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CHARACTERIZATION OF CYCLODEXTRIN-CARBOPOL INTERACTIONS BY DSC AND FTIR

Carmen Rodríguez-Tenreiro, Carmen Alvarez-Lorenzo, A. Concheiro and J. J. Torres-Labandeira[*]

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782 - Santiago de Compostela, Spain

Abstract

The interactions between Carbopol and β-cyclodextrin (BCD) or hydroxypropyl-β-cyclodextrin (HPBCD) were studied by differential scanning calorimetry (DSC) and FTIR spectroscopy. Aqueous solutions of both components were desiccated by freeze-drying or heating in an oven (films) at various temperatures. The use of different drying procedures allowed their influence on the interactions to be studied. The evolution of the Carbopol glass-transition was also evaluated by DSC using first heating runs up to different temperatures. Disappearance of the Carbopol glass-transition was observed in the freeze-dried systems prepared with either of the cyclodextrins and in the films that contained HPBCD. The changes in the FTIR band of Carbopol at 1700 cm^{-1} confirmed the existence of interactions with both cyclodextrins, especially with HPBCD. This information may be useful for optimising the solubilizing capacity and controlled release performance of aqueous Carbopol-cyclodextrin systems.

Keywords: Carbopol, cyclodextrin, DSC, film, freeze-dried, FTIR, glass-transition, Lorentzian deconvolution

Introduction

Cyclodextrins are cyclic oligosaccharides that are able to form inclusion complexes with several drugs thus changing their solubility and other physicochemical and biopharmaceutical properties [1, 2]. The concomitant presence of cyclodextrins and hydrophilic polymers in gels and tablets has recently been shown to be a useful way of modulating their swelling, adhesiveness and drug release behaviour [3, 4]. Furthermore, when cyclodextrins are combined with polymers, such as cellulose ethers and poly(vinylpyrrolidone), a solubilizing synergistic effect is observed [1, 5, 6]. Although this phenomenon has been reported in several publications, the mechanisms involved are still not well established. The proportion of the drug solubilized usually exceeds the stoichiometry of the inclusion complexes, which suggests the contributions of surfactant-like effects and of molecular aggregation [6].

* Author for correspondence: E-mail: ffjuant@usc.es

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Poly(acrylic acid) derivatives, and in particular Carbopol®, are hydrophilic polymers commonly used in pharmaceutical technology [7]. No information about the possible interactions between Carbopol and cyclodextrins, or about the effects of blends on drug hydrosolubilization, has been reported. The presence of a high density of carboxylic acid groups in the Carbopol network and of numerous hydroxyl groups in the cyclodextrins suggests that strong associative phenomena can occur [8]. Interactions between two amorphous substances can be observed as changes in their glass-transition temperatures, T_g [9], or in shifts in the characteristic IR absorption bands of some chemical groups [10]. Although cyclodextrins are known to crystallize as hydrated [11] glass transitions have been also reported and attributed to amorphous portions [12].

The aim of this study was to investigate the interactions between Carbopol and two cyclodextrins with different substitution characteristics. To carry out the work, films and freeze-dried systems were obtained from aqueous dispersions of both components. The analysis by quick characterization techniques, such as DSC and FTIR, of these systems and of physical mixtures should provide evidence of the interactions that could be induced in solution.

Experimental

Materials

Carbopol® 71G (batch C7075GJ013) was provided by BFGoodrich Europe, UK. β-cyclodextrin (BCD) and hydroxypropyl-β-cyclodextrin (HPBCD) (D.S. 4.6) were from Laisa-Roquette (Barcelona, Spain) and Janssen Pharmaceutische (Belgium), respectively.

Preparation of Carbopol-cyclodextrin blends

To aqueous solutions of cyclodextrin (15 mM), amounts of Carbopol were added to obtain a final concentration of 0.25% (mass/vol). The mixtures were stirred until the polymer was completely dispersed. Each solution was divided into three portions to be desiccated in an oven at 37 and at 70°C, to yield films, and for freeze-drying in Labconco Lyph-lock 6 apparatus (–34°C, 48 h) after frozen by immersion in liquid nitrogen.

As references, physical mixtures of cyclodextrin and Carbopol (50:50/ by mass) were prepared by mixing in a Turbula T2C mixer (Schweiz) for 10 minutes, and films of pure Carbopol were obtained by drying a 0.25% Carbopol aqueous dispersion at 37 and 70°C.

Differential scanning calorimetry

DSC experiments were carried out, in duplicate, using a DSC Q100 (TA Instruments, New Castle, DE, USA) with a refrigerated cooling accessory (RCS). Nitrogen was used as the purge gas at a flow rate of 50 mL min^{-1}. The calorimeter was calibrated for baseline using no pans, for cell constant and temperature using indium (melting

point 156.61°C, enthalpy of fusion 28.71 J g^{-1}), and for heat capacity using sapphire standards. All experiments were performed using non-hermetic aluminium pans, in which 2–5 mg of blend were accurately weighed, and then just covered with the lid. The samples were heated from 30 to 150, 200 or 250°C, then cooled to 0°C, and finally heated again to 300°C, always at 10 K min^{-1}.

Fourier transform infrared spectroscopy (FTIR)

Spectra were recorded using a FTIR Mattson ATR Spectra-Tech spectrometer (Germany) over the range 400–4000 cm^{-1} using the KBr pellet technique. Lorentzian deconvolution of Carbopol carbonyl groups was performed using a multi-peak curve-fitting software (Microcal Origin 5.0, Northampton, MA). The hydrogen-bonding percentage between Carbopol and cyclodextrin was calculated using the following equation [10]:

$$H\% = [A_{1730}/(A_{1730}+A_{1700})]\cdot 100$$

where A_{1730} and A_{1700} are the area of the peaks at 1730±5 cm^{-1} and at 1700±5 cm^{-1}, respectively.

Results and discussion

Blends of Carbopol-cyclodextrin were desiccated by different techniques to study the influence of the preparation procedure on the visualization of the interactions. The behaviour of the pure components was used as a reference. DSC curves of pure Carbopol films prepared at 37 and 70°C presented three characteristic peaks; a broad endotherm between 50 and 100°C caused by evaporation of some water that remains in the film after desiccation (not observed in the second heating run), a step in the baseline around 133°C that is characteristic of its glass-transition, and a last endotherm, close to 250°C, that reflects the polymer decomposition process [13]. Cyclodextrins did not provide films and were analysed as the initial powder. The DSC curve for β-cyclodextrin powder shows the endotherm of evaporation of water adsorbed between 100 and 170°C, a glass-transition at 216°C, and finally the decomposition signal above 300°C [14]. The glass-transition of BCD could only be clearly observed in the first heating run.

Taking into account the thermal behaviour of each component, we carried out a first screening of the best conditions to detect changes in the T_g of the components when mixed. The maximum temperature of the first heating run seemed to be a critical parameter. Different DSC curves of physical mixtures and films were obtained as the conditions of the first scan were changed (Fig. 1). For example, when the physical mixture was initially heated to 250°C, neither the T_g of Carbopol nor the T_g of BCD was clearly observed, but two broad endotherms due to a) water evaporation and b) overlaping T_g of BCD with the beginning of polymer melting and decomposition. The second heating scan showed a glass-transition at a much greater temperature, around 200°C, than the Carbopol T_g. This behaviour suggests that, at the high tem-

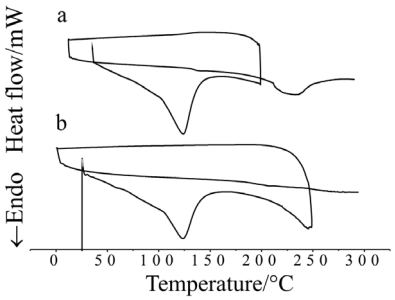

Fig. 1 DSC curves of the physical mixture Carbopol-BCD systems obtained applying a first heating until a – 250°C and b – 200°C

perature reached in the first heating run, the miscibility of both components is promoted, even in the physical mixture, and that the single relatively high T_g shown in the second run reflects the stiffness of the Carbopol/BCD complexes obtained, probably through hydrogen bonding [9].

In contrast, if the first heating run was stopped at 200°C, the Carbopol T_g was detected again in the second run of the physical mixtures, where a melting-decomposition endotherm at 225–250°C also appears. Similar results were found for the films, but the films were more heat-sensitive; i.e. the Carbopol T_g was only detected in the second run when the maximum temperature of the first heating run was 150°C. The same tendency was observed for Carbopol/HPBCD systems. Therefore, to avoid artefacts caused by temperature-induced association phenomena, all the subsequent experiments were carried out with first heating runs up to 150°C. Since the first runs only displayed water evaporation endotherms, only the second heating runs were used to analyse the cyclodextrin/Carbopol interactions.

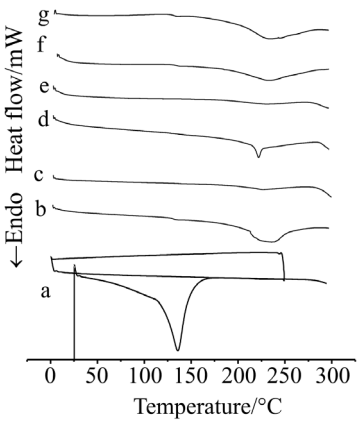

Fig. 2 DSC curves of a – BCD; b – physical mixture Carbopol+BCD; c – Carbopol-BCD blends dried under different conditions: oven at 37°C; d – oven at 70°C, e – freeze-drying; pure Carbopol film dried f – at 37°C and g – at 70°C

Figure 2 shows the DSC second heating runs of β-cyclodextrin/Carbopol blends obtained by physical mixing, oven desiccation or freeze-drying.

A change in the T_g of Carbopol in the DSC curves of the systems can provide information about its miscibility with the cyclodextrins (Table 1). The DSC results indicate that the Carbopol/BCD interaction can be only observed for the freeze-dried blends, because for the other two systems it is possible to observe a glass-transition around 133°C, which is associated with Carbopol. This result is supported by the presence of the endotherm of Carbopol decomposition in the physical mixture and in both kinds of films. The behaviour of the films did not seem to be affected by the temperature used to obtain them.

Table 1 Glass-transition temperature values of Carbopol and cyclodextrin blends after desiccation under different conditions. T_g values were reproducible to about ± 1°C

Systems		T_g/°C
Carbopol	37°C dried film	131.7
	70°C dried film	131.7
BCD	Pure	216.2
BCD:Carbopol	Physical mixture	130.3
	37°C dried film	134.4
	70°C dried film	127.4
	Freeze-dried	–
HPBCD	Pure	225.3
HPBCD:Carbopol	Physical mixture	131.1
	37°C dried film	–
	70°C dried film	–
	Freeze-dried	–

As in the case of pure BCD, the DSC curve of HPBCD shows a broad endotherm, between 50 and 150°C, owing to its dehydration [15], a glass-transition at 225°C and decomposition above 300°C. The main difference from the β-cyclodextrin/Carbopol mixtures was that, in the HPBCD/Carbopol systems, a glass-transition around the T_g of Carbopol was only recorded for the physical mixture. Both films and freeze-dried systems neither presented any T_g nor decomposition peaks (Fig. 3). These observations indicate that a stronger interaction in water occurs between HPBCD and Carbopol and that the complexes show a high thermal stability.

Further information was obtained from the analysis of the FTIR spectra of the films and the freeze-dried systems (Fig. 4). Cyclodextrins show the characteristic saccharide peaks around 1000–1200 cm^{-1} and the bent hydroxyl groups at water at 1635 cm^{-1} [16–18]. The broad band of Carbopol carboxyl groups at 1700 cm^{-1} is attrib-

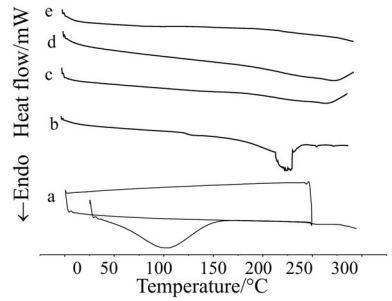

Fig. 3 DSC curves of a – HPBCD; b – physical mixture Carbopol+HPBCD; c – Carbopol -HPBCD blends dried under different conditions: oven at 37°C; d – oven at 70°C and e – freeze-drying

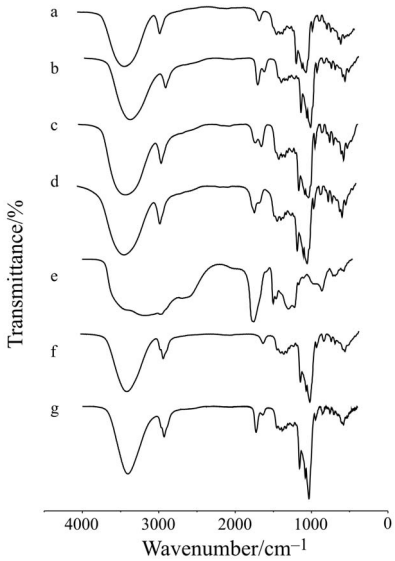

Fig. 4 FTIR spectra of a – BCD; b – Carbopo-BCD freeze-dried; c – film of Carbopol+ BCD dried at 37°C; d – film of Carbopol+BCD dried at 70°C; e – pure Carbopol film dried at 70°C; f – HPBCD and g – Carbopol-HPBCD freeze-dried

uted to the existence of two carbonyl populations; one corresponding to the intra- and intermolecular hydrogen bonding and another due to free carbonyl groups [8, 19].

The Carbopol carbonyl band moves to a higher vibration frequency (1715–1726 cm^{-1}) in the presence of cyclodextrins, indicating a diminution of the internal hydrogen bonding of Carbopol and the formation of new bonds with the cyclodextrins (Fig. 5). This shift is more intense in the FTIR spectra of blends containing HPBCD (1726 cm^{-1}) than in the β-cyclodextrin ones (1715–1721 cm^{-1}). The shift was a function of the desiccation procedure only in the case of BCD/Carbopol blends. As

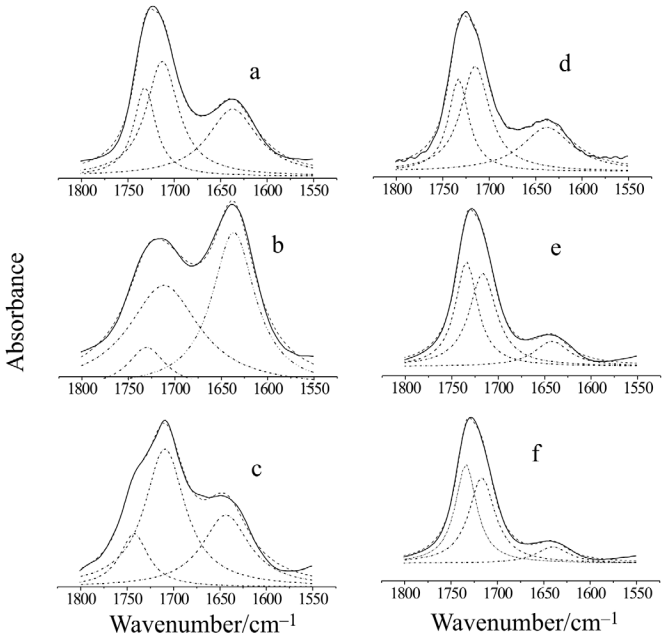

Fig. 5 Lorentzian curve-fitting of peaks between 1800 and 1600 cm^{-1} of FTIR spectra: a – Carbopol-BCD freeze-dried blend; b – films of Carbopol+BCD dried at 37°C; and c – at 70°C; d – Carbopol-HPBCD freeze-dried blend and films of e – Carbopol+HPBCD dried at 37°C; and f – at 70°C. The continuous line represents the absorbance observed; the dashed line the absorbance simulated for the Carbopol/cyclodextrin system; and the fine dashed lines, the simulated absorbances at 1700, 1730, 1636 cm^{-1}

found before in the DSC curves, the interaction in these blends is stronger in the freeze-dried systems (1721 cm^{-1}) than in the films (1715 cm^{-1}). It has been widely reported that hydrogen-bonding interactions between complementary polymers are promoted during freeze-drying [20]. A similar effect is expected to occur for the cyclodextrin/Carbopol systems.

Table 2 The percentage (H) of Carbopol carboxyl groups bound to the hydroxyl groups of cyclodextrins, estimated from Lorentzian multi-peak deconvolution of the FTIR spectrum bands between 1800–1600 cm^{-1}[9]

Systems		H%
BCD : Carbopol	37°C dried film	17.3
	70°C dried film	21.5
	Freeze-dried	34.3
HPBCD : Carbopol	37°C dried film	47.9
	70°C dried film	48.7
	Freeze-dried	38.2

To estimate the percentage of hydrogen bonding with cyclodextrins, the overlapped bands of Carbopol carbonyl groups and cyclodextrin water bending were deconvoluted into three peaks by Lorentzian curve-fitting. The ratio of the areas of the carbonyl bands (Table 2) indicates that, although hydrogen bonding occurs with both cyclodextrins, the interactions are notably more intense with HPBCD, especially in the films, than with BCD. For BCD, the application of the freeze-drying technique considerably enhances the hydrogen bonds with Carbopol.

Conclusions

The results obtained from the analysis of Carbopol/cyclodextrin systems by DSC and FTIR techniques indicate that Carbopol interacts with both cyclodextrins in aqueous medium, especially with HPBCD, probably because it has a greater content of pendant hydroxyl groups, that are more accessible for establishing hydrogen bonds. Therefore, HPBCD/Carbopol blends can show different properties to those of each component separately. For BCD, the use of a freeze-drying procedure seems to be necessary for such interactions to be detected. The results obtained also draw attention to the importance of careful selection of the DSC experimental conditions to elucidate the interactions.

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