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Indomethacin and cyclodextrin complexes

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Summary

Different complexes of indomethacin and both β-cyclodextrin (βCD) and hydroxypropyl β-cyclodextrin (HPβCD) were prepared using different methods: kneading, spray-drying and neutralization followed by freeze-drying. The complexes obtained were studied in the solid phase by differential scanning calorimetry (DSC), thermomicroscopy (TM), and infrared spectroscopy (IR), and in the liquid phase by ^{1}H-NMR. The results showed that the nature of the end products depends on the method of preparation. The neutralization technique led to a true inclusion of sodium indomethacin in the cyclodextrin cavity, while the nature of the spray-dried product, indomethacin (acid form)/cyclodextrin, was not well defined. The kneading method did not lead to a real inclusion. In any case, the complexes obtained may be of great value as rapidly dissolving forms of indomethacin in water.

Introduction

During the last decade, cyclodextrins and their derivatives have aroused considerable interest in the pharmaceutical field, due to their potential to form complexes with many varieties of drug molecule (Duchêne, 1987; Szejtli, 1988). The resulting complexes generally lead to an improvement in some of the characteristics of the guest molecules, e.g. stability, solubility and bioavailability. The complexes can be obtained in different ways, in liquid or solid medium. It is then essential that specific tools may be required to achieve complete characterization of the end product. Indomethacin, a non-steroid anti-inflammatory, anti-pyretic and analgesic agent, has been widely used in therapeutics (O'Brien et al., 1984).

The aim of this work is to prepare complexes of indomethacin/β-cyclodextrin or hydroxypropyl/β-cyclodextrin, using different methods: kneading, spray-drying, neutralization followed by freeze-drying methods (Tsuruoka et al., 1981; Tokumura et al., 1984; Bootsma et al., 1989). Selective physicochemical determinations based on different scanning calorimetry, thermomicroscopy, infrared spectroscopy and proton nuclear magnetic resonance were used to analyze the complexes.

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Their aqueous solubility improvement was also determined.

Materials and Methods

Materials

β-Cyclodextrin (βCD, Kleptose®) and hydroxypropyl β-cyclodextrin (HPβCD, DS = 0.40) were supplied by Roquette Frères (Lestrem, France). Indomethacin (IM) (free acid form) was purchased from Sigma Chemical Co. (St. Louis, U.S.A.).

Preparation methods

Kneading method β-Cyclodextrin (4.4 mmol) and water (1.7 ml) were mixed together in a mortar so as to obtain a homogeneous paste. Indomethacin (2.2 mmol) was then added slowly, whilst grinding. The mixture was then ground for 1 h. During this process, an appropriate quantity of water was added to the mixture in order to maintain a suitable consistency. The paste was dried in an oven at 40 °C for 24 h. The dried complex was pulverized into a fine powder. Only the β-cyclodextrin was used for this method, since HPβCD led to a very sticky product that was very hard to grind.

Spray-drying method Indomethacin (37.2 mmol) and cyclodextrins (24.8 mmol) were dissolved respectively in 1 l of 95% ethanol and in 1 l of distilled water, and mixed at 70 °C before spray-drying. Spray-drying was performed in a Niro Atomizer (Copenhagen, Denmark) under the following conditions: flow rate, around 40 ml/min; inlet temperature, 140 °C; outlet temperature, 75 °C; atomizing air pressure, 6 kg/cm^2. The yield of the spray-drying process was about 60%. The spray-dried products were washed rapidly with cold acetone to eliminate free indomethacin. It was proved that indomethacin remained stable after the spray-drying process by HPLC assay.

Neutralization method Sodium hydroxide (0.1 N) was added very slowly by a pump to the cyclodextrin solutions containing indomethacin powder until the pH of this solution became stabilized at about 7.5. (The pH of the solution was always kept under 8 to avoid degradation of the indomethacin.) After filtration, the pH of the solution was adjusted to 6 using hydrochloric acid (0.1 N). This solution was then filtered again and freeze-dried (Usifroid, Maurepas, France). HPLC assay showed that the degradation of indomethacin was less than 1%.

Characterization methods

Differential scanning calorimeter (DSC) measurements were carried out using a Dupont Instruments 910 differential scanning calorimeter, at a scanning rate of 10 °C/min.

An Olympus BH-2 microscope, connected to the Mettler FP 5 heating system, was used to achieve the thermomicroscopy analysis.

Infrared absorption spectra (IR) were derived using a Perkin-Elmer 257 Grating infrared spectrophotometer (KBr disc method).

^{1}H-NMR experiments were performed at 600.13 and 500.13 MHz with Bruker AM 600 and WM 500 NMR spectrometers at 303 K. The study reported in this work concerns only the NaIM/βCD complexes (Djedaïni et al., 1990).

Solubility and dissolution studies

The solubility of indomethacin and its complexes was determined at 25 °C after 24 h of agitation. This short period of agitation was chosen intentionally, with a view to checking whether there were differences between the tested products. The dissolution rates of indomethacin from the complexes at 37 °C and 100 rpm were measured in an apparatus (USP XX paddle apparatus) connected to the spectrophotometer by a peristaltic pump, so that the absorbance was monitored automatically at 320 nm.

Results

Complex prepared by the kneading method

The DSC curves of the solid complex, and its physical mixture are shown in Fig. 1.

The thermograms were quite similar in the two cases. The endothermic peak of indomethacin appeared at 161 °C. This was confirmed by the thermomicroscopy analysis. However, indomethacin

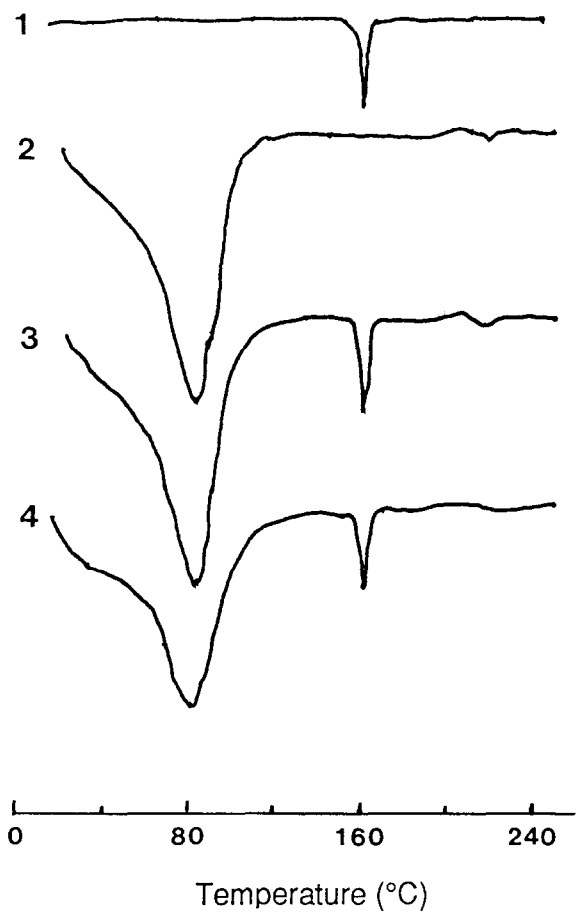


Fig. 1. DSC thermograms of indomethacin (acid form) and its kneaded complex. (1) Indomethacin; (2) β-cyclodextrin; (3) physical mixture IM/βCD; (4) complex IM/βCD.

fusion appeared to be more definite in the case of the physical mixture, than for the complex. This may be explained by a better dispersion of the indomethacin microcrystals in the β-cyclodextrin in the case of the complex. The IR spectra (Fig. 2) did not show any difference between the main indomethacin absorption bands on the one hand, and the complex and physical mixture on the other.

The complex obtained by the kneading method did not seem to be a true inclusion. In fact,

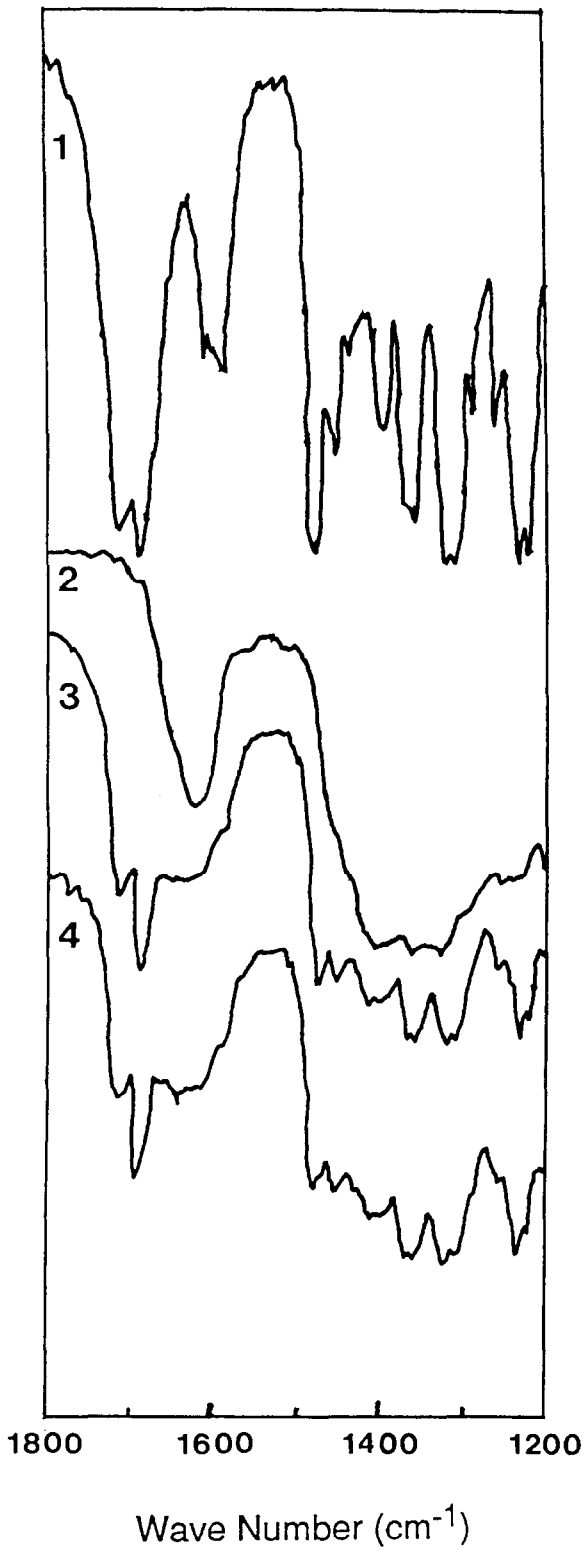


Fig. 2. IR spectra of indomethacin and its kneaded complex. (1) Indomethacin; (2) β-cyclodextrin; (3) physical mixture IM/βCD; (4) complex IM/βCD.

TABLE 1

Percentage of indomethacin before and after acetone washing (6 °C for 20 s)

Preparation method and CD used	% IM (w/w)	
	Before	After
Kneading		
-βCD	13.9	2.5
Spray-drying		
-βCD	21.2	13.5
-HPβCD	18.8	12.5
Neutralization		
-βCD	12.2	11.8
-HPβCD	11.0	10.7

washing with cold acetone eliminated most of the indomethacin (Table 1).

The solubility results (mg/ml), carried out in pH 6 phosphate buffer show that the presence of cyclodextrins leads to an improvement in solubility of indomethacin (indomethacin, 0.066; physical mixture IM/βCD, 0.5; complex IM/βCD, 0.63). However, there does not seem to be any significant difference in the improvement caused by the complex compared with that resulting from the physical mixture.

On the other hand, as may be seen in Fig. 3, the indomethacin dissolution rate from the complex is clearly increased compared with that of the physical mixture and indomethacin alone. At 3 min, nearly 95% of indomethacin is dissolved from the kneaded complex, compared with only 39% from the physical mixture.

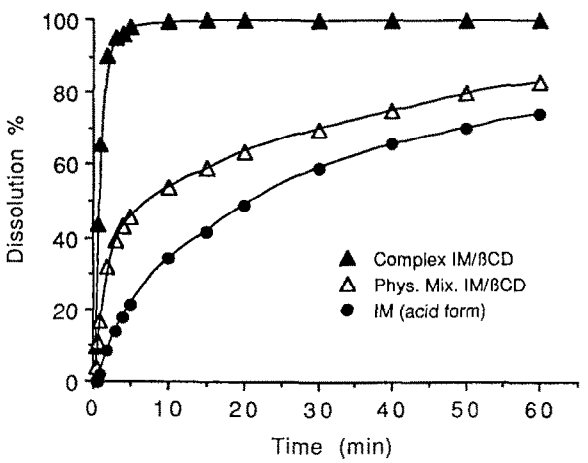


Fig. 3. Dissolution profiles of indomethacin and its kneaded complex in pH 6 phosphate buffer at 100 rpm and 37 °C.

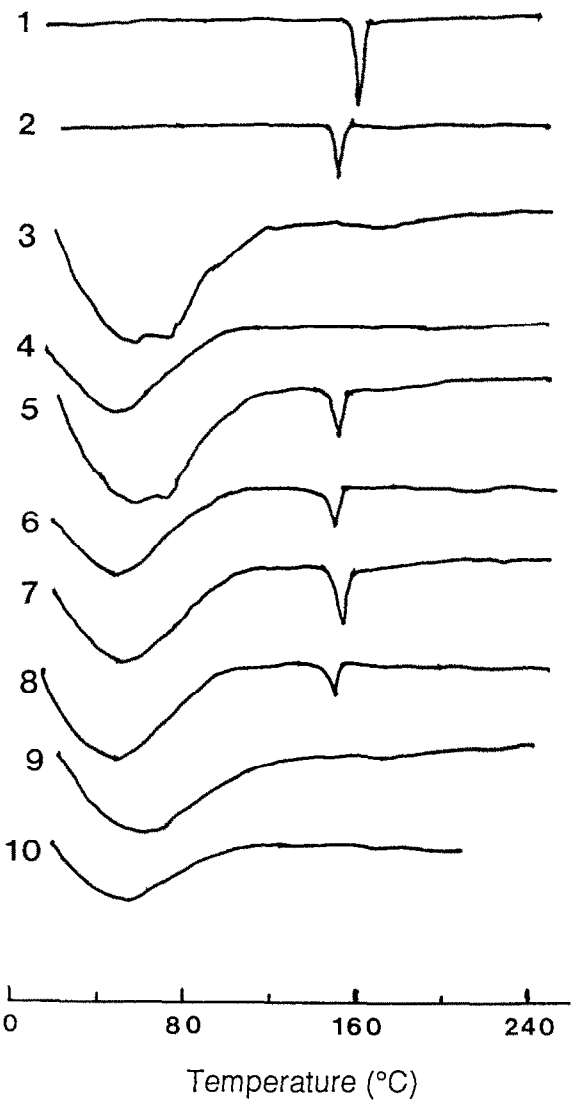


Fig. 4. DSC thermograms of indomethacin and its complexes prepared by the spray-drying method. (1) Indomethacin; (2) spray-dried IM; (3) β-cyclodextrin; (4) HPβCD; (5) physical mixture IM/βCD; (6) physical mixture IM/HPβCD; (7) spray-dried product IM/βCD; (8) spray-dried product IM/HPβCD; (9) complex (washed) IM/βCD; (10) complex (washed) IM/HPβCD.

Complexes prepared by the spray-drying method

The thermograms (Fig. 4) of the spray-dried product exhibit an indomethacin polymorph fusion peak at 154°C (O'Brien et al., 1984). However, after washing the spray-dried product with acetone, this fusion peak disappears. This is attributed to elimination of indomethacin adsorbed on the cyclodextrins. It should be noted that a determination carried out on the washed complex proved the subsistence of indomethacin (Table 1). The complexes obtained (after washing) are composed of about 1 mol of indomethacin to 2 mol of cyclodextrins.

The indomethacin fusion observed by thermomicroscopy for the spray-dried products and the physical mixtures, and the absence of this fusion for the washed complex, confirm the results obtained by DSC.

The IR spectra (Fig. 5) of spray-dried indomethacin and the physical mixture can virtually be superimposed. On the other hand, in the case of the complex, the disappearance of the carbonyl absorption band (around 1680 cm^{-1}) may be observed. These results serve to confirm the existence of a strong interaction between indomethacin and the cyclodextrins.

The solubility results (mg/ml) were as follows: spray-dried IM, 0.01; physical mixture, IM/βCD, 0.084; complex IM/βCD, 0.098; physical mixture, IM/HPβCD, 1.3; complex IM/HPβCD, 3.3. In fact, solubility is increased from 8 to 100 times, respectively, for the physical mixtures IM/βCD and IM/HPβCD, compared with 10 to 300 times for the corresponding complexes. It should be noted that the solubility studies were performed in distilled water (pH 6.4), not in phosphate buffer, with the aim of avoiding the formation of NaIM. Thus, the value of 0.01 mg/ml corresponds to the true solubility of indomethacin (acid form).

The dissolution of indomethacin (acid form) from the complexes is faster than from the physi-

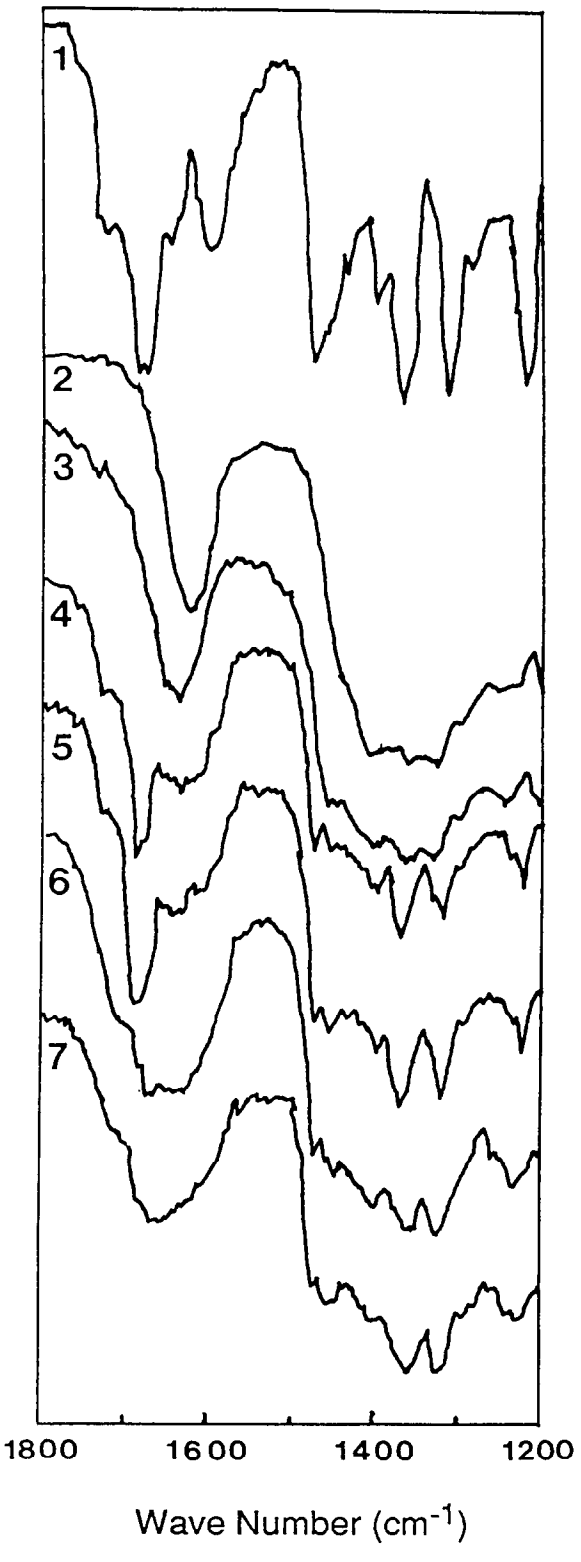


Fig. 5. IR spectra of indomethacin and its complexes prepared by the spray-drying method. (1) Spray-dried IM; (2) β-cyclodextrin; (3) HPβCD; (4) physical mixture IM/βCD; (5) physical mixture IM/HPβCD; (6) complex IM/βCD; (7) complex IM/HPβCD.

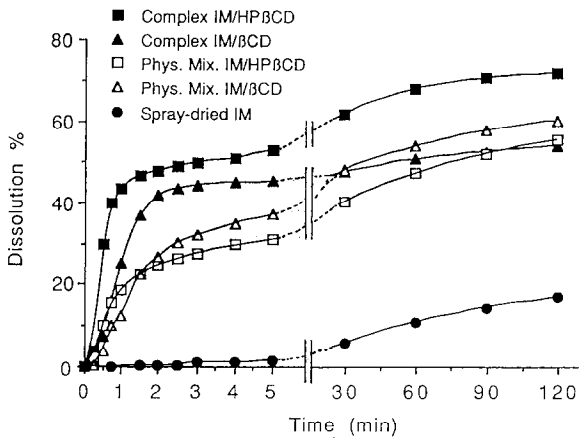


Fig. 6. Dissolution profiles of indomethacin and its complexes prepared by the spray-drying method in distilled water (pH 6.4) at 100 rpm and 37 °C (100% dissolution corresponds to 10 mg of indomethacin per l, under non-sink conditions).

cal mixtures as shown in Fig. 6. At 2 min, the quantity of indomethacin dissolved from HPβCD and βCD complexes is 1.9 and 1.6 times greater than from the physical mixtures with HPβCD and βCD. The complex with HPβCD results in the fastest dissolution of indomethacin. However, it is important to point out that 100% dissolution is not reached at the end of 2 h, and this applies in all cases (Lin et al., 1990).

Inclusion compounds prepared by the neutralization method

The thermograms of NaIM/βCD and NaIM/HPβCD inclusion compounds (Fig. 7) failed to show the characteristic peaks of NaIM (143, 167 and 182 °C), whereas the peaks appeared again for the physical mixtures. The results of thermomicroscopy analysis, besides confirming those of the DSC, enable observation of the following for sodium indomethacin (NaIM) alone (amorphous form): fusion at 143 °C, followed by partial recrystallization at 167 and 182 °C, and then total fusion around 250 °C.

As shown in Fig. 8, the IR spectra of sodium indomethacin, its physical mixtures and its inclusion compounds show similar characteristic absorption bands.

In the specific case of the inclusion compounds obtained by neutralization, the reality of an NaIM inclusion was confirmed by an NMR study. This study also proved that the inclusion stoichiometry is 1 : 1 (Djedaïni et al., 1990). However, NMR did not confirm the existence of an inclusion in a liquid medium of the complex obtained by the spray-drying method (Wouessidjewe et al., 1990).

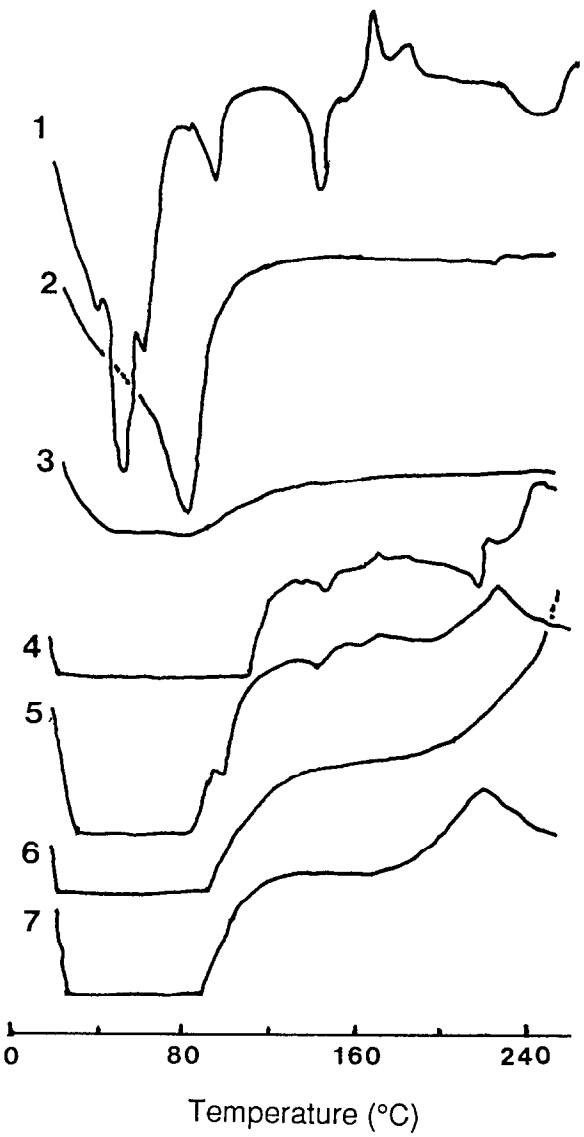
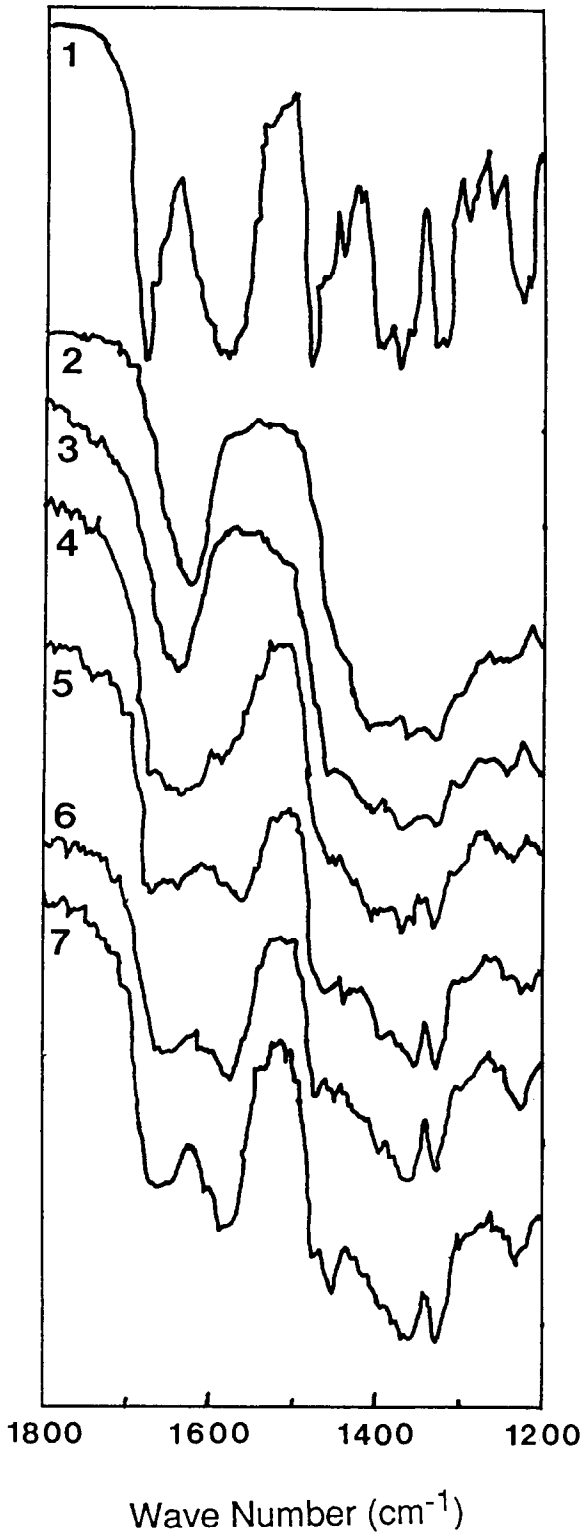


Fig. 7. DSC thermograms of sodium indomethacin (NaIM) and its inclusion compounds prepared by the neutralization method. (1) Sodium indomethacin; (2) β-cyclodextrin; (3) HPβCD; (4) physical mixture NaIM/βCD; (5) physical mixture NaIM/HPβCD; (6) inclusion compound NaIM/βCD; (7) inclusion compound NaIM/HPβCD.



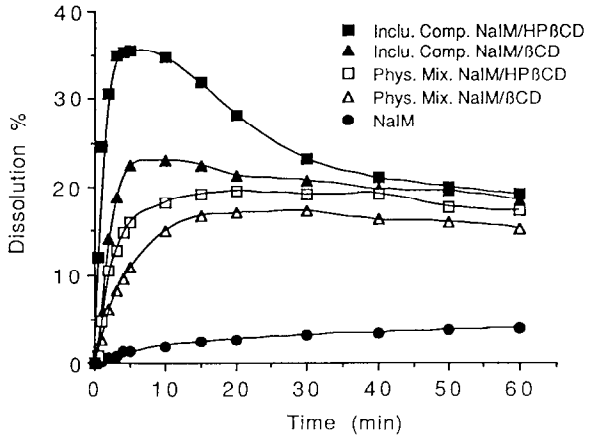


Fig. 9. Dissolution profiles of sodium indomethacin and inclusion compounds in gastric medium (pH 1.4) at 100 rpm and 37 °C (100% dissolution corresponds to 10 mg of indomethacin per liter, under non-sink conditions).

The following solubility results (mg/ml) were obtained in pH 6 phosphate buffer: NaIM, 0.11; physical mixture, NaIM/βCD, 1.4; inclusion compound, NaIM/βCD, 1.5; physical mixture NaIM/HPβCD, 21; inclusion compound, NaIM/HPβCD, 21. The inclusion compounds, as well as physical mixtures, significantly increased the solubility of indomethacin in pH 6 phosphate buffer.

The results of in vitro release in the gastric medium (pH 1.4) (Fig. 9) show the difference between physical mixtures and inclusion compounds. The dissolution rate order is the following:

Inclusion compounds > physical mixtures

> sodium indomethacin

The decrease in indomethacin concentration observed in Fig. 9 is due to the recrystallization of

Fig. 8. IR spectra of sodium indomethacin and its inclusion compounds. (1) Sodium indomethacin; (2) β-cyclodextrin; (3) HPβCD; (4) physical mixture NaIM/βCD; (5) physical mixture NaIM/HPβCD; (6) inclusion compound NaIM/βCD; (7) inclusion compound NaIM/HPβCD.

indomethacin in acid medium. HPβCD yields the best result (Lin et al., 1990).

Discussion

Various methods of preparing complexes

In various works which are found in the literature, more or less contradictory results appear to emerge concerning indomethacin and cyclodextrin complexes, and especially their type, stoichiometry and geometry (Kurozumi et al., 1975; Szejtli and Szente, 1981; Lin and Kao, 1989; Backensfeld et al., 1990).

In this work, we have shown that the type of product obtained can depend on the preparation procedure: the neutralization method leads to the inclusion of sodium indomethacin, whereas indomethacin in the acid form appears to be included in the cyclodextrins by the spray-drying method. The form of the drug molecule in the cyclodextrin cavity has a significant effect during application. Indomethacin in the non-ionized form and in the molecular state can be directly bioavailable.

Kneading seems to be of great interest depending on the objectives required. In fact, this is the method chosen if one needs to obtain a simple increase in solubility and dissolution rate, without requiring the formation of true inclusions.

Moreover, it is a technique which is potentially industrializable, on condition that a powerful mixer/kneader is available and that the manufacturing operating parameters are well defined.

Another important factor is the type of cyclodextrin employed. In fact, complexes obtained with hydroxypropyl β-cyclodextrin, which is more water-soluble, in every case exhibit better solubility and dissolution rate compared with the β-cyclodextrin complexes.

Characterization of the complexes obtained

Because of direct visualization of the fusion phenomena, the thermomicroscopy technique serves to complete and confirm the results obtained by DSC. It is moreover a direct technique, easy to implement. NMR has shown itself to be a precise and reliable technique which, with respect to the NaIM/βCD inclusion compounds, has enabled the comfirmation of the existence of the inclusion as well as its stoichiometry (1 : 1) (Djedaïni et al., 1990).

However, with respect to the acid form of the complex (IM/βCD) obtained by spray-drying, the characterization results do not all follow the same pattern. In fact, although the NMR analyses in liquid medium do not lead to the conclusion of a true inclusion (Wouessidjewe et al., 1990), the thermal behaviour (DSC) of the product obtained (Fig. 4), and particularly the presence of the indomethacin after acetone washing of the complex (Table 1) lead us to believe in the existence of an interaction between indomethacin and the cyclodextrins whose nature is yet to be determined. Without being able to state definitively that there is a true inclusion, it would seem that the acid form of indomethacin is highly dispersed in the cyclodextrin.

To conlcude, the value of this work has been to discuss the various preparation methods of complexes of indomethacin and cyclodextrins. The possibility of using several different and sometimes complementary physicochemical characterization methods enables better definition of the products obtained.

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