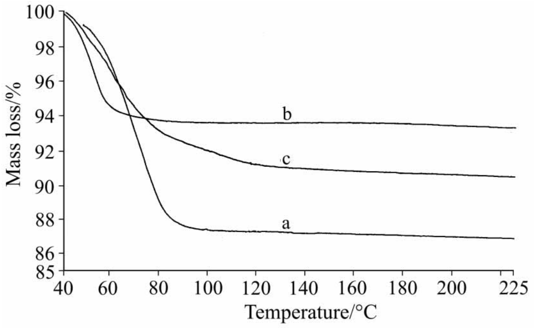

Fig. 2 TG curves for the cyclodextrins: a – BCD; b – HPBCD and c – GCD (heated in flowing nitrogen at 10 K min^{-1} in open platinum pans)

Mixtures of benzoic acid with the cyclodextrins

Representative thermal analysis results are illustrated and the quantitative information extracted from these results is summarised in Table 4. Figure 3 shows the DSC curves for the 1:1 molar ratio physical and kneaded mixtures of BA with BCD. The DSC curve for BCD alone, curve a, shows a dehydration endotherm from 50 to 120°C, with ΔH=266 kJ mol^{-1} and a reversible transition exotherm around 220°C. The DSC curve for BA, curve d, shows a sharp melting endotherm (ΔH=16 kJ mol^{-1}, onset 117°C). The DSC curve for the physical mixture, curve b, shows a dehydration endotherm at 64 to 104°C, with ΔH=238 kJ (mol BCD)$^{-1}$ and a much decreased endotherm at onset 122°C (*m.p.* of BA) with ΔH=14 kJ (mol BA)$^{-1}$. The kneaded mixture, curve c, showed a dehydration endotherm at about 60 to 111°C with ΔH=243 kJ (mol BCD)$^{-1}$ and very small endotherm onset 122°C with ΔH about 1 kJ (mol BA)$^{-1}$. The decrease in the endotherm associated with the melting of BA is an indication of an interaction between BA and BCD. The TG and DTG curves (not illustrated) show an initial mass loss for the physical mixture from 48 to 80°C of 12%. The total mass loss at 125°C is about 20%, i.e. a further 8%. This further loss is less than the expected value for almost complete sublimation/evaporation/decomposition of 10% by mass of BA in the mixture, but the total of 20% is very close to that expected from the behaviour of the individual constituents. The TG curve for the

Table 4 Summary of the expected and observed thermal behaviour of 1:1 molar ratio mixtures of BA and SA with cyclodextrins (*p*=physical mixture and *k*=kneaded mixture)

1:1 mixtures		Expected			Observed			
Mixture	Acid by mass/ %	Mass loss CD/ %	$\Delta H_{\mathrm{dehyd.}}$/ kJ (mol CD)$^{-1}$	ΔH_{melt}/ kJ (mol acid)$^{-1}$	Mass loss CD/%		$\Delta H_{\mathrm{dehyd.}}$/ kJ (mol CD)$^{-1}$	ΔH_{melt}/ kJ (mol acid)$^{-1}$
BA/BCD	9.7	10.3	266	16	*p*	12.0	234	14
					k	8.5	243	1
BA/HPBCD	7.9	5.5	64	16	*p*	6	158	0
					k	5	63	0
BA/GCD	8.6	8.2	73	16	*p*	10	74	20
					k	4	0	0
SA/BCD	10.8	10.2	266	23	*p*	12	281	9
					k	13	74	0
SA/HPBCD	8.9	5.5	64	23	*p*	12	19	0
					k	2	0	0
SA/GCD	9.6	8.1	73	23	*p*	14	123	2
					k	5	0	0

kneaded mixture shows an initial mass loss of 8.5% from 50 to 80°C. This value is slightly less than the expected value of 10% (given above). The total mass loss is 13.5% (i.e. a further loss of 5%), which is less than the expected value of 20%. The measured values are compared with the expected values, calculated from the proportions of the constituents of the mixtures in Table 4.

Interaction between BA and BCD is indicated in both the physical and the kneaded mixtures as shown by both the DSC and TG results. At the very least, this interaction causes a decrease in the extent and rate of evaporation of BA.

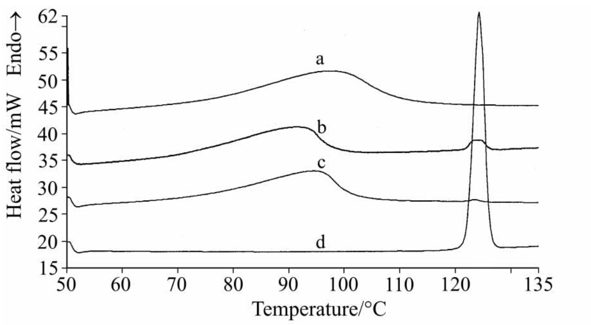

Fig. 3 DSC curves for the pure components and for 1:1 molar ratio mixtures of BA with BCD: a – pure BCD; b – physical mixture; c – kneaded mixture and d – pure BA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

The DSC curves for the 1:1 molar ratio physical and the kneaded mixtures of BA with HPBCD (Fig. 4) are qualitatively similar to Fig. 3. The DSC curve for HPBCD (Fig. 4, curve a) shows an endotherm from 55 to 100°C with ΔH=64 kJ mol^{-1}. It also shows a very small double reversible transition exotherm around 170°C, not accompanied by a mass loss, as shown by the TG curve [11], (Fig. 2, curve b). The DSC curve for the physical mixture (Fig. 4, curve b) shows a broad dehydration endotherm from 53 to 111°C, with ΔH=158 kJ $(\text{mol HPBCD})^{-1}$ and no endotherm associated with the melting of BA. The absence of the endotherm associated with the melting of BA is an indication of interaction between BA and HPBCD. Similar results for the kneaded mixture (Fig. 4, curve c) show the absence of the endotherm associated with the melting of BA, but there is a broad dehydration endotherm from 53 to 102°C, with ΔH=63 kJ $(\text{mol HPBCD})^{-1}$.

The TG curves for the 1:1 molar ratio BA/HPBCD mixtures (not illustrated) show that the mass losses are greatly decreased in both, the physical and the kneaded mixtures. For the physical mixture, the mass loss from 48 to 95°C of about 6% is close to the expected value of 5.5% for the loss of water from the mixture containing 92.1% by mass of HPBCD. The total mass loss of 7% at 140°C (i.e a further loss of 1%), is significantly less than the expected value for almost complete evaporation /decomposition of 8% by mass of BA in the mixture. For the kneaded mixture, the initial mass loss is about 5% from 50 to 110°C. This value is similar to that of the physical mixture. The total mass loss of about 6% (i.e loss of a further 1%) is less than the expected value for 8% mass loss of BA from the mixture. The conclusion reached

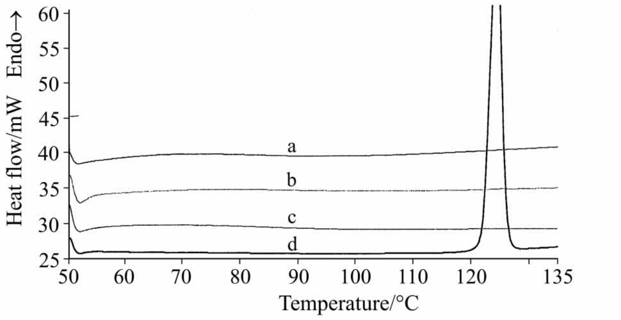

Fig. 4 DSC curves for the pure components and for 1:1 molar ratio mixtures of BA with HPBCD: a – pure HPBCD; b – physical mixture; c – kneaded mixture and d – pure BA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

from both DSC and TG curves is that there is significant interaction between BA and HPBCD. These results are summarised in Table 4.

The DSC curve for pure GCD (Fig. 5, curve a) shows a broad dehydration endotherm from 60 to 110°C, with ΔH=73 kJ mol^{-1}. There is also a very small reversible transition endotherm around 230°C. The DSC curve for the 1:1 molar ratio physical mixture of BA/GCD (curve b) shows two endotherms: a dehydration endotherm from 62 to 97°C, with ΔH about 74 kJ $(\mathrm{mol\ GCD})^{-1}$ and an endotherm with onset at 62°C, with ΔH about 20 kJ $(\mathrm{mol\ BA})^{-1}$. The DSC curve for the kneaded mixture (curve c) shows no dehydration endotherm as well as no endotherm associated with the melting of BA. There is greater interaction between BA and GCD than in the physical mixture.

The TG curves for the 1:1 molar ratio physical and kneaded mixtures of BA and GCD (not illustrated) show an initial mass loss for the physical mixture of 10% from 55 to 110°C. This is close to the value of 8.2% expected for the loss of water from GCD in the mixture containing 91.4% by mass of GCD. There is no additional mass loss at about 140°C, hence no mass loss related to evaporation of BA. For the kneaded mixture, the initial mass loss of 4% from 42 to 70°C is less than the expected 8.2% (see above). The total mass loss at 140°C is about 5% (i.e. a further loss of 1%). Evap-

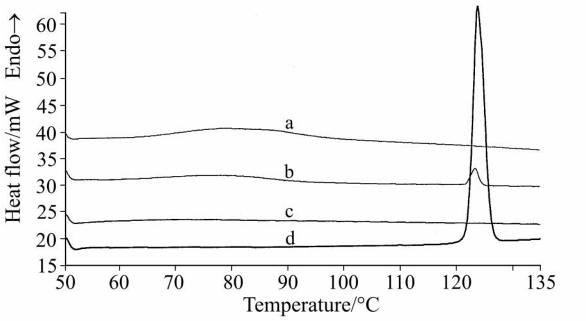

Fig. 5 DSC curves for the pure components and for 1:1 molar ratio mixtures of BA with GCD: a – pure GCD; b – physical mixture; c – kneaded mixture and d – pure BA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

oration of all the BA would lead to a mass loss of 8.6%. There is thus an extensive interaction between BA and GCD in the kneaded mixtures as shown by both the DSC and TG results, which are summarised in Table 4.

Mixtures of salicylic acid with the cyclodextrins

The DSC curve for SA (Fig. 6, curve d) shows the sharp melting endotherm of SA with onset 158°C. The DSC curve for a 1:1 molar ratio physical mixture of SA with BCD (Fig. 6, curve b) shows two endotherms: a dehydration endotherm from 61 to 114°C, with ΔH=281 kJ (mol BCD)$^{-1}$ and a very small endotherm with onset at 144°C, with ΔH about 9 kJ (mol SA)$^{-1}$. The DSC curve for the kneaded mixture (curve c) shows a broad double (overlapped) dehydration endotherm from 63 to 118°C, with ΔH=74 kJ (mol BCD)$^{-1}$. The absence of the endotherm associated with the melting of SA is an indication of an interaction between SA and BCD.

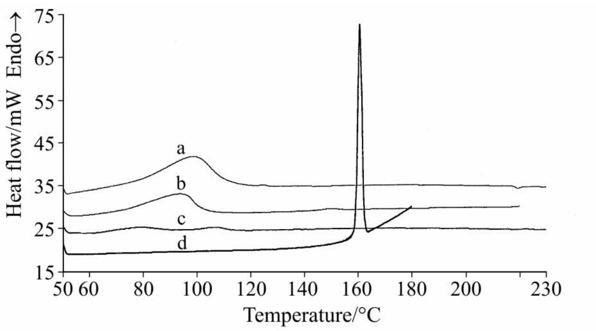

Fig. 6 DSC curves for the pure components and for 1:1 molar ratio mixtures of SA with BCD: a – pure BCD; b – physical mixture; c – kneaded mixture and d – pure SA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

The TG curve for the 1:1 molar ratio physical mixture of SA with BCD (not illustrated) shows a two-stage mass loss, the first stage between 46 and 60°C (4%) and the second between 60 and 80°C (8%). The overall mass loss from 60 to 80°C is close to the expected value of 10% for the loss of water from the BCD in the mixture containing 89.2% BCD. The total mass loss at 140°C is about 22% (i.e. a further loss of 10%). This is close to the expected value for almost complete evaporation/decomposition of 11% SA by mass in the mixture. The TG curve for the kneaded mixture shows mass losses to occur in three stages from 47 to 130°C. The mass loss from 47 to 50°C is about 1%, the mass loss from 50 to 80°C is about 3% and the last mass loss is about 7% from 80 to 130°C. Mass was lost slowly after this temperature (130°C) and by 220°C, a total of 16% (i.e. a further loss of 3%) had been lost. This is less than the 11% which would have accompanied the complete evaporation/decomposition of SA. The changes in thermal behaviour of the individual components in the mixture indicate interaction between the two compounds. These results are summarised in Table 4.

The DSC curves for the 1:1 molar ratio physical and the kneaded mixtures of SA with HPBCD are shown in Fig. 7. The DSC curve for the physical mixture (curve b) shows a dehydration endotherm from 53 to 80°C, with ΔH=19 kJ (mol HPBCD)$^{-1}$ and no other endotherm was observed. The DSC curve for the kneaded mixture (curve c) did not show any endotherm associated either with dehydration of the HPBCD (curve a) or the melting of SA (curve d).

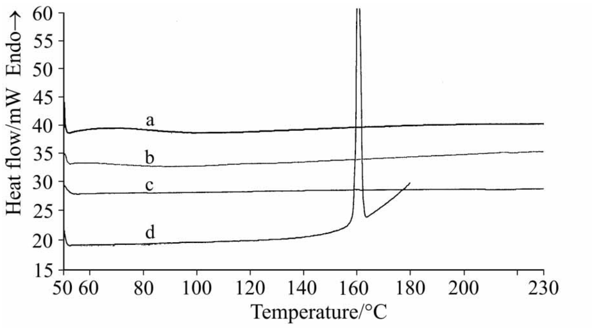

Fig. 7 DSC curves for the pure components and for 1:1 molar ratio mixtures of SA with HPBCD: a – pure HPBCD; b – physical mixture; c – kneaded mixture and d – pure SA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

The physical mixture undergoes a mass loss from 45 to 70°C of about 5% and another mass loss from 70 to 120°C of 7%. This total mass loss of 12% is much higher than the expected mass loss of 5.5% for the loss of water in pure HPBCD in the mixture containing 91.1% by mass of HPBCD. The curve also does not show any mass loss above 140°C. For the kneaded mixture, the mass loss from 48 to 120°C is 2%, which is less than the value expected of 5.5%. The total mass loss of 5% by 220°C, is less than the expected value for the complete evaporation/decomposition of 9% by mass of HPBCD in the mixture. The thermal behaviour indicates interaction between SA and HPBCD. These results are summarised in Table 4.

The DSC curve for pure GCD (Fig. 8, curve a) shows a dehydration endotherm from 60 to 110°C, with ΔH=73 kJ mol^{-1}. The DSC curve for the 1:1 molar ratio physical mixture (curve b) shows a dehydration endotherm from 61 to 130°C, with ΔH=123 kJ (mol GCD)$^{-1}$ and a very small endotherm, with onset at 141°C and ΔH about 2 kJ (mol SA)$^{-1}$. The DSC curve for the kneaded mixture (curve c) is almost featureless. The absence of the endotherm associated with the melting of SA in the curve for the kneaded mixture is an indication of interaction between SA and GCD.

The TG curve for the physical mixture (not illustrated) shows a mass loss of 5% from 50 to 85°C, followed by another mass loss of 9% between 85 and 140°C. The total mass loss by 140°C is 14%. The mass losses expected from the behaviour of the components would be 8.1 and 9.6%. For the kneaded mixture, the mass loss occurs in two stages, with the first loss being 2% followed by a further mass loss of 3%. This is less than the expected value of 8% for the loss of water from pure GCD in the mixture containing 90.4% by mass of GCD. A mass loss related to the total evaporation/de-

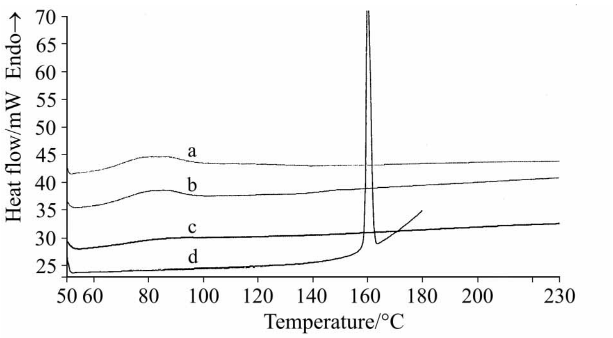

Fig. 8 DSC curves for the pure components and for 1:1 molar ratio mixtures of SA with GCD: a – pure GCD; b – physical mixture; c – kneaded mixture and d – pure SA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

composition of the 9.6% SA is not observed and this indicates that an interaction has occurred. These results are summarised in Table 4.

X-ray powder diffraction studies

The cyclodextrins

The X-ray powder patterns for the three cyclodextrins are shown in Fig. 9. BCD is the most crystalline of the three and HPBCD the least. Interaction between a guest molecule and a cyclodextrin host will usually change the crystalline structure of the CD and hence the X-ray diffraction pattern. The diffuse nature of an X-ray powder pattern may be an indication of inclusion of a guest molecule into the cavity of the host compounds (CD), but changes may also result from the mixing process, especially when kneading is involved. From comparisons of the patterns for the pure components and their physical and kneaded mixtures, it may be possible to infer if there is an interaction between the two components. All the mixtures were in 1:1 molar ratios and were prepared as described under experimental.

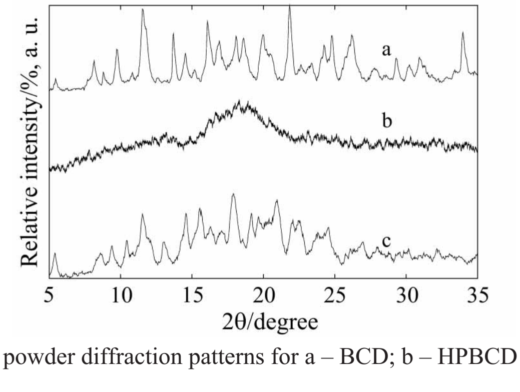

Fig. 9 X-ray powder diffraction patterns for a – BCD; b – HPBCD and c – GCD

Mixtures of benzoic acid with the cyclodextrins

Figure 10 shows the X-ray powder diffraction patterns of the pure components and of the mixtures of benzoic acid with BCD. The XRD patterns for the physical mixture contains mainly superimposed features of the pure components. The pattern for the kneaded mixture is different and indications are that there is significant interaction between BA and BCD after such treatment.

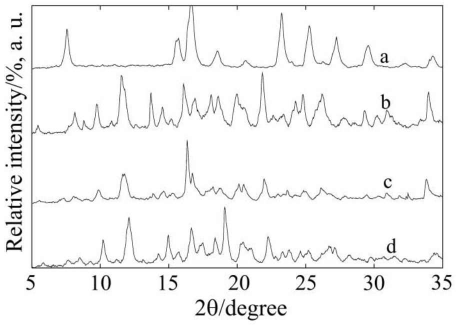

Fig. 10 X-ray powder diffraction patterns for a – BA; b – BCD; c – BA/BCD physical mixture and d – BA/BCD kneaded mixture (mixtures are 1:1 molar ratios)

The XRD pattern of HPBCD (Fig. 11) is diffuse to start with so changes are difficult to determine. The absence of even the strongest reflections of BA suggests interaction resulting in a still amorphous compound.

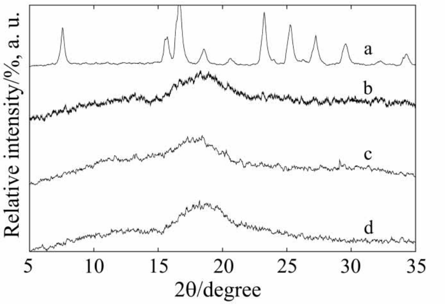

Fig. 11 X-ray powder diffraction patterns for a – BA; b – HPBCD; c – BA/HPBCD physical mixture and d – BA/HPBCD kneaded mixture (mixtures are 1:1 molar ratios)

The XRD pattern of the physical mixtures of BA with GCD (Fig. 12) shows many of the features of the pure components, while the pattern for the kneaded mixture is much more diffuse indicating a less-crystalline compound.

Mixtures of salicylic acid with the cyclodextrins

Figure 13 shows the X-ray powder diffraction patterns of the pure components and of the 1:1 molar ratio mixtures of salicylic acid (SA) with BCD. The XRD pattern of the

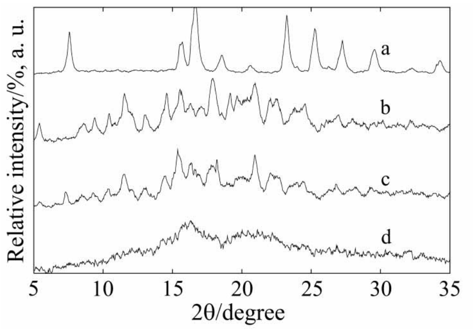

Fig. 12 X-ray powder diffraction patterns for a – BA; b – GCD; c – BA/GCD physical mixture and d – molar BA/GCD kneaded mixture (mixtures are 1:1 molar ratios)

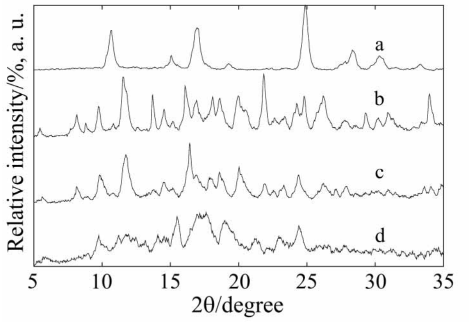

Fig. 13 X-ray powder diffraction patterns for a – SA; b – BCD; c – SA/BCD physical mixture and d – SA/BCD kneaded mixture (mixtures are 1:1 molar ratios)

physical mixture shows some of the features of the pure components and the pattern of the kneaded mixture shows the greatest changes with decreasing crystallinity.

The XRD pattern for the kneaded mixture of SA with HPBCD (Fig. 14) is diffuse and similar to HPBCD. The pattern of the physical mixture indicates less interaction between SA and HPBCD. Behaviour is very similar to that of BA/HPBCD.

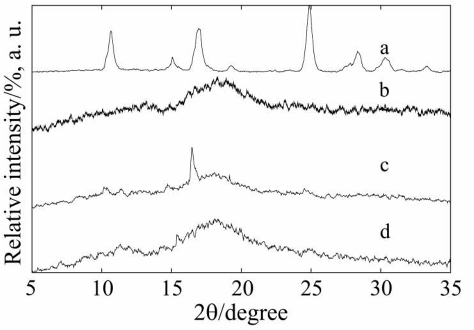

Fig. 14 X-ray powder diffraction patterns for a – SA; b – HPBCD; c– SA/HPBCD physical mixture and d – SA/HPBCD kneaded mixture (mixtures are 1:1 molar ratios)

The XRD pattern for the physical mixture of SA with GCD (Fig. 15) shows superimposed features of the pure components but is more diffuse than that of the physical mixture. The peak for SA at about 24° is prominent in the XRD pattern of the kneaded mixture. Indications are that interaction between SA and GCD is not as extensive as between BA and GCD (Fig. 12).

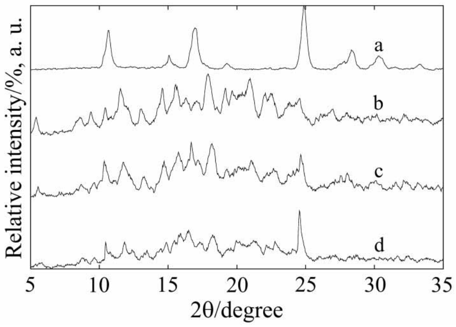

Fig. 15 X-ray powder diffraction patterns for a – SA; b – GCD; c – SA/GCD physical mixture and d – SA/GCD kneaded mixture (mixtures are 1:1 molar ratios)

Comparison of the XRPD patterns for the kneaded mixtures of BA and of SA with the cyclodextrins shows that the extent of interaction with a given cyclodextrin does differ for the two acids.

Infrared spectroscopic studies

The use of infrared spectroscopy (IR) is not always suitable for the study of inclusion because the absorption bands arising from the cyclodextrin structure may interfere with the bands of any included molecule. The C=O (carbonyl carbon) absorption region (around 1700 cm^{-1}) is sometimes useful for studying the interactions of the guest and host compounds [12]. In this study many infrared spectra were recorded and examined, but the shielding effect of the cyclodextrins on the spectral features of the acids was too great for any conclusions to be drawn regarding interactions.

Discussion

The thermal behaviour of the mixtures can provide an indication of possible inclusion of the potential guest molecules into the cavities of the cyclodextrins, although other types of interaction cannot be ruled out. Generally, the kneaded mixtures would be expected to show greater changes in thermal behaviour. The main, not entirely conclusive, indication of interaction is the disappearance of the melting endotherm of the potential guest in the DSC curves of the mixture. In ideal situations, one could determine the amount of interaction by varying the proportions of guest to host and using any measured enthalpy of melting as an indication of the amount of guest that has not interacted. Inclusion of a guest in a CD cavity will also generally displace all or some of the water originally in the cavity, so changes in the expected dehydration endotherms of the CDs in the DSC curves of the mixtures may be an additional indication of inclusion.

Confirmation of interactions, such as inclusion, requires use of additional techniques such as IR and XRPD. The most conclusive evidence comes from single-crystal X-ray structure determinations. Indications from XRPD patterns of the formation of a non-crystalline powder are also not conclusive evidence of inclusion, because these changes could be the result of grinding and/or kneading.

The results summarised in Table 4 indicate that there are interactions in 1:1 molar ratio mixtures of BA and SA with all three cyclodextrins. Changes in thermal behaviour are generally greater for kneaded mixtures than for physical mixtures. The main change is disappearance of the melting endotherm of BA or of SA in the DSC curves for the kneaded mixtures. In some mixtures, the endotherms corresponding to dehydration of the CD were decreased in size. This could result from displacement of water from the cavity of the CD by inclusion of BA or SA, or a decrease in the energy requirements for dehydration in the presence of BA or SA.

The exception to this trend is the behaviour of the SA/GCD mixtures where the enthalpy of dehydration was increased. This could indicate the inclusion of additional atmospheric moisture during the mixing process or formation of hydrate of guest molecule, which then is included in the CD cavity. There is evidence that kneading process can displace water from the CDs and alter their crystallinity.

HPBCD had the greatest effect on the behaviour of both BA and SA, even in physical mixtures. Physical mixing of SA was more successful in producing interaction than physical mixing of BA. It would appear, very qualitatively, that the additional –OH group in SA enhances interaction with CDs.

From thermal analysis it is, of course, not possible to separate the interactions caused by mixing from those produced by subjecting the mixture (be it physical or kneaded) to a heating programme. It is here that XRD and IR results on unheated mixtures can provide important information at the molecular level. Determining whether some kind of interaction may have occurred is relatively simple compared to determining the nature of the interaction.

TG can support the indications of DSC by providing quantitative information on the water content of the CD, which could be expected to be changed by the occurrence of inclusion. TG can also reveal the extent of evaporation/decomposition of the guest from the mixture. The guest must, of course, undergo some thermal event, such as melting or vaporisation at temperatures below those at which CD itself degrades [14].

References

1 K. B. Lipkowitz, Chem. Rev., 98 (1998) 1829.
2 S. Fanali and M. Sinibaldi, J. Chromatogr. A, 442 (1988) 371.
3 E. Siimer and M. Kurvits, Thermochim. Acta, 116 (1987) 249.
4 T. Aree and N. Chaichit, Carbohyd. Res., 338 (2003) 439.
5 M.-J. Huang, J. D. Watts and N. Bodor, Int. J. Quantum Chem., 65 (1997) 1135.

6 Y. Nakai, S. Nakajima, K. Yamamoto, K. Terada and T. Konno, Chem. Pharm. Bull., 26 (1978) 3419.
7 Y. Nakai, K. Yamamoto, K. Terada and H. Horibe, Inclusion Phen., 2 (1984) 523.
8 Y. Nakai, S. Nakajima, T. Oguchi, E. Yonemochi and T. Hanawa, Chem. Pharm. Bull., 39 (1991) 1532.
9 T. Hanawa, E. Yonemochi, T. Oguchi, Y. Nakai and K. Yamamoto, J. Incl. Phen. Mol. Recog. Chem., 15 (1993) 91.
10 I. Tsukushi, O. Yamamuro and H. Suga, Thermochim. Acta, 200 (1992) 71.
11 M. K. Rotich, B. D. Glass and M. E. Brown, J. Therm. Anal. Cal., 64 (2001) 681.
12 M. K. Rotich, B. D. Glass and M. E. Brown, J. Therm. Anal. Cal., 73 (2003) 687.
13 F. Giordano, G. Bruni and G. P. Bettinetti, J. Thermal Anal., 38 (1992) 2683.
14 S. Li and W.C. Purdy, Chem. Rev., 92 (1992) 1457.
15 S. M. Botella, M. A. Martin, B. del Catillo, J. C. Mendez, L. Vazquez and D. A. Lerner, J. Pharm. Biomed. Anal., 14 (1996) 909.
16 J. Li, N. Zhang, X. Li, J. Wang and S. Tian, J. Thermal Anal., 49 (1997) 1527.
17 L. Szente, Comprehensive Supramolecular Chemistry, Ed. J. L. Atwood, Pergamon, New York 1996, Chapter 7.