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Solid-state β-cyclodextrin complexes containing indomethacin, ammonia and water. I. Formation studies

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Abstract

Five complexes were prepared with β-cyclodextrin and the insoluble, non-steroidal, anti-inflammatory drug indomethacin. The complexes were found to contain drug, water and ammonia in several unique combinations. It was theorized the complexes were tri-molecular in nature and their formation was controlled by a hydrophobic/hydrophilic balance created within the β-cyclodextrin ring cavity prior to complex formation. Each complex was characterized by ultraviolet, infrared, nuclear magnetic resonance, powder X-ray diffraction, differential scanning calorimetry, and thermogravimetric techniques. These characterizations revealed distinct differences among the five complexes.

Keywords: β-cyclodextrin; Indomethacin; Complex formation; Ultraviolet; Infrared; Nuclear magnetic resonance; X-ray diffraction; Differential scanning calorimetry; Thermogravimetric analysis

1. Introduction

Cyclodextrins are water-soluble, cyclic oligomers comprised of 6–8 U of glucopyranose bonded together by α-(1,4) linkages. The most common form is β-cyclodextrin, which is comprised of 7 U of glucopyranose. β-Cyclodextrin is known to form complexes with gas, liquid and solid guest compounds. Complex formation occurs when the cyclodextrin molecule entraps a guest compound (Szejtli, 1982). In pharmaceutical formulation, complex formation may improve the aqueous solubility of a hydrophobic drug (Frank, 1975; Uekama et al., 1983); consequently improving its dissolution characteristics (Uekama et al., 1979; Seo et al., 1983; Uekama et al., 1983).

Several published reports (Hamada et al., 1975; Kurozumi et al., 1975; Nambu et al., 1978; Szejtli and Szente, 1981; Szente et al., 1985; Duchene et

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al., 1987; Fromming et al., 1990; Myles et al., 1990; Wouessidjewe et al., 1990; Lin et al., 1991, 1992; Liu et al., 1992) discuss the nature of the indomethacin β-cyclodextrin complex. These reports are diametric about complex characteristics and formation mechanisms. This study will attempt to further elucidate the complex formation mechanism and to examine the similarities and differences among various indomethacin complexes.

2. Materials

Indomethacin USP was obtained from Kalipharma Pharmaceutical, Elizabeth, NJ, pharmaceutical grade β-cyclodextrin was obtained from Sanraku, Tokyo, Japan and ammonium carbonate was obtained from Fisher Scientific, Medford, MA.

2.1. Complex preparation

The indomethacin-β-cyclodextrin complexes were prepared as follows: 16 g of β-cyclodextrin were dissolved in aqueous solutions containing 2.4, 4.8, 7.3, 9.6 and 14.5×10^{-2} M ammonia. Each solution was heated to 57 ± 1°C to dissolve the β-cyclodextrin. Once β-cyclodextrin was dissolved completely an excess of indomethacin was added to the solutions. All dispersions were stirred at 20 rpm for 4 h, filtered, and dried for approximately 12 h in a hot-air oven at 70 ± 1°C. The heating process removed ammonium carbonate (decomposes on heating) and water yielding the complexes. Each complex was an opaque glaze that varied in color from light to brownish yellow. Each complex was powdered with a mortar and pestle and stored at room temperature in light resistant containers. Five complexes (A–E) were obtained by using this method.

3. Analytical methods

3.1. Indomethacin, ammonia and water assay

A high performance liquid chromatographic (HPLC) assay method was developed to measure quantitatively indomethacin and its two hydrolytic degradation products. The method can detect, on-column, 0.005 μg of indomethacin as well as its two hydrolytic degradation products. The column (250×4.6 mm) was obtained from Alltech Associates and contained RP18 stationary phase with a mean particle size of 5 μm. Mobile-phase consisted of 65% acetonitrile and a 35% aqueous phase containing 50 mM triethylamine adjusted to pH 3.3 with phosphoric acid. The pump flow rate and the injection volume were 1.5 ml/min and 20 μl, respectively. Peak-area quantitation was performed by a Hewlett Packard 3390A integrator. Calibration plots were prepared by plotting the peak-area ratio (indomethacin/internal standard) against the indomethacin concentration. Calibration standards ranged from 1 to 9 μg/ml indomethacin. Samples were prepared by dissolving 50 mg of each complex in water containing 2×10^{-4} M ammonium hydroxide (used to solubilize). A 0.5 ml aliquot was removed and added to 9.4 ml of methanol to which 0.1 ml of 4.22×10^{-3} M phenylbutazone was added as an internal standard.

The ammonia content of each complex was determined by using a Nessler's reagent calorimetric method (Jenkins et al., 1957). This method has a maximum sensitivity limit of 1 μg/ml ammonia. Samples were prepared by dissolving 50 mg of each complex in 50 ml of water containing 2 ml of Nessler's reagent. Standard solutions were prepared by adding a known quantity of ammonia stock solution (prepared from ammonium chloride) to 2 ml of Nessler's reagent. Solutions were brought to a 50 ml volume with water. The color intensity was estimated visually in triplicate by comparing each sample solution to the standard solutions.

The water content of each complex was determined using thermogravimetric analysis (TGA) with the DUPONT 1090B/1091 thermal analyzer. Analysis was performed by first computing the total percent weight loss from the thermal transition occurring from 25 to 130°C and subtracting the percent ammonia content to yield the percent water content. This approach was used because TGA was not specific for water loss and the total

weight loss was attributed to water and ammonia. Samples were desiccated over calcium sulfate for 72 h prior to assay to remove surface absorbed water. Samples were prepared by placing a 14–16 mg sample into a platinum boat. The nitrogen flow rate was 100 ± 10 ml/min and a the heating rate was 5°C/min.

3.2. Physicochemical characterization

Each complex was subjected to ultraviolet (UV), infrared (IR), proton nuclear magnetic resonance (NMR), and X-ray diffraction spectral analyses. In addition, differential scanning calorimetry (DSC) was used to characterize the thermal behavior.

The UV absorbance spectrum for each complex was obtained using a Bausch and Lomb Spectronic 2000 spectrophotometer. Samples were prepared by dissolving indomethacin and each complex in 2×10^{-4} M ammonia hydroxide solution to obtain a 2.2×10^{-4} M indomethacin solution. The samples were scanned for absorbance from 400 to 200 nm.

The IR spectrum for each complex was obtained using a Perkin Elmer 1420 ratio-recording spectrometer. Samples were prepared by the potassium bromide disk method and scanned for absorbance from 4000 to 650 per cm.

NMR spectra was obtained with a Varian T-60 spectrometer (60 MHz). Samples were prepared by dissolving either 30 mg of indomethacin, β-cyclodextrin, or each complex with 20 mg of anhydrous sodium carbonate (used to solubilize) into 0.5 ml of D_2O containing 0.75% 3-(trimethylsilyl) propionic-2,2,3,3,d4 acid, sodium salt, as an internal standard. Analysis parameters were as follows: spinning rate 40 rps, sweep time 250 s, sweep width 500 Hz, radio frequency power level 0.05, and spectrum amplitude 40.

X-ray diffraction patterns of indomethacin, β-cyclodextrin and each complex was obtained with a Siemens diffractometer. Samples were prepared using the powder fraction that passed through a 200 and was retained by a 260 mesh sieve. This sieve fraction represented an arithmetic mean particle size of 6.70×10^{-2} mm. The powder fraction was then pressed gently without imparting texture into an aluminum sample holder having a cavity with the following dimensions: $19.0 \times 6.5 \times 1.6$ mm. Instrumental parameters were as follows: nickel-filtered copper Kα radiation was used at 30 kV and 28 mA, time constant (S) 10, intensity (counts/S) 2×10^2, scanning rate 2°/min, chart speed 1 cm/min, and scan range 6–40° of the diffraction angle 2θ.

DSC analysis was performed with the DUPONT 1090B/1091 thermal analyzer. Samples were prepared by placing 10–14 mg of sample into an aluminum pan which was covered and crimped for analysis. Samples were desiccated over calcium sulfate for 72 h prior to assay in an effort to remove surface absorbed water. Thermograms were analyzed qualitatively by examining both the peak temperature and the endothermal transition contour. The nitrogen flow rate was 50 ± 10 ml/min and the heating rate was 5°C/min.

4. Results and discussion

4.1. Indomethacin, ammonia and water assay

The indomethacin, ammonia and water content and the aqueous ammonia concentration used to prepare each complex, are reported in Table 1. To obtain the indomethacin-β-cyclodextrin complexes reported in this study a simple acid-base neutralization method was employed. By adjusting the aqueous ammonia (base) concentration the indomethacin (acid) quantity encapsulated within the β-cyclodextrin ring cavity could be controlled. The complexed indomethacin content was found to range from approximately 8–20% (Table 1). Furthermore, a visual comparison of each complex showed the color to vary from a light to a brownish yellow with increasing drug content.

HPLC analysis did not detect indomethacin degradation products suggesting that β-cyclodextrin was able to protect indomethacin against alkaline hydrolysis during the preparation pro-

Table 1
Indomethacin-β-cyclodextrin complexes

Complex	Aqueous ammonia ($\times 10^{-2}$ M)	Complex composition (%)		
		Indomethacin[a]	Water	Ammonia
A	2.41	7.69 ± 0.48	9.88	0.20
B	4.82	10.75 ± 0.66	8.53	0.41
C	7.25	13.95 ± 0.67	6.28	0.62
D	9.62	16.27 ± 1.81	5.47	0.73
E	14.50	20.84 ± 0.87	5.48	0.73

[a] Mean $\pm$ S.D. of three determinations.

cess. Therefore, it was postulated the carbonyl group attaching the 1-para-chlorobenzoyl group to the nitrogen of the 5-methoxy-2-methylindole-3-acetic acid group was protected from hydrolysis by β-cyclodextrin. The carbonyl group must have been present either within or in close proximity to the β-cyclodextrin ring cavity.

4.2. Indomethacin, ammonia and water relationships

The plot of complex indomethacin content against the aqueous ammonia concentration (Fig. 1) fit a second-order least-squares regression ($r^2 = 0.9996$). By using Eq. (1) one could predict the amount of indomethacin included into the β-cyclodextrin ring cavity for a given concentration of ammonia in water.

$$Y = 4.20 + 1.50X + -2.42 \times 10^{-2}X^2 \quad (1)$$

where Y is the percent indomethacin, X is the molar ammonia concentration, and 4.20, 1.50 and -2.42 are the regression constants.

The complex preparation method was developed in our laboratory to obtain a complex for use in a solid-dosage form. A solid-state complex was not obtained by using the reported conventional preparation techniques such as the crystallization, coprecipitation, or kneading methods (Saenger, 1980). Attempts to prepare a complex in methanol, ethanol, or chloroform were also unsuccessful.

Several relationships were observed among the percent indomethacin, ammonia and water content of the various complexes. Fig. 2 shows the ammonia content increased with increasing indomethacin content. Fig. 3 shows the water con-

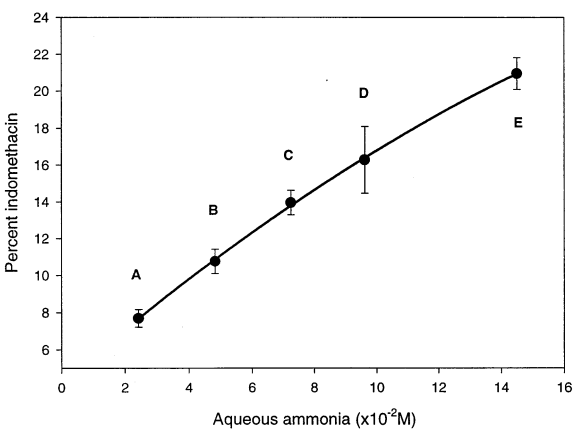

Fig. 1. Indomethacin content against the aqueous ammonia concentration for five complexes.

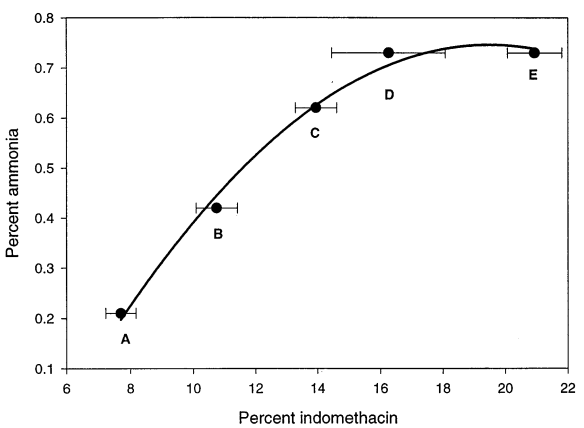

Fig. 2. Ammonia content against indomethacin content for five complexes.

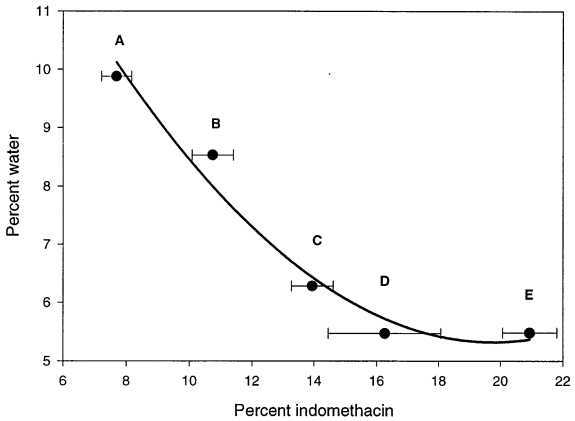

Fig. 3. Water content against indomethacin content for five complexes.

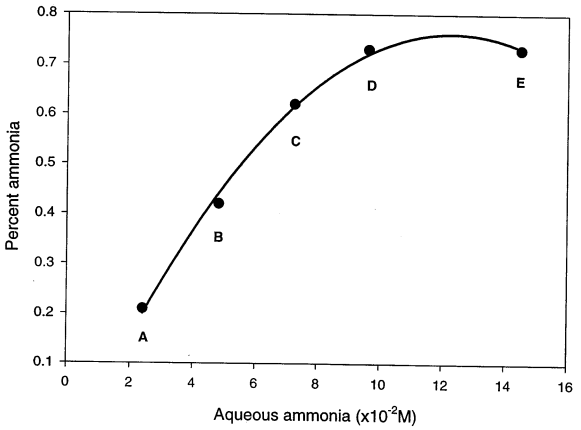

Fig. 5. Ammonia content against the aqueous ammonia concentration.

tent decreased as the indomethacin content increased. Fig. 4 shows the ammonia content decreased linearly as the water content increased. Considering Figs. 2–4 it was postulated that trimolecular complexes had formed based on an interdependence among indomethacin, ammonia, and water.

Fig. 5 shows a linear relationship among the ammonia content of complexes A–D and the aqueous ammonia concentration used in the preparation solution. Fig. 5 suggests these β-cyclodextrin complexes become saturated with ammonia at 9.6×10^{-2} M. Considering Fig. 5 it was postulated that complex formation was dependent on the aqueous ammonia concentration used to prepare the complexes.

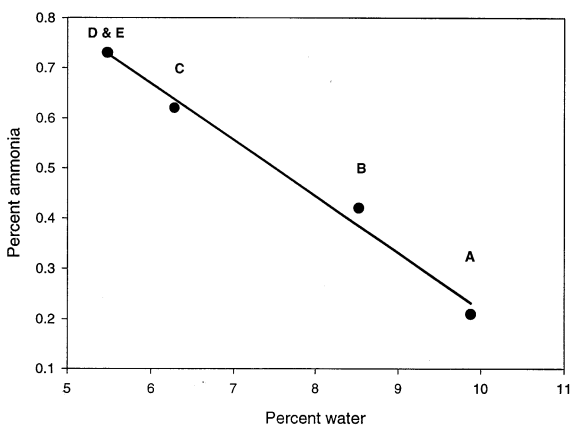

Fig. 4. Ammonia content against water content for five complexes.

The water content of complexes A and B (8.5 and 9.9%) was found to be higher than the hydrated β-cyclodextrin powder (8.4%). In principle, complex formation will occur through the replacement of high-energy water molecules (Szejtli, 1982). Since complexes A and B contained more water than the hydrated β-cyclodextrin (8.4%) it was postulated that polar binding and not water replacement was responsible for complex formation (Bergeron et al., 1977; Bergeron, 1984). Since complexes C–E contained less water than the hydrated β-cyclodextrin powder and complexes A and B, it was postulated that either polar binding or water molecule replacement could have been responsible for complex formation (Tabushi et al., 1978; Nakai et al., 1985; Celebi and Nagai, 1988).

Supported by previous findings (Bergeron et al., 1977, 1978; Bergeron, 1984) it was postulated that indomethacin carboxylate anion hydration was the predominant factor in controlling complex formation. For example, the higher water and lower ammonia content of complex A (Fig. 4) suggest a significant degree of carboxylate anion hydration and ingress into the β-cyclodextrin ring cavity. For complexes D and E the lower water content and higher ammonia content (Fig. 4) suggest a lesser degree of carboxylate anion hydration and ingress into the β-cyclodextrin ring

cavity. Intermediary were complexes B and C. The lower indomethacin content of complex A was explained by postulating a highly-hydrated carboxylate anion had extensively occupied the available space within the β-cyclodextrin ring cavity. The higher indomethacin content in complexes D and E was explained by postulating that one or more lesser-hydrated carboxylate anions had weakly penetrated the β-cyclodextrin ring cavity yielding a complex with a higher indomethacin content. The higher ammonia content of complexes D and E (Table 1) suggests that more cationic binding sites were available within the β-cyclodextrin ring cavity to adjoin to the carboxylate anion. In summary, it was postulated that when the β-cyclodextrin ring cavity was hydrated extensively the indomethacin carboxylate anion could ingress and bind firmly. When the β-cyclodextrin ring cavity was not hydrated extensively the carboxylate anion could not ingress wholly and bind firmly to the β-cyclodextrin ring cavity. Therefore, it was concluded the β-cyclodextrin ring cavity hydration was the predominant factor responsible for the formation of complexes A–E.

Considering crystallographic studies of other β-cyclodextrin complexes (Le Bas and Rysanek, 1987) it is known that β-cyclodextrin prefers to form a dimeric structure that enlarges the ring cavity. The dimers are either linked by hydrogen bonds involving the hydroxyl groups or directly through an intermolecular water network. However, they all display a partial water network. It is postulated that β-cyclodextrin has the ability to maintain this dimer structure in aqueous solution. Such a ring cavity expansion favors hydrophobic substrate binding with indomethacin.

Considering the tendency of β-cyclodextrin to form a solvated dimeric structure, indomethacin complexation was related to formation of a partially solvated water and ammonia network within the β-cyclodextrin ring cavity. The presence of ammonia in the complexes was explained as follows: either the ammonium salt of indomethacin had formed a complex or a quantity of ammonia had remained within the β-cyclodextrin ring cavity following complex formation.

It was postulated that ammonia had formed a weak complex rapidly in solution by replacing a portion of the hydrated water of β-cyclodextrin prior to the addition of indomethacin. This water and ammonia inclusion would have created a unique hydrophobic/hydrophilic balance within the β-cyclodextrin ring cavity controlled by the aqueous ammonia concentration. Following the addition of indomethacin a further complex formation would have occurred based on the unique water and ammonia ratio within the β-cyclodextrin ring cavity. Thus, the ability to control the complexed indomethacin content was explained.

4.3. Physicochemical characterization

4.3.1. UV spectrophotometric analysis

In UV analysis a bathochromic shift or band broadening has been observed in the spectrum of an UV active guest compound complexed with β-cyclodextrin (Szejtli, 1982). There were no observed shifts in the λ maxima of indomethacin (318 and 265 nm) when complexed with β-cyclodextrin. However, the data in Table 2 suggest the UV absorbance at both λ maxima had increased when compared to pure indomethacin. In summary, complex formation was suggested by the increased UV absorbance of indomethacin when in the presence of β-cyclodextrin.

4.4. IR analysis

The complex A–E IR spectra (Fig. 6 shows complex E as an example) resembled the hydrated

Table 2
The ultraviolet absorbance[a] of indomethacin and its cyclodextrin complexes at 318 and 265 nm

Sample	Absorbance (318 nm)	Absorbance (265 nm)
Indomethacin	0.147 ± 0.004	0.377 ± 0.010
Complex A	0.166 ± 0.004	0.427 ± 0.002
Complex B	0.202 ± 0.005	0.523 ± 0.010
Complex C	0.187 ± 0.017	$0.487 + 0.052$
Complex D	0.187 ± 0.008	$0.490 + 0.025$
Complex E	0.182 ± 0.011	0.485 ± 0.024

[a] Mean $\pm$ S.D. of three determinations.

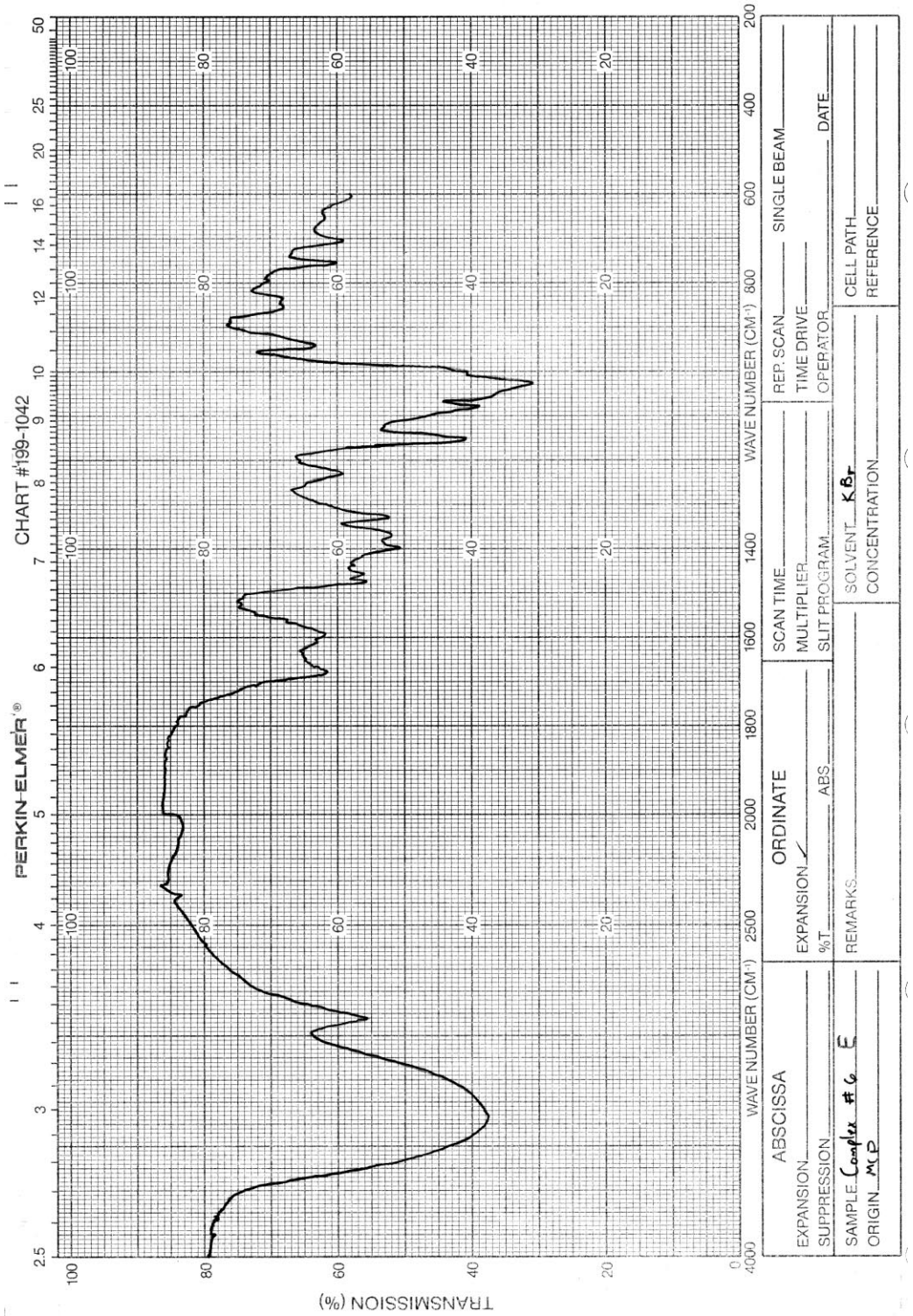

Fig. 6. The infrared spectrum of complex E.

Table 3
Proton nuclear magnetic resonance chemical shifts (ppm) of indomethacin, β-cyclodextrin and each complex

IMC	βCD	A	B	C	D	E
2.10	3.60	2.30	2.25	2.05	2.05	2.05
3.50	3.65	3.65	3.45	2.25	2.25	2.25
4.10	3.90	3.80	3.65	3.45	3.45	3.45
6.15	4.00	4.05	3.80	3.60	3.60	3.65
6.20	4.90	5.00	4.00	3.80	3.85	3.80
6.80	4.95	5.30	4.90	3.95	4.20	4.25
7.05	5.20		5.00	4.90	4.90	4.95
7.15			5.25	4.95	5.05	5.25
				5.20	5.10	7.30
						7.60
						7.75

IMC, indomethacin; βCD, β-cyclodextrin.

β-cyclodextrin spectrum (Fig. 7). All complex IR spectra show no features similar to pure indomethacin. However, HPLC analysis has shown the complexes to contain indomethacin. IR analysis of a 20% indomethacin/β-cyclodextrin physical mixture (Fig. 8) shows the presence of the two carbonyl bands of indomethacin at 1690 and 1720 per cm. These bands were absent in the complex A–E spectra. The absence of indomethacin features in the complex A–E spectra show β-cyclodextrin has altered the IR characteristics of indomethacin.

An examination of complex C, D (not shown) and E (Fig. 6) spectra revealed two small but distinct bands at 1590 and 1680 per cm. These bands were attributed to the two carbonyl bands of indomethacin which had been shifted and diminished as a result of complex formation. Alternately, the IR spectra of complexes A and B (not shown) show no evidence of these two new bands; thus, suggesting a more complete shielding and a deeper penetration of the carboxylate group. This conjecture further supports the previously-mentioned theory suggesting that complex formation was controlled by the hydrophobic/hydrophilic balance of the β-cyclodextrin ring cavity.

4.5. Proton NMR analysis

The chemical shifts (ppm) of indomethacin, β-cyclodextrin and each complex are reported in Table 3. The appearance of new chemical shifts in each complex was attributed to complex formation. The new chemical shift observed at 2.25 ppm may not be atypical since it was attributed to 5-methoxy-2-methylindole-3-acetic acid an indomethacin degradation product, and may have been formed following sample preparation. A careful examination of the complex E NMR spectrum revealed several chemical shifts located at greater than 6 ppm. These shifts were attributed to the aromatic chemical shifts of indomethacin altered through complex formation.

4.6. X-ray diffraction analysis

To examine crystallinity and provide further evidence of complex formation, X-ray diffraction analysis was performed. The diffraction angles of indomethacin, β-cyclodextrin, each complex and a physical mixture of indomethacin and β-cyclodextrin are reported in Table 4. X-ray diffraction was capable of proving complex formation by verifying the crystalline reflections of each complex was unique from that of indomethacin, β-cyclodextrin, and the physical mixture. Clear differences were identified among the diffraction patterns of each complex.

4.7. DSC analysis

DSC analysis was used to characterize indomethacin, β-cyclodextrin and each complex. Examination of the endothermal transitions of each complex indicate distinct differences from that of pure indomethacin, β-cyclodextrin and a physical mixture as reported in Table 5. The physical mixture showed no evidence of complex formation.

Three meaningful endothermal transitions were observed in each complex thermogram: (1) a large transition with a peak temperature in the range of 105–125°C; (2) one or two small transitions with a peak temperature in the range of 145–160°C; and (3) a small transition with a peak temperature in the range of 209–236°C as reported in Table 5. The first and third transitions were attributed to β-cyclodextrin, and the second transition was attributed to indomethacin.

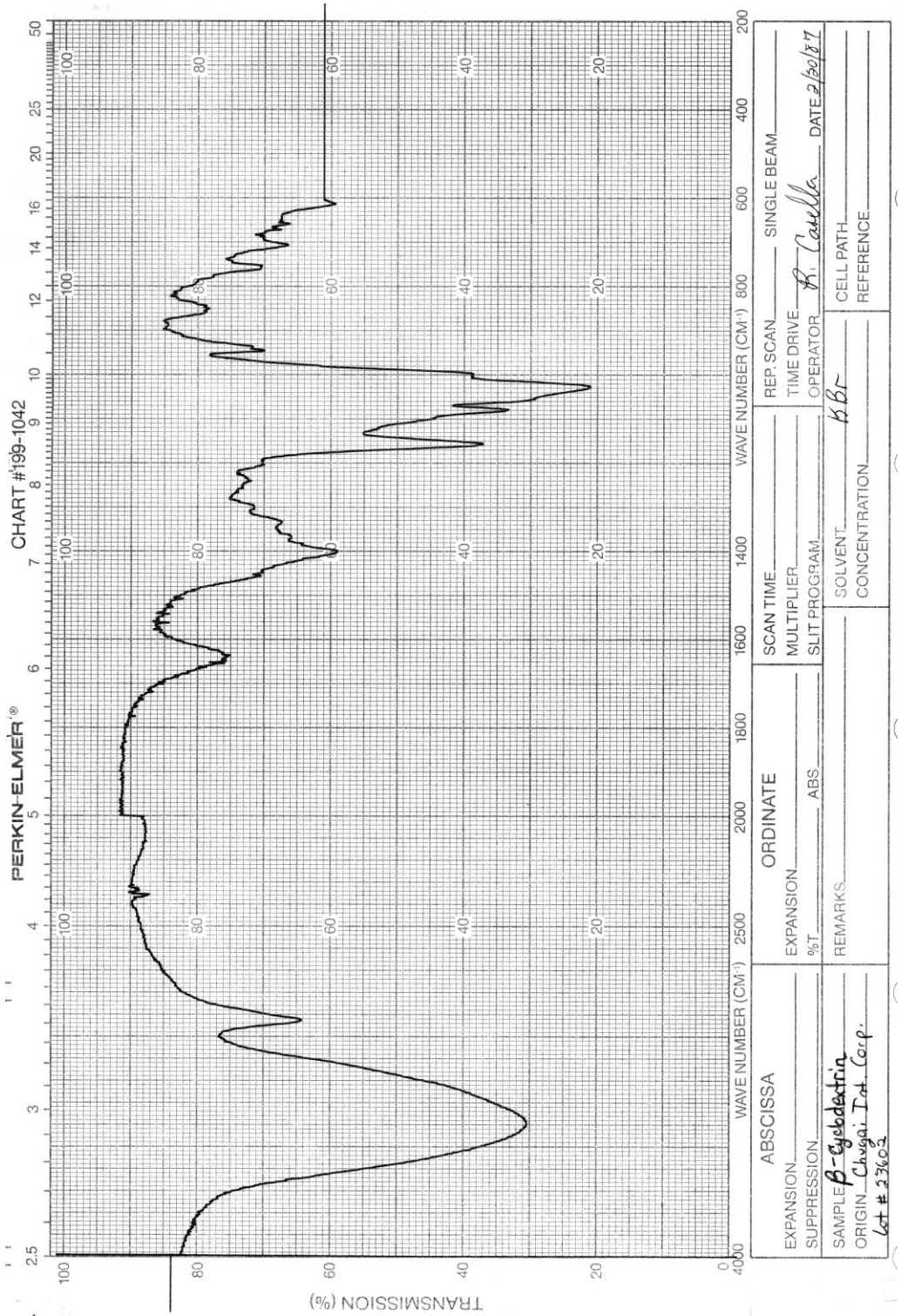

Fig. 7. The infrared spectrum of β-cyclodextrin.

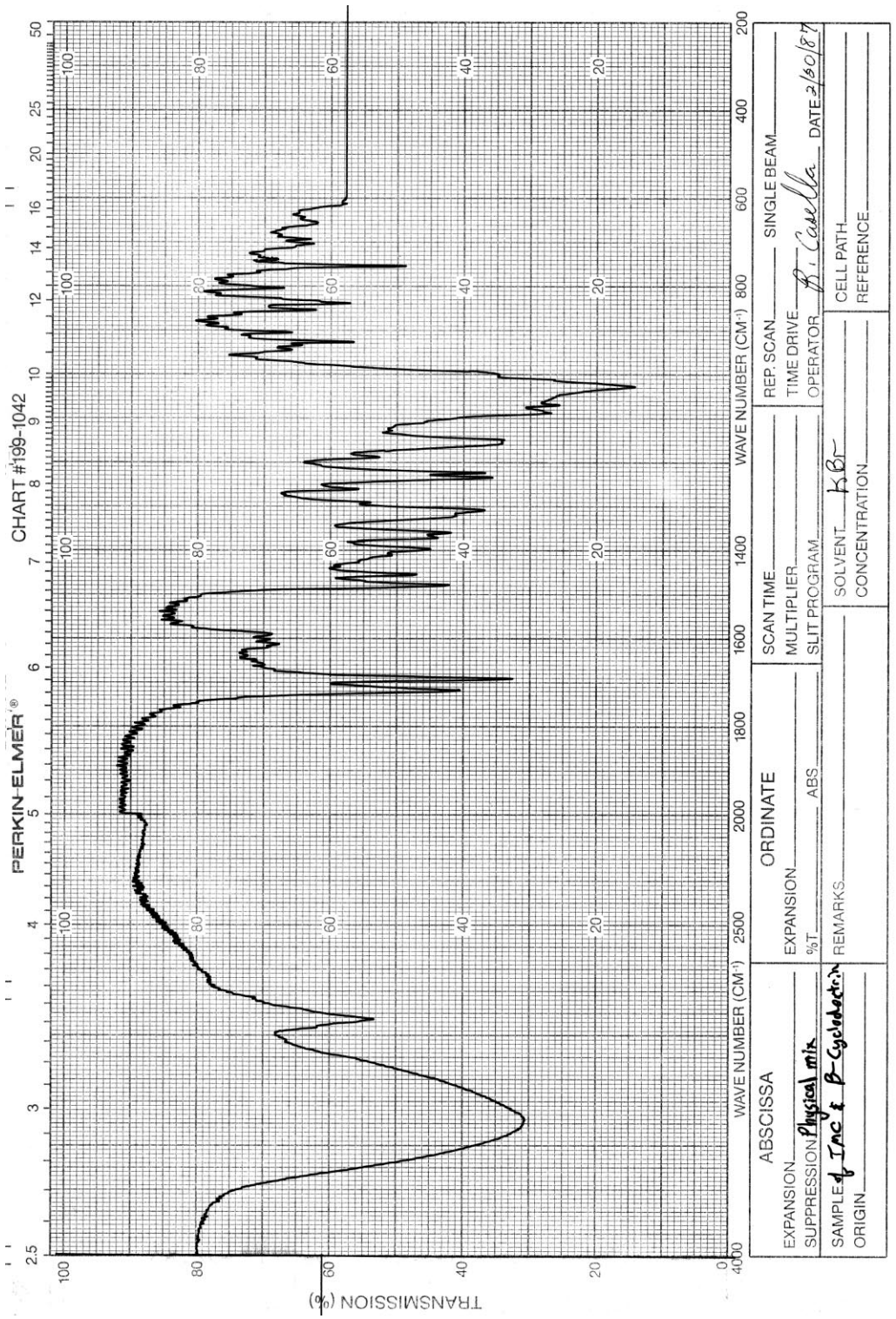

Fig. 8. The infrared spectrum of a physical mixture of indomethacin and β-cyclodextrin.

Table 4
The diffraction angles (°2Θ) of indomethacin, β-cyclodextrin, each complex and a physical mixture of indomethacin and β-cyclodextrin

IMC	βCD	A	B	C	D	E	PM
10.10	9.00	9.00	7.00	9.50	9.25	8.00	7.75
11.75	9.50	10.50	8.75	10.00	10.50	9.75	9.00
12.75	10.50	10.75	10.50	10.50	12.25	11.75	9.50
16.50	11.50	12.25	12.25	11.75	14.50	14.50	10.50
17.00	12.25	14.50	14.50	12.50	15.25	15.50	11.50
18.50	14.50	15.50	15.25	14.50	15.75	17.50	12.25
19.50	15.25	17.00	15.75	15.50	17.00	18.50	14.50
21.75	16.00	18.00	17.00	17.50	17.50	20.50	15.25
23.25	17.00	18.75	17.75	21.75	18.50	21.00	16.00
24.00	17.75	19.50	18.50	22.25	19.50	21.50	16.75
25.75	18.75	20.75	19.50	23.00	20.50	23.00	18.00
26.50	19.50	21.25	20.50	24.00	21.00	23.75	19.25
27.50	21.00	24.50	21.00	26.50	22.50	26.00	20.75
28.25	21.50	26.00	22.50	28.00	23.00	34.50	21.50
29 00	22.50	27.00	24.00	32.00	24.00	35.50	22.75
29.25	24.25	29.00	26.75	37.00	25.00		24.00
30.50	25.00	31.00	30.75	37.50	31.00		25.00
33.00	27.00	34.75	35.00		32.00		25.50
33.50	28.50	35.25			34.50		26.50
34.10	31.00						29.00
35.00	32.00						31.00
37.50	34.50						34.00
	35.50						35.00
							35.25

IMC, indomethacin; βCD, β-cyclodextrin; PM, indomethacin/β-cyclodextrin physical mixture.

The transitional temperatures observed in the range of 145–160°C were attributed to the melting temperatures of the three common polymorphic forms of indomethacin: I (160°C), II (154°C) and III (147°C) (Borka, 1974). An exothermal transition at 57°C in complex A was attributed to the amorphous form of indomethacin (Borka, 1974). Considering IR and X-ray diffraction data confirming complex formation, the transitions were attributed to different forms of complexed indomethacin. The transitional temperatures and the attributed form of indomethacin are reported in Table 6.

The thermogram of complex A (Fig. 9) was found initially to exhibit an exothermal transition at 57°C that was attributed to amorphous in-

Table 5
Endothermal transition temperatures (°C) of indomethacin, β-cyclodextrin and each complex

IMC	βCD	A	B	C	D	E	PM
160	113	118	118	106	117	111	113
	222	154	154	152	123	147	160
		160	160	223	150	156	222
		218	220		160		

IMC, indomethacin; βCD, β-cyclodextrin; PM, indomethacin/β-cyclodextrin physical mixture.

Table 6
Transitional temperatures (°C) and physical forms of indomethacin

Complex	Transition temperature	Indomethacin form
A	57, 154, 160	I, II, amorphous[a]
B	154, 160	I, II
C	152	II
D	147–150, 160	I, II and III
E	147, 156	II, III

[a] See text.

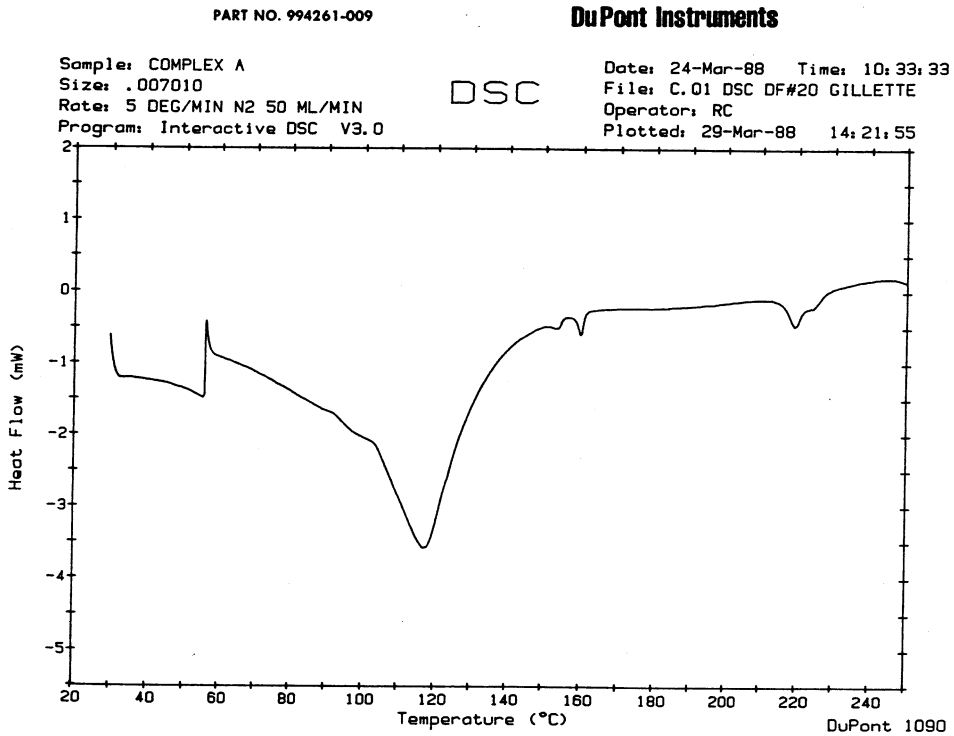

Fig. 9. The DSC thermogram of complex A.

domethacin. A second and third DSC thermogram performed 1 and 2 years later failed to exhibit this exotherm but exhibited an endothermal transition at 160°C. Thus, it was postulated that amorphous indomethacin had converted to Form I. Such a physical inter-conversion has been reported previously (Borka, 1974; Imaizumi et al., 1980).

Examination of the complex D (Fig. 10) and E (not shown) thermograms revealed an endothermal doublet at 117 and 123°C in complex D and a shouldered endotherm at 111°C in complex E. Both thermograms show two small endotherms between 145 and 160°C. Considering the endothermal contours it was postulated that each thermogram was composed of two or more overlapping thermograms. Thus, complexes D and E may contain one or more unique complexes. In support of this finding several other investigators have made similar interpretations (Rosanske and Connors, 1980; Miyahara and Takahashi, 1982; Wong et al., 1983).

5. Conclusions

A method was developed to prepare several indomethacin and β-cyclodextrin complexes. This method would allow one to control the quantity of indomethacin encapsulated within the β-cyclodextrin ring cavity.

Tri-molecular complexes were formed considering the relationships observed among complexed indomethacin, ammonia and water.

UV, IR, NMR, X-ray diffraction and DSC techniques were used to verify complex formation. These methods could be used to identify distinct differences among the various complexes.

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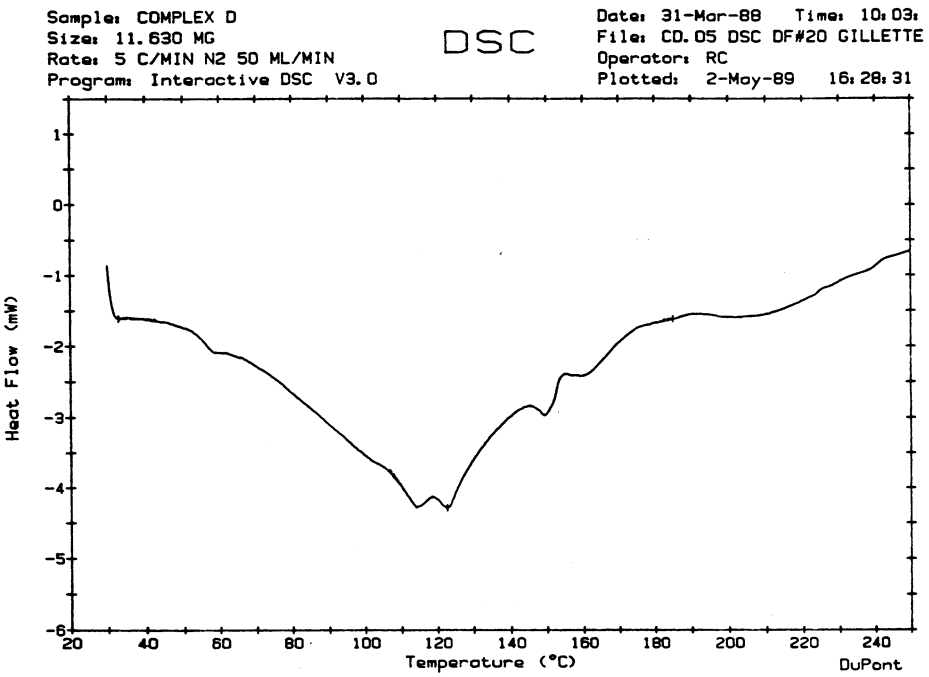

Fig. 10. The DSC thermogram of complex D.

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