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THERMAL STUDIES ON MIXTURES OF AMINOSALICYLIC 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]Glass School of Pharmacy, James Cook University, Townsville, Queensland 4811, Australia

Abstract

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

Comparison of the effects of the different cyclodextrins on the behaviour of the individual aminosalicylic acid isomers shows that hydroxypropyl-β-cyclodextrin has the greatest interaction with 3-aminosalicylic acid and 5-aminosalicylic acid, followed by γ-cyclodextrin, while β-cyclodextrin generally shows the least interaction. For 4-aminosalicylic acid, the effect of γ-cyclodextrin seems to be more marked than for 3-aminosalicylic acid and 5-aminosalicylic acid.

Keywords: aminosalicylic acids, cyclodextrins, decarboxylation, DSC, TG, XRD

Introduction

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 the ‘parent’ benzoic and salicylic acids for reference purposes, has been reported [1]. In addition to their pharmaceutical uses [1–9], such reactants are of interest because the existence of ranges of isomers allows for comparison of behaviour. In this study, three different cyclodextrins (β-, hydroxypropyl-β-, and γ-cyclodextrin, abbreviated to BCD, HPBCD and GCD, respectively) with different size cavities (see below) were used. The composition and method of preparation of the drug/cyclodextrin mixtures are important and 1:1 molar ratios of drug to cyclodextrin have been tested in simple physical mixtures and in mixtures prepared by kneading the constituents in the presence of ethanol (see below). Results are compared with the behaviour of mixtures of benzoic (BA) and salicylic (SA) acids with the same three cyclodextrins [10].

Zerrouk *et al.*[11] attempted to prepare inclusion complexes of 5-aminosalicylic acid (5-ASA) with α-cyclodextrin (ACD) and BCD, from aqueous solution and by a kneading method. 5-ASA is sensitive to both light and oxygen and complex formation with CDs is expected to improve its stability. The DSC curve for 5-ASA showed sharp

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

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melting at 297°C. This melting endotherm was not observed in the DSC curves of 1:1 molar ratio physical mixtures of 5-ASA/ACD and 5-ASA/BCD. The authors point out that this is usually regarded as evidence of inclusion, but that inclusion could occur because of the heating process rather than the physical mixing [12]. Both solution and solid-state studies suggested that there was greater interaction of 5-ASA with BCD than with ACD. This was supported by observations using hot-stage microscopy and SEM. Electron-spray mass spectrometry gave peaks corresponding to both 5-ASA/ACD and 5-ASA/BCD complexes. XRD patterns of the kneaded and physical mixtures indicated that kneading increased the extent of complexation.

An indication of host-guest interaction is the disappearance of the melting endotherm of the potential guest in the DSC curves of the mixtures. Measurements of the enthalpy of melting are 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.

Experimental

Materials

Details of the aminosalicylic acids (ASA) used are given in [1] and of the cyclodextrins (BCD, HPBCD and GCD) in [10].

Preparation of drug/cyclodextrin mixtures

1:1 molar ratio physical and kneaded mixtures of the samples and cyclodextrins were prepared as described in [10].

Equipment

Thermal analyses were carried out on a Perkin Elmer Series 7 TG (linked to a Perkin Elmer 2000 FTIR via a heated interface and a gas cell) and DSC as described in [10].

X-ray powder diffraction patterns and IR spectra were recorded for the pure materials and their mixtures as described in [10].

Results and discussion

Thermal behaviour of the aminosalicylic acids

The thermal behaviour of the aminosalicylic acids [1] is summarised in Table 1.

Table 1 Thermal behaviour of the aminosalicylic acids [1]

Acid	DSC			TG	
	T_{onset}/°C	ΔH/J g^{-1}	ΔH/kJ mol^{-1}	T_{onset}/°C	Mass loss/%
3-ASA	220	607	92.8	180	95
4-ASA	133	168	25.6	120	100
5-ASA	270	579	88.6	190	100

Thermal behaviour of the cyclodextrins

The thermal behaviour of the individual cyclodextrins has been described in detail and illustrated in [10]. The main results are summarised in Table 2.

Table 2 Thermal behaviour of the cyclodextrins [10]

Cyclodextrin	DSC			TG	
	T_{onset}/°C	ΔH/J g^{-1}	ΔH/kJ mol^{-1}	T_{range}/°C	Mass loss/%
BCD	75	234	266	40–130	11.4
HPBCD	58	45	64	40–120	6.0
GCD	67	56	73	40–120	9.0

Mixtures with cyclodextrins

DSC and TG runs were performed on 1:1 molar ratio physical and kneaded mixtures ([10], Experimental, for preparation) of 3-ASA, 4-ASA and 5-ASA with BCD, HPBCD and GCD. Results for the mixtures are compared qualitatively with those for the pure constituents, recorded under similar conditions, and with the results obtained [10] for 1:1 molar ratio mixtures of benzoic and salicylic acids with the same three cyclodextrins. Quantitative details are given in Tables 3, 4 and 5.

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 [13]. 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 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 [14]. Care has to be taken to explore the possible influences of the kneading process, which can alter the water content and affect the crystallinity of the CDs.

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.

Table 3 Summary of the expected and observed thermal behaviour of 1:1 molar ratio mixtures of 3-ASA with the cyclodextrins (*p*=physical mixture and *k*=kneaded mixture

1:1 molar ratio mixtures		Expected			Observed		
Mixture	Acid by mass/%	Mass loss CD/%	$\Delta H_{dehyd.}$/ kJ (mol CD)$^{-1}$	ΔH_{melt}/ kJ (mol acid)$^{-1}$	Mass loss CD/%	$\Delta H_{dehyd.}$/ kJ (mol CD)$^{-1}$	ΔH_{melt}/ kJ (mol acid)$^{-1}$
3-ASA/BCD	11.9	10.0	266	92.8	*p* 8.5 *k* 2.0	252 0	59 69
3-ASA/HPBCD	9.8	5.4	64	92.8	*p* 5.0 *k* 5.0	100 61	5 0
3-ASA/GCD	10.6	8.1	73	92.8	*p* 7.0 *k* 3.0	163 65	69 10

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

1:1 molar ratio mixtures		Expected			Observed		
Mixture	Acid by mass/%	Mass loss CD/%	$\Delta H_{dehyd.}$/ kJ (mol CD)$^{-1}$	ΔH_{melt}/ kJ (mol acid)$^{-1}$	Mass loss CD/%	$\Delta H_{dehyd.}$/ kJ (mol CD)$^{-1}$	ΔH_{melt}/ kJ (mol acid)$^{-1}$
4-ASA/BCD	11.9	10.0	266	25.6	*p* 5.5 *k* 2.0	184 181	32 14
4-ASA/HPBCD	9.8	5.4	64	25.6	*p* 5.5 *k* 1.0	36 0	89 0
4-ASA/GCD	10.6	8.1	73	25.6	*p* 5.0 *k* 12.0	69 182	0 0

Table 5 Summary of the expected and observed thermal behaviour of 1:1 mole ratio mixtures of 5-ASA with the cyclodextrins (*p*=physical mixture and *k*=kneaded mixture)

1:1 molar ratio 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)$^{-1}$
5-ASA/BCD	11.9	10.0	266	88.6	*p* 13.0 *k* 12.0	255 199	199 122
5-ASA/HPBCD	9.8	5.4	64	88.6	*p* 13.5 *k* 6.0	72 52	0 0
5-ASA/GCD	10.6	8.1	73	88.6	*p* 5.0 *k* 6.0	61 120	80 67

Mixtures of the aminosalicylic acids with the cyclodextrins

The DSC curves of the aminosalicylic acid isomers, 3-ASA, 4-ASA and 5-ASA [1], (in uncrimped aluminium pans) are compared in Fig. 1. The DSC curve for 3-ASA (Fig. 1, curve a) shows an endotherm with onset at 220°C, followed by an exotherm. The DSC curve for 4-ASA (curve b) shows a melting endotherm with onset 133°C and ΔH=26 kJ mol^{-1}. The DSC curve for 5-ASA (curve c) shows an endotherm with ΔH=89 kJ mol^{-1} and onset 270°C.

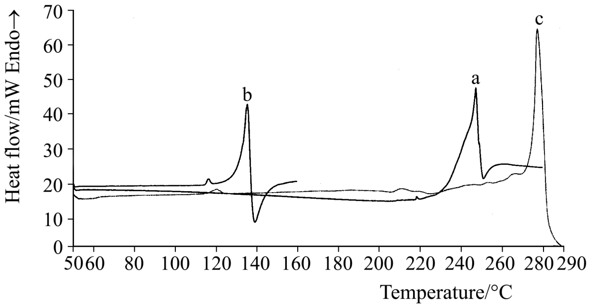

Fig. 1 DSC curves for the aminosalicylic acids: a – 3-ASA; b – 4-ASA and c – 5-ASA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

The TG curves for the aminosalicylic acid isomers are compared in Fig. 2.

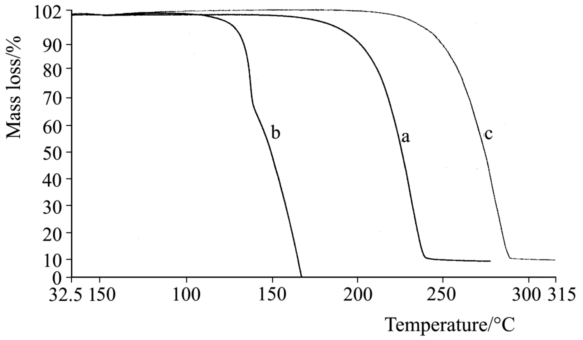

Fig. 2 TG curves for the aminosalicylic acids: a – 3-ASA; b – 4-ASA and c – 5-ASA (heated in flowing nitrogen at 10 K min^{-1} in open platinum pans)

Mixtures of 3-aminosalicylic acid (3-ASA) with the cyclodextrins

The DSC curve for a 1:1 molar ratio physical mixture of 3-ASA and BCD (Fig. 3, curve b) shows a dehydration endotherm between 70 and 110°C and a broad endotherm overlapping with the BCD reversible transition exotherm around 220°C (curve a). The curve for the kneaded mixture (curve c) exhibits no dehydration endotherm, but shows the BCD reversible transition exotherm around 220°C near the onset of a broad 3-ASA melting endotherm at 229°C. The broadening of the endotherm associated with the melt-

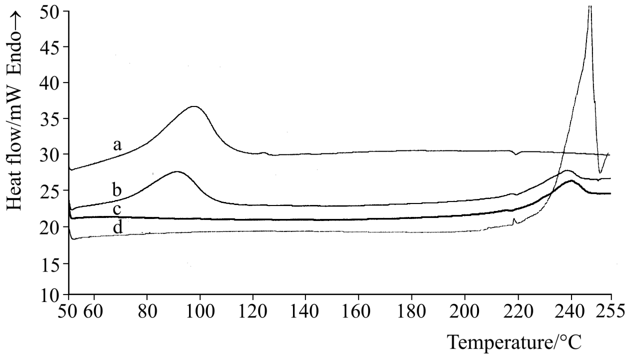

Fig. 3 DSC curves for the pure components and for 1:1 molar ratio mixtures of 3-ASA with BCD: a – pure BCD; b – physical mixture; c – kneaded mixture and d – pure 3-ASA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

ing of 3-ASA (curve d) is an indication of some, but not extensive, interaction in both mixtures. The disappearance of the dehydration endotherm for BCD in the DSC curve for the kneaded mixture could indicate that the water has been displaced from the BCD cavity during the kneading process. This displacement could be by 3-ASA molecules or by the kneading solvent (ethanol). If the latter was the reason, some indication should be seen of the endothermic removal of the solvent.

The TG curve for a 1:1 molar ratio kneaded mixture of 3-ASA with BCD (not illustrated) confirms the displacement of water from the BCD cavity and shows no indication that the kneading solvent was retained. Details of the mass-losses are given in Table 3.

The DSC curve for a 1:1 molar ratio physical mixture of 3-ASA with HPBCD (Fig. 4, curve b) shows a dehydration endotherm and a much decreased melting endotherm for 3-ASA (compare curve d) from 218 to 230°C. The curve for the kneaded mixture (curve c) shows a dehydration endotherm between 53 and 97°C. No

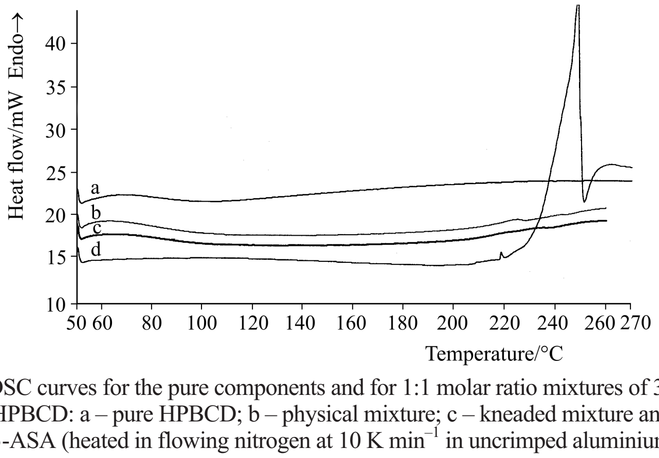

Fig. 4 DSC curves for the pure components and for 1:1 molar ratio mixtures of 3-ASA with HPBCD: a – pure HPBCD; b – physical mixture; c – kneaded mixture and d – pure 3-ASA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

endotherm associated with the melting of 3-ASA is visible. The decrease in the dehydration endotherm of HPBCD and the virtual disappearance of the melting endotherm of 3-ASA are indications of interaction in the mixtures. The increased dehydration endotherm of the physical mixture could indicate that the remaining water in the cavity interacts with the ASA present, thus inhibiting its removal. The TG results (not illustrated, but summarized in Table 3) showed no significant differences between physical and kneaded mixtures.

The DSC curve for a 1:1 molar ratio physical mixture of 3-ASA with GCD (Fig. 5, curve b) shows a dehydration endotherm between 60 and 139°C and an endotherm associated with melting of 3-ASA (onset 226°C). For the kneaded mixture (curve c), the dehydration endotherm is from 53 to 102°C and a small broad endotherm at onset 223°C. Broadening of the melting endotherm for 3-ASA is an indication of some, but not extensive, interaction in the mixtures. The decreased enthalpy values (Table 5) for dehydration of GCD in the kneaded mixtures is an indication of water displacement from the GCD cavity by either 3-ASA or the kneading solvent (ethanol). The TG results are summarised in Table 5.

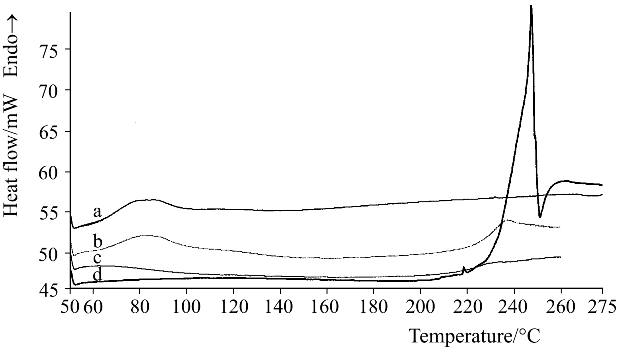

Fig. 5 DSC curves for the pure components and for 1:1 molar ratio mixtures of 3-ASA with GCD: a – pure GCD; b – physical mixture; c – kneaded mixture and d – pure 3-ASA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

Mixtures of 4-aminosalicylic acid (4-ASA) with the cyclodextrins

The DSC curve for a 1:1 molar ratio physical mixture of 4-ASA and BCD (Fig. 6, curve b) shows a dehydration endotherm from 64 to 102°C. There was no evidence of the normal melting endotherm of 4-ASA (compare curve d) at about 133°C but there was a double endotherm (complex) (onset 156°C). The curve for the kneaded mixture (Fig. 6, curve c) showed a dehydration endotherm from 73 to 108°C and a broad complex endotherm from 148 to 164°C. The absence of endotherms associated with the melting of 4-ASA is an indication of an interaction between 4-ASA and BCD. This is supported by the slight decrease in the enthalpy values for the dehydration of BCD (Table 4) that could indicate the displacement of water in the CD cavity by a guest compound. The TG results (not illustrated, but summarized in Table 4) indicate interaction between 4-ASA and BCD for both mixtures.

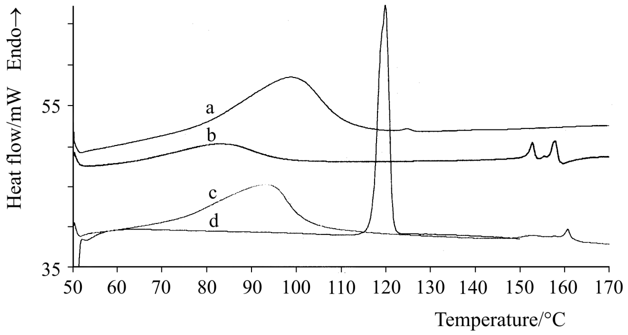

Fig. 6 DSC curves for the pure components and for 1:1 molar ratio mixtures of 4-ASA with BCD: a – pure BCD; b – physical mixture; c – kneaded mixture and d – pure 4-ASA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

The DSC curve for a 1:1 molar ratio physical mixture of 4-ASA with HPBCD (Fig. 7, curve b) showed a dehydration endotherm and a broad endotherm (onset 108°C). No endotherms or exotherms were observed for the kneaded mixture (curve c). The broadening of the melting endotherm for 4-ASA in the DSC curve for the physical mixture and the decrease in the enthalpy value (Table 4) are all indications of some interaction between 4-ASA and HPBCD. The interaction increases in the kneaded mixture as indicated by the complete absence of features expected for 4-ASA in the DSC curve. The TG results (not illustrated, but summarized in Table 4) support the occurrence of interaction between 4-ASA and HPBCD in kneaded mixtures.

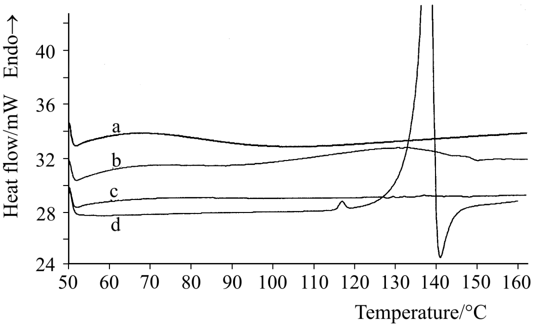

Fig. 7 DSC curves for the pure components and for 1:1 molar ratio mixtures of 4-ASA with HPBCD: a – pure HPBCD; b – physical mixture; c – kneaded mixture and d – pure 4-ASA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

The DSC curve for a 1:1 molar ratio physical mixture of 4-ASA with GCD (Fig. 8, curve 9b) shows a dehydration endotherm from 64 to 101°C and no endotherm at 122°C associated with melting of 4-ASA. For the kneaded mixture (curve c), there is only one endotherm (dehydration) from 53 to 99°C. The absence of the endotherm associated with the melting of 4-ASA is an indication of interaction of the 4-ASA with GCD. TG results (Table 4) support the occurrence of interaction between 4-ASA and GCD in both mixtures.

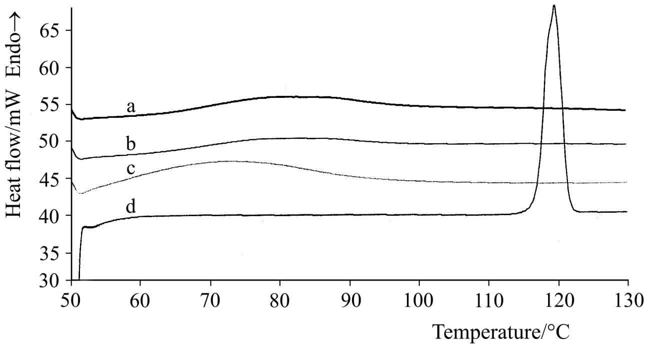

Fig. 8 DSC curves for the pure components and for 1:1 molar ratio mixtures of 4-ASA with GCD: a – pure GCD; b – physical mixture; c – kneaded mixture and d – pure 4-ASA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

Mixtures of 5-aminosalicylic acid (5-ASA) with the cyclodextrins

The DSC curve for a 1:1 molar ratio physical mixture of 5-ASA and BCD (Fig. 9, curve b) shows a dehydration endotherm from 66 to 114°C, a reversible transition exotherm around 220°C and a broad endotherm associated with the melting of 5-ASA (compare curve d) with onset at 254°C. The kneaded mixture (curve c) shows a dehydration endotherm from 66 to 109°C, a reversible exotherm around 220°C, and an endotherm associated with melting of 5-ASA with onset at 260°C. The broadening of the endotherms and the decreased enthalpy values (Table 5) indicate some, but not extensive, interaction between 5-ASA and BCD. The TG results (Table 7) show that the dehydration of the CD is the best indicator in investigating interaction between 5-ASA and BCD.

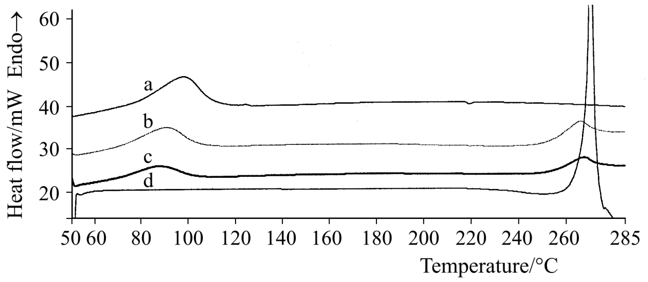

Fig. 9 DSC curves of the pure components and for 1:1 molar ratio mixtures of 5-ASA with BCD: a – pure BCD; b – physical mixture; c – kneaded mixture and d – pure 5-ASA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

The DSC curve for a 1:1 molar ratio physical mixture of 5-ASA with HPBCD (Fig. 10, curve b) shows only a decreased dehydration endotherm from 55 to 99°C. The kneaded mixture (curve c) shows an endotherm from 148 to 169°C and a revers-

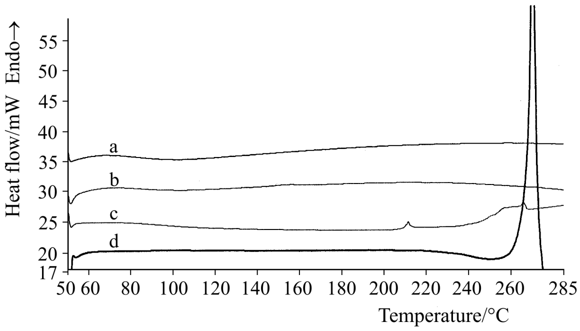

Fig. 10 DSC curves of the pure components and for 1:1 molar ratio mixtures of 5-ASA with HPBCD: a – pure HPBCD; b – physical mixture; c – kneaded mixture and d – pure 5-ASA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

ible transition exotherm around 210°C. There is a small broad endotherm, onset 240°C in the melting region. The absence or decreased size of the endotherm associated with the melting of 5-ASA is an indication of some interaction between 5-ASA and HPBCD. The TG results (Table 5) are complicated by the fact that 5-ASA and HPBCD decompose at almost the same temperatures.

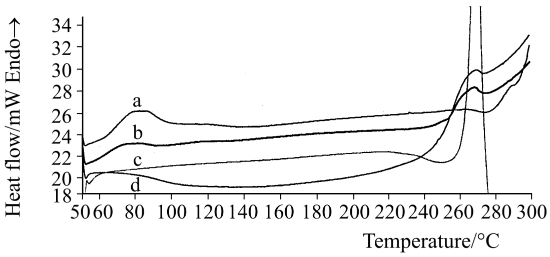

Fig. 11 DSC curves of the pure components and for 1:1 molar ratio mixtures of 5-ASA with GCD: a – pure GCD; b – physical mixture; c – kneaded mixture and d – pure 5-ASA (heated in flowing nitrogen at 10 K min^{-1} in uncrimped aluminium pans)

Figure 11 shows the DSC curves for the 1:1 molar ratio physical and the kneaded mixtures of 5-ASA with GCD. The DSC curve for the physical mixture (curve b) shows a dehydration endotherm from 62 to 95°C and a broad endotherm associated with the melting of 5-ASA with onset 254°C. The DSC curve for the kneaded mixture (curve (c)) shows a dehydration endotherm from 55 to 98°C and a broad endotherm with onset 246°C. There is also a reversible transition exotherm around 220°C. The TG results (Table 5) indicate some interaction between 5-ASA and GCD in both mixtures.

X-ray powder diffraction studies

The powder patterns for the three isomers of ASA are very different as shown in Fig. 12.

Figure 13 shows the X-ray powder diffraction patterns of the pure components and of 1:1 molar ratio mixtures of 3-ASA with BCD. The pattern of the kneaded mix-

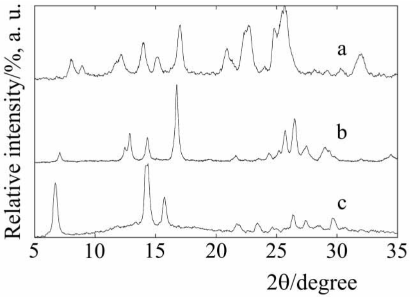

Fig. 12 X-ray powder diffraction patterns for a – 3-ASA; b – 4-ASA and c –5-ASA

ture is less detailed than that of the physical mixture. The large peak at about 2θ=12° for BCD also persists in the mixtures.

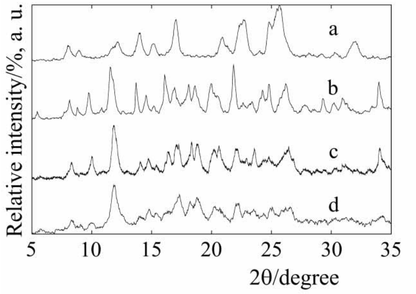

Fig. 13 X-ray powder diffraction patterns for a – 3-ASA; b – BCD; c – 3-ASA/BCD physical mixture and d – 3-ASA/BCD kneaded mixture. (Mixtures are 1:1 molar ratios)

The XRPD pattern for HPBCD (Fig. 14) is diffuse and this shows its amorphous nature. The patterns for the 1:1 molar ratio physical and kneaded mixture of 3-ASA with HPBCD are similar to each other and as diffuse as that of the HPBCD host.

The XRD patterns of the 1:1 molar ratio kneaded and physical mixtures of 3-ASA with GCD (Fig. 15) differ considerably. The pattern for the physical mixture

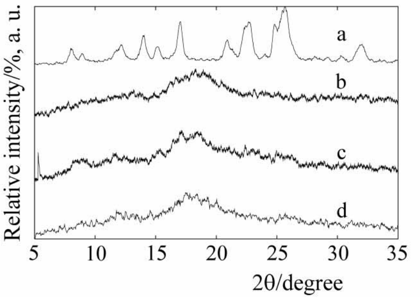

Fig. 14 X-ray powder diffraction patterns for a – 3-ASA; b – HPBCD; c – 3-ASA/HPBCD physical mixture and d – 3-ASA/HPBCD kneaded mixture. (Mixtures are 1:1 molar ratios)

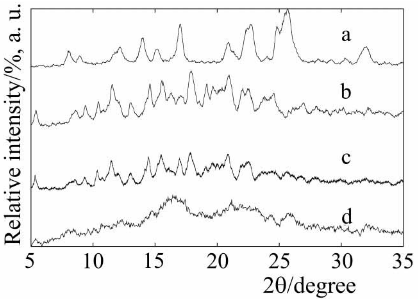

Fig. 15 X-ray powder diffraction patterns for a – 3-ASA; b – GCD; c – 3-ASA/GCD physical mixture and d – 3-ASA/GCD kneaded mixture. (Mixtures are 1:1 molar ratios)

shows some of the features of the patterns of the pure components. The pattern for the kneaded mixture is more diffuse.

The pattern for the 1:1 molar ratio physical mixture of 4-ASA with BCD (Fig. 16) shows some of the features of pure BCD and of pure 4-ASA. The pattern for the kneaded mixture is still crystalline but different from that of the physical mixture.

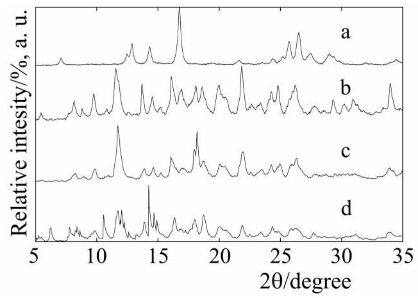

Fig. 16 X-ray powder diffraction patterns for a – 4-ASA; b – BCD; c – 4-ASA/BCD physical mixture and d – 4-ASA/BCD kneaded mixture. (Mixtures are 1:1 molar ratios)

The XRD patterns of the 1:1 molar ratio physical mixture of 4-ASA with HPBCD (Fig. 17) shows superimposition of some of the features of the pattern of 4-ASA on the diffuse pattern of HPBCD. Kneading of the mixture results in a diffuse pattern closer to that of HPBCD.

The patterns of the 1:1 molar ratio physical and the kneaded mixtures of 4-ASA with GCD (Fig. 18) are very different. The pattern of the physical mixture is close to that of GCD, but the kneading process appears to have produced a different, more crystalline compound.

The XRD pattern of 5-ASA is different from, and simpler than, that of 4-ASA (Fig. 12). The pattern for the 1:1 molar ratio physical mixture of 5-ASA with BCD (Fig. 19) shows some of the features of the patterns of pure BCD and pure 5-ASA. The kneading process results in a compound that has a pattern closer to that of the host BCD.

For 1:1 molar ratio mixtures of 5-ASA with HPBCD, the differences between the patterns of the kneaded mixture and the physical mixture (Fig. 20) are very marked and indicate significant interaction between the two compounds with the for-

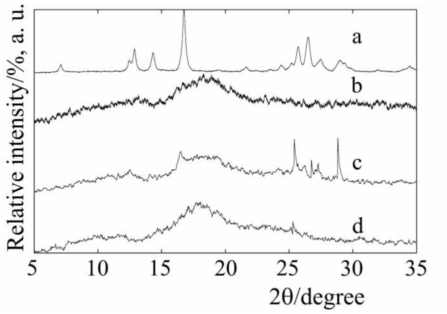

Fig. 17 X-ray powder diffraction patterns for: a – 4-ASA; b – HPBCD; c – 4-ASA/HPBCD physical mixture and d – 4-ASA/HPBCD kneaded mixture. (Mixtures are 1:1 molar ratios)

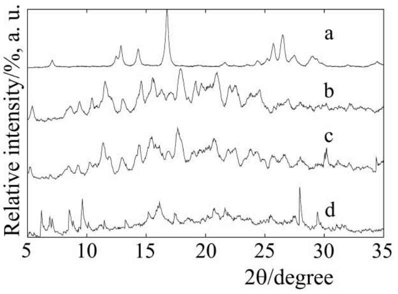

Fig. 18 X-ray powder diffraction patterns for a – 4-ASA; b – GCD; c – 4-ASA/GCD physical mixture and d – 4-ASA/GCD kneaded mixture. (Mixtures are 1:1 molar ratios)

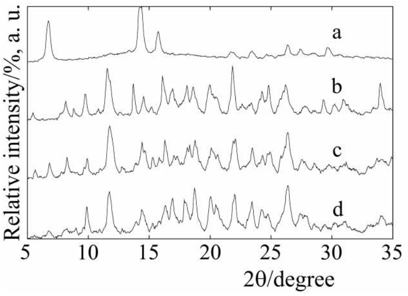

Fig. 19 X-ray powder diffraction patterns for a – 5-ASA; b – BCD; c – 5-ASA/BCD physical mixture and d – 5-ASA/BCD kneaded mixture. (Mixtures are 1:1 molar ratios)

mation of crystalline substances. The behaviour is similar to that observed for 4-ASA/HPBCD mixtures.

The pattern for a 1:1 molar ratio physical mixture of 5-ASA with GCD (Fig. 21) shows some of the features of the patterns of pure GCD and pure 5-ASA. The pattern for the kneaded mixture is more diffuse.

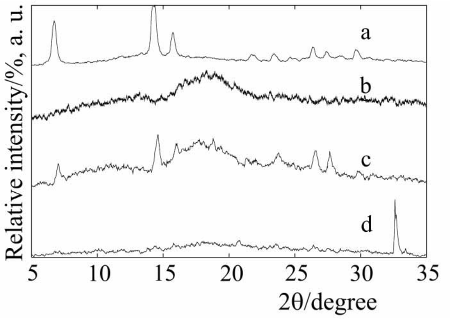

Fig. 20 X-ray powder diffraction patterns for a – 5-ASA; b – HPBCD, c – 5-ASA/HPBCD physical mixture and d – 5-ASA/HPBCD kneaded mixture. (Mixtures are 1:1 molar ratios)

Comparison of the XRD patterns of the 1:1 molar ratio kneaded mixtures of the three ASA isomers with BCD (curves d) in Figs 13, 16 and 19) shows that the patterns are all different from each other and from that of pure BCD. The pattern for the 3-ASA/BCD mixture is the least crystalline and that for the 5-ASA/BCD mixture is the most crystalline.

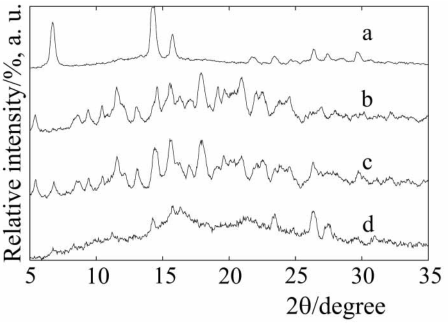

Fig. 21 X-ray powder diffraction patterns for: a – 5-ASA; b – GCD; c – 5-ASA/GCD physical mixture and d – 5-ASA/GCD kneaded mixture. (Mixtures are 1:1 molar ratios)

A similar comparison for the three ASA isomers with HPBCD (curves d) in Figs 14, 17 and 20) shows that their patterns are more diffuse than the XRPD patterns for the pure components. The pattern for the kneaded mixture of 3-ASA with HPBCD is the most diffuse.

The XRD pattern for the 1:1 molar ratio kneaded mixture of 4-ASA with GCD shows the greatest crystallinity. The patterns for the kneaded mixtures of 3-ASA and 5-ASA with GCD are much more diffuse (curves d) in Figs 15, 18 and 21).

Infrared spectra

The IR spectra of the three isomers, 3-ASA, 4-ASA and 5-ASA, are very different from each other as shown in Fig. 22. Gujrathi and Jose [14] interpreted these differ-

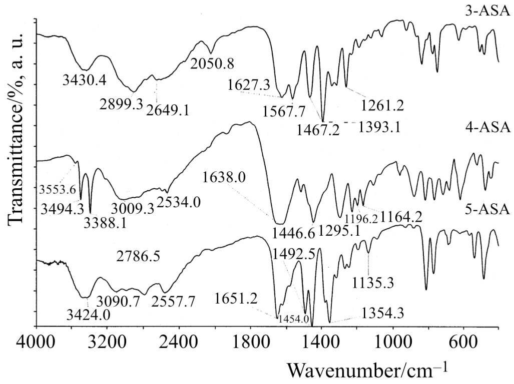

Fig. 22 IR spectra for a – 3-ASA; b – 4-ASA and c – 5-ASA

ences as arising from the existence of 3-ASA and 5-ASA as dipolar groups (NH_3^+ and COO^-) characteristic of zwitterionic molecules, while 4-ASA has neutral groups (NH_2 and COOH). The spectra for 3-ASA and 5-ASA show strong bands in the region of 3100–2500 cm^{-1}. The NH_2 group absorption bands which are expected at higher regions are noticeably absent in these two acids. The hydrochloride salts show the same bands in this region [14] with broad peaks at 2850 and 2870 cm^{-1}, which are ascribed to NH_3^+ absorptions. The absence of the NH_2 and the presence of NH_3^+ absorptions indicates that 3-ASA and 5-ASA consist of dipolar molecules in solid state. These observations were supported by the absence of absorption bands due to COOH and presence of COO^- (1560 and 1575 cm^{-1} for 3-ASA and 5-ASA, respectively).

The IR spectrum for 4-ASA shows NH_2 group absorptions at 3495 and 3395 cm^{-1}. The OH stretching bands of the phenolic and carboxylic acid groups are broad at about 3020 and 2870 cm^{-1}, respectively.

The spectra of the physical and the kneaded mixtures of 3-ASA and BCD (not illustrated) are very similar to each other, but differ from that of BCD over the region 1000 to 1800 cm^{-1}. Similar conclusions hold for the 3-ASA/HPBCD mixtures. Some features of the spectrum of 3-ASA are discernible in the spectra of both mixtures. The spectra of 3-ASA and GCD mixtures suggest slightly more interaction, because of the more marked disappearance of the spectral features of 3-ASA in the spectrum of the kneaded mixture than in the physical mixture.

There are significant differences in the spectra of the physical and kneaded mixtures of 4-ASA and BCD (not illustrated). Traces of the prominent bands (3496 and 3389 cm^{-1}) of 4-ASA are apparent, superimposed on the broad band in that region associated with BCD, in the spectrum of the physical mixture. Other spectral features of 4-ASA are more noticeable in the spectrum of the kneaded mixture, particularly around 2600 and below 900 cm^{-1}. For 4-ASA/HPBCD mixtures, the spectra (not illustrated) show considerable similarity between the physical and the kneaded mixtures and HPBCD itself. The features of the 4-ASA spectrum do not influence the spectra of the mixtures as much as they do in the BCD mixtures.

The results for 4-ASA/GCD mixtures (not illustrated) are similar to those for the 4-ASA/HPBCD mixtures. The spectrum of the physical mixture suggests that there is less interaction than in the kneaded mixture which is similar to that of pure GCD.

The differences between the spectra of the physical and the kneaded mixtures of 5-ASA and BCD (not illustrated) are very noticeable. The physical mixture shows some spectral features of pure 5-ASA, suggesting that the kneading process promotes interaction between 5-ASA and BCD. The spectral features of the physical and kneaded mixtures of 5-ASA with HPBCD (not illustrated) are very similar to each other but show differences to the spectra of the pure components.

For mixtures of 5-ASA and GCD, the spectra of the physical and the kneaded mixtures are very similar and many of the spectral features of the pure 5-ASA are evident.

Although the IR spectra contain a lot of information, this information is difficult to interpret even qualitatively. Little is known about the screening effects of cyclodextrin host on the absorptions of the guest molecule

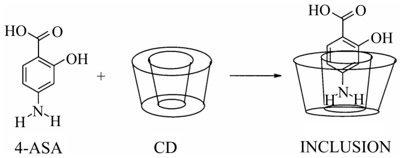

Fig. 23 Possible mode of inclusion of 4-ASA into the cavity of a cyclodextrin

On the assumption that the guest molecule is only partially accommodated in the CD cavity, it is possible to speculate which functional groups of the guest would be shielded (at least partially) by the CD molecule. The N–H absorption band for all the guest compounds is observed to have disappeared in most mixtures, so it is suggested that this end of the ASA molecule is within the CD cavity as illustrated for 4-ASA in Fig. 23. Single crystal X-ray diffraction studies and solid-state NMR studies might be able to verify this suggestion.

Discussion

The conditions used in preparing the physical mixtures are very mild, yet the resulting behaviour of these mixtures differs considerably from that predicted from the individual components. It is thus difficult to find examples of mixtures where little or no interaction has occurred. The kneading procedure, does, also produce changes in the crystallinity and water content of the CDs.

Generally, as expected, the kneaded mixtures show greater changes in thermal behaviour from that of the individual components than do the physical mixtures but the changes in the physical mixtures are also significant.

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 XRPD 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. From thermal analysis, the disappearance of the melting endotherms of the ASAs in the DSC curves of the mixtures with the CDs is the main indicator of an 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 [15].

Szente [15] has formulated some of the questions, which need to be answered concerning the nature of the interactions of the mixtures of potential guests with host CDs. These include determining whether the guest actually enters the CD cavity and how much of the guest remains outside the cavity. An additional aspect, seen in the present study, is the fate of water molecules already hosted within the CD cavity when the CD is mixed with another potential guest substance. Various possibilities of interaction exist. The guest can replace all the water and this expelled water can be lost from the mixture during, or soon after, the mixing process. This would be clearly shown by both disappearance of the dehydration endotherm from the DSC curves of the mixtures and the absent, or decreased, initial mass loss in the TG curves.

The next possibility would be that all, or most, of the water expelled from the CD cavities remains, although more loosely-bound, in the mixture and is released on heating with a similar mass-loss to that for the individual CD, but a decreased enthalpy of dehydration. Alternatively, some of the water molecules may share the CD cavity with the guest molecule, *G*, forming a type of hydrate, $G\cdot nH_2O$, stabilised within the cavity and behaving differently to pure guest, *G*.

Another possibility is that the guest molecules may only enter the cavity during the heating programme when the water molecules are expelled. Because dissociation of host-guest complexes will be endothermic and the formation of host-guest complexes could be close to thermally neutral, an apparent disappearance of, or marked decrease in the size of, the dehydration endotherm for the host CD could be observed.

Comparison of the effects of the different CDs on the behaviour of individual ASA isomers shows that HPBCD has the greatest interaction with 3-ASA and 5-ASA, followed by GCD, while BCD generally shows the least interaction. For 4-ASA, the effect of GCD seems to be more marked than for 3-ASA and 5-ASA. Reasons for these observations must involve the cavity sizes of the CDs and the molecular structures of the acids.

The main result of this study is thus that all substituted aminobenzoic acids studied appear to interact with all three of the cyclodextrins used, in particular after kneading. There are differences in the behaviour of different isomers and also differences in the behaviour of individual cyclodextrins. HPBCD has the disadvantage, from the point-of-view of identifying its interactions, of being non-crystalline to start with. Most of the mixtures show decreases in crystallinity relative to the individual constituents.

Kneading of the cyclodextrins with the kneading solvent (ethanol) in the absence of any other potential guest molecules, showed that HPBCD became more crystalline, while BCD became less crystalline, with negligible changes for GCD.

A few of the mixtures, notably 3-ASA/HPBCD, 4-ASA/HPBCD, 4-ASA/GCD and 5-ASA/HPBCD showed increased crystallinity and, presumably, obtaining a crystalline diffraction pattern for a mixture which differs significantly from the patterns of the guest substance and from that of the host CD (if it is crystalline), is a better indication of inclusion than obtaining a diffuse pattern. This would be worthy of further study using single-crystal X-ray diffraction techniques and, possibly, solid-state NMR.

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