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CYCLODEXTRIN INCLUSION OF *p*-HYDROXYBENZOIC ACID ESTERS

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Abstract

Complexes between members of a homologous series of alkylparabens and β-cyclodextrin (β-CD) have been prepared by both kneading and co-precipitation methods and their behaviour studied by differential scanning calorimetry (DSC), thermogravimetric (TG), infrared (IR) and powder X-ray diffraction (PXRD) techniques. PXRD revealed that complexation did occur by both the kneading and co-precipitation methods. DSC and IR techniques confirmed these results and TG indicated the presence and number of water molecules in each complex.

Keywords: alkylparabens, cyclodextrin inclusion

Introduction

p-Hydroxybenzoic acid esters or parabens (Fig. 1) are widely used as typical preservatives for cosmetics, food products and pharmaceutical formulations.

Parabens are often used in combination to take advantage of synergistic effects, are active over a wide pH range, have a broad spectrum of antimicrobial activity and are most effective against yeasts and moulds [1]. In general the antimicrobial activity, antiseptic action and clinical safety of parabens increase with the elongation of the alkyl moiety. However, practical use of parabens with longer alkyl chains has been limited because of their low solubility in water. The solubilities of parabens in both pure water and in the presence of 2-hydroxypropyl-β-cyclodextrin have been the subject of recent studies [2, 3]. Cyclodextrins (CDs) are water-soluble, hydrophobic torus-shaped cyclic oligosaccharides with a hydrophilic outer surface and a hydropho-

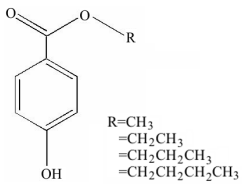

Fig. 1 Chemical structure of the paraben molecules

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bic central cavity. Complexation with CDs has been shown to improve some physico-chemical properties of drug molecules such as stability or aqueous solubility [4–6]. In this work, solid-state inclusion complexes with β-cyclodextrin in 1:1 molar ratio with each paraben have been prepared using the co-precipitation and kneading techniques. The resulting properties of these species have been characterised by thermal, infrared and powder X-ray diffraction analyses. Studies involving the use of thermal methods in the characterization of pure cyclodextrins [7] and their inclusion complexes with drugs [8–10] have recently appeared in this journal.

Experimental

Materials

β-cyclodextrin (β-CD), was obtained from Cyclolab, Hungary and was used as received. Methyl-, ethyl-, propyl- and butyl paraben were purchased from Sigma Chemical Company [St. Louis, Missouri, USA] and were used without any further purification.

Sample preparation

Co-precipitated materials were prepared by the addition of an equimolar amount of drug to a hot (~45°C), saturated aqueous solution of β-CD. Kneaded materials were obtained by initially preparing a homogeneous paste of the cyclodextrin by mixing the CD in a mortar with water. To this CD paste the paraben was added and the mixture was kneaded for 1 h. During this process, an appropriate quantity of water was added to the mixture in order to maintain a suitable consistency. Physical mixtures were prepared in the same molar ratio by simple blending of the individual components with a mortar and pestle.

Analytical methods

Both the thermogravimetric analysis and differential scanning calorimetry experiments were performed on a Perkin Elmer PC7-Series instrument. All TG and DSC runs were performed at a heating rate of 10°C min^{-1} over a heating range of 30–300°C. The DSC was run under dry nitrogen with a flow rate of 30 mL min^{-1}. Infrared spectra of both the pure and complexed materials were recorded on a Perkin Elmer 983 IR spectrophotometer. Samples were prepared by grinding the material in nujol mull® and run over the range 1000–4000 cm^{-1}. Powder X-ray diffraction patterns were collected on a Philips PW1050/25 vertical goniometer using Ni-filtered CuK_α-radiation (λ=1.5418 Å). Scans were carried out in a step mode at a scan speed of 0.1° 2θ min^{-1}, step size 0.1° 2θ.

Results and discussion

The DSC traces of the methyl-, ethyl-, propyl- and butyl paraben complexes together with the traces of the appropriate uncomplexed drugs and the CD-paraben physical

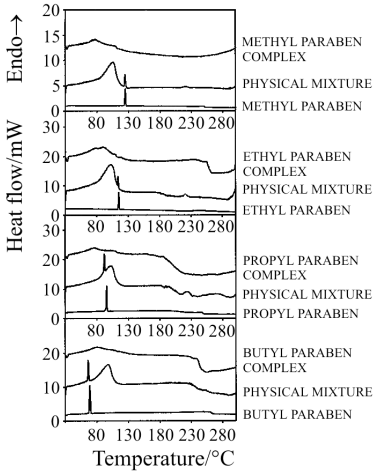

Fig. 2 DSC traces of the β-CD paraben complexes, 1:1 physical mixtures and uncomplexed parabens

mixtures are shown in Fig. 2. The characteristic fusion endotherms for methyl-, ethyl-, propyl-, and butyl paraben are 126, 116, 96 and 69°C, respectively, and are clearly visible in the DSC traces of the uncomplexed drug and physical mixtures. In each case the disappearance of the fusion endotherm was observed in the DSC traces of the complexes, which is attributed to complexation of the drug inside the cyclodextrin cavity [11].

TG traces were recorded to quantify the water content. The average numbers of calculated water molecules per β-CD molecule were found to be 7.2, 7.0, 7.0 and 7.3 for the methyl-, ethyl-, propyl- and butyl paraben complexes respectively. Water was lost over a wide temperature range of 30–130°C. This event was reflected in the DSC traces (Fig. 2), which showed a broad asymmetric endotherm in the corresponding temperature range. The asymmetric shape indicates that water loss from these complexes is a multi-step process. As is usually the case for β-CD complexes there is no well-defined melting point. In all four complexes, the onset of decomposition begins well below the decomposition of the β-CD molecule, which occurs above 290°C. This event is reflected in the TG traces by further mass loss from 200°C and is therefore associated with decomposition of guest molecules included in the complex. Very large mass losses are observed in the TG traces from 300°C onwards for all the complexes, confirming the decomposition of the β-CD molecules.

IR spectra were recorded for all preparations and the carbonyl stretching frequency was monitored. For the pure methyl-, ethyl-, propyl- and butyl paraben the υ(C=O) was measured and found to occur at 1679, 1672, 1675, 1678 cm^{-1} respectively. The carbonyl stretching frequency for the complexes shifted to the significantly higher frequencies of 1715, 1708, 1712, 1708 cm^{-1}. This indicates that the C=O bond is stronger in the complexed drug due to the absence of the strong hydrogen bonding (C=O···H–O) found in the crystals of the uncomplexed guest molecules [2].

PXRD traces of all preparations were recorded. Those for the kneaded and corresponding co-precipitated materials were similar, indicating that they are the same crystalline phase. It was recently shown [12] that the majority of cyclodextrin inclusion complexes containing organic guests can be classified into various isostructural series, each of which possesses a distinctive 'reference' PXRD pattern. The term 'isostructural' is used here in the sense defined by Kálmán and Párkányi [13] to denote the fact that the complexes have the same space group with similar unit cell dimensions and a similar internal arrangement of molecules. Close matching of an experimental pattern for a putative complex with a reference pattern for a particular isostructural series proves that the material is an inclusion complex [12]. Using this procedure, only the PXRD pattern of the putative complex is recorded while those of the separate components and the physical mixture are not required. Thus, it was found that the traces of Fig. 3 have similar profiles to those of the reference patterns shown in Fig. 4, which represent β-CD inclusion complexes crystallizing in the space groups P1 and C2 with unit cell dimensions of approximately a≈15.6, b≈15.6, c≈15.9 Å, α≈102, β≈102, γ≈104° and a≈19.2, b≈24.5, c≈15.9 Å, β≈109° respectively. In making the comparison, near equality of the angular positions of peaks (determined by the unit cell dimensions) is the criterion, not necessarily peak intensities [12]. The patterns for the two isostructural series (Fig. 4) are subtly different, but both are based on 'channel packing' of complex units. The advantage of this method is that in addition to indicating complex formation unequivocally, the nature of the overall crystalline packing is hence also known from the isostructural series identified. Sin-

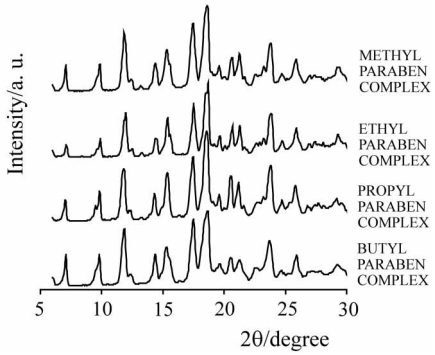

Fig. 3 PXRD traces of the β-CD paraben complexes

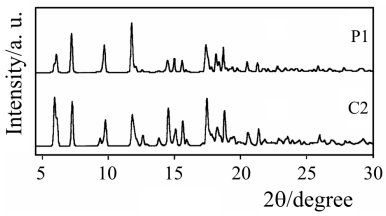

Fig. 4 PXRD reference patterns for two closely related isostructural series of β-CD inclusion complexes

gle crystal X-ray analyses are in progress to determine the detailed modes of inclusion of the guests.

Conclusions

In this study solid-state paraben-cyclodextrin inclusion complexes were prepared in an attempt to improve the aqueous solubility of paraben molecules. Inclusion complex formation was achieved by co-precipitation and kneading techniques. This was inferred from a combination of thermal analysis, IR and PXRD techniques. PXRD traces of all the complexes are in close match indicating that these complexes are isostructural. Comparison of the common PXRD trace with reference patterns indicates that the crystal structures are based on channel packing of the complex units.

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