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ORIGINAL ARTICLE

# Synthesis and characterization of poly(ethylene glycol) based β-cyclodextrin polymers

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**Abstract** A series of novel water soluble β-cyclodextrin (βCD) polymers has been synthesized from functionalized poly(ethylene glycol) (PEG). The chemical composition of the polymers has been characterized by $^1$H NMR and the βCD content is found to be between 48 and 33% (w/w). The molecular weight has been determined by Size Exclusion Chromatography (SEC) and depends on the ratio between βCD and PEG, varying from $2.1 \times 10^4$ to $8.6 \times 10^4$ g mol$^{-1}$. The physico chemical properties have been characterized by differential scanning calorimetry (DSC), viscometry and isothermal titration calorimetry (ITC). ITC shows that the polymers have association constants comparable to βCD with different guest molecules, indicating a good accessibility of the CDs.

**Keywords** Cyclodextrin polymer · Poly(ethylene glycol) copolymer · Inclusion complex · ITC

## Introduction

Due to their ability to form complexes with a wide range of hydrophobic molecules, cyclodextrins (CDs) have been used for decades in science as well as in industry [1]. In pharmaceutics CDs and CD derivatives are used to improve e.g. solubility, stability and bioavailability of many drugs [2, 3]. Several drug delivery systems based on CDs have been elaborated for e.g. nasal-, dermal- and ophthalmic drug delivery [4]. In recent years cyclodextrin polymers (CD-polymers) have gained increasing attention in biomedical science. Several types of CD polymers have been synthesized, e.g. branched polymers by reacting CDs with epichlorohydrin [5], linear polymers with pending CDs [6, 7] and linear polymers with CDs incorporated into the backbone [8]. The use of CD-polymers offers some advantages compared with native CDs. CD-polymers are e.g. known to form nanoparticles or gels in aqueous media when associated with different hydrophilic polymers [9–11]. These systems can be applied in e.g. drug delivery applications. Furthermore, hydrophilic CD-polymers are gaining increasing attention in the field of gene therapy where several cationic polymeric CD-systems have been successfully used to transfect plasmide DNA in in vitro experiments [12, 13]. One of the major drawbacks of other non-viral cationic vectors such as poly-L-lysine is their fairly high in vivo and in vitro toxicity [8]. Compared to these cationic vectors, polymeric CD-systems have low toxicity but maintain high transfection efficiency [12]. Due to these promising results, new biocompatible CD-polymers are attractive candidates as gene transfection agents as well as for drug delivery in general.

PEG is well known for its biocompatibility and is used in numerous biomedical applications. Several publications on synthesis of PEG hydrogels have been published [14], as well as PEG-βCD conjugates [15], yet relative few deal with polymers based on cyclodextrin and PEG. Cesteros and coworkers describe the synthesis of polymers by cross linking diisocyanate functionalized PEG and β-cyclodextrin (βCD) [16]. These polymers are however insoluble in water and hence incompatible with several applications where water soluble polymers are needed such as for DNA

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vectors as well as for the formation of nanoparticles in aqueous solution [9, 12, 13].

Here we report a convenient synthesis and characterization of a novel water soluble βCD polymer made from poly(ethylene glycol) bis(carboxymethyl) ether (PEG600-diacid). The synthesis route is illustrated in Fig. 1 and a schematic representation of the PEG/βCD-polymers is illustrated in Fig. 2. Compared to the previously described PEG based cyclodextrin polymers, these new polymers are specifically designed for biomedical applications since the polymer backbones are degradable through the PEG/CD ester bonds which are hydrolytically or enzymatically cleavable [17, 18].

## Experimental section

### Materials

Oxalyl chloride 96.0% (Fluka, Germany), poly(ethylene glycol) bis(carboxymethyl) ether (Mn 600, Aldrich, Steinheim, Germany), βCD (Beta W7 Pharma, Wacker-Chemie, Burghausen, Germany), dichloromethane (DCM, 98%, Aldrich, Steinheim, Germany), *N*,*N*-dimethylformamide (DMF, 99.8%, $H_2O$ ≤0.01%, Fluka, Germany), pyridine (anhydrous, 99.8%, Aldrich, Steinheim, Germany), 4-(dimethylamino)pyridine (DMAP, 99%, Aldrich, Steinheim, Germany), tetrabutylammonium bromide (TBA, Aldrich, Saint-Quentin Fallavier, France), 1-adamantane acetic acid (AdaAA, Aldrich, Saint-Quentin Fallavier, France) were used as received unless otherwise noted. 2-(1-Adamantyl) ethyl trimethylammonium bromide (AdaTMA) and the copolymer βCD/epichlorohydrin (pβCD) were synthesized as previously described [13]. pβCD presents a molecular weight $M_w$ of $1.6 \times 10^5$ g $mol^{-1}$ and a βCD content of 59% (w/w) determined by $^1$H NMR.

### Synthesis

All glassware was dried at 130 °C for 2 h and cooled in a desiccator prior to use. βCD was dried at 115 °C in vacuum over night.

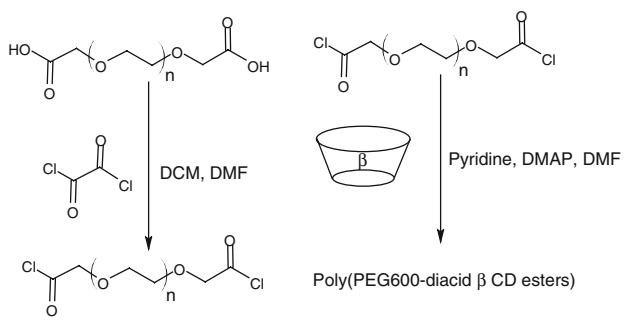


**Fig. 1** Reaction scheme for the synthesis of PEG/CD polymers

### *PEG600-diacyl chloride*

In a three necked round bottom flask equipped with magnetic stirring and drying tube, a catalytic amount of DMF (a drop of 100 μL DMF in 1 mL DCM) was added to a solution of PEG600-diacid (18.8 g, 31.4 mmol) in 30 mL of DCM. The solution was cooled to 0 °C in an ice bath. A solution of oxalyl chloride (23.9 g, 188.4 mmol) in 20 mL DCM was added dropwise. After complete addition, the mixture was allowed to warm to ambient temperature and was stirred over night. DCM and excess oxalyl chloride were removed in vacuo. The resulting oil was used without further purification. Yield: 19.9 g (95%).

### *Poly(PEG600-diacid βCD esters)*

βCD (2.0 g, 1.76 mmol) was dissolved in 100 mL DMF under nitrogen atmosphere. The adequate amount of PEG600-diacylchloride (2.24–3.93 g, 3.52–6.16 mmol) was dissolved in 5 mL DMF and added to the βCD solution. Pyridine (5.7–10 mL) and DMAP (100 mg) were added and the temperature elevated to 80 °C. The solution was stirred under nitrogen for 24 h. Solvent was removed in vacuo and the remaining solid was dissolved in 100 mL MilliQ water. pH was adjusted to approximately 7 by addition of saturated sodium bicarbonate solution. The polymers were dialyzed against MilliQ water for 5 days and freeze dried yielding white/yellow solids.

### Characterization

$^1$H NMR analyses were conducted in deuterated water with a Brucker DRX400 spectrometer (5 mm TXI (H/C/N) xyz-gradient probe) with a delay time (d1) set for 30 s. SEC was made in MilliQ water with 0.1 mol $L^{-1}$ $NaN_3$ (columns TSK-gel type SW 4000-3000 and detection by a Wyatt miniDawn light scattering (LS) detector and a Wyatt Optilab Rex. refractive index detector).

Dialysis was made with Spectrum Spectra/Por, MWCO 6000-8000 25.5 mm diameter, 5 mL/cm. Freeze drying of the polymers was made on a Heto CT 60e. The DSC measurements were done with a Diamond DSC Perkin Elmer apparatus. Indium was used to calibrate the system ($T_f$ = 156.4 °C and $\Delta H_f$ = 28.4 J $g^{-1}$). Ten milligram of copolymer were set in a sealed aluminium cap and analysed using a temperature rate of 10 °C/min in a temperature range of −100 to +80 °C.

For viscometry experiments, all polymer solutions were prepared in MilliQ water 1 day before the experiments in order to allow the samples to reach equilibrium. Solution viscosities were determined with a 10 mL Ubbelohde suspended level viscometer settled in a water bath at 25 °C. The concentration range of the copolymer solutions was

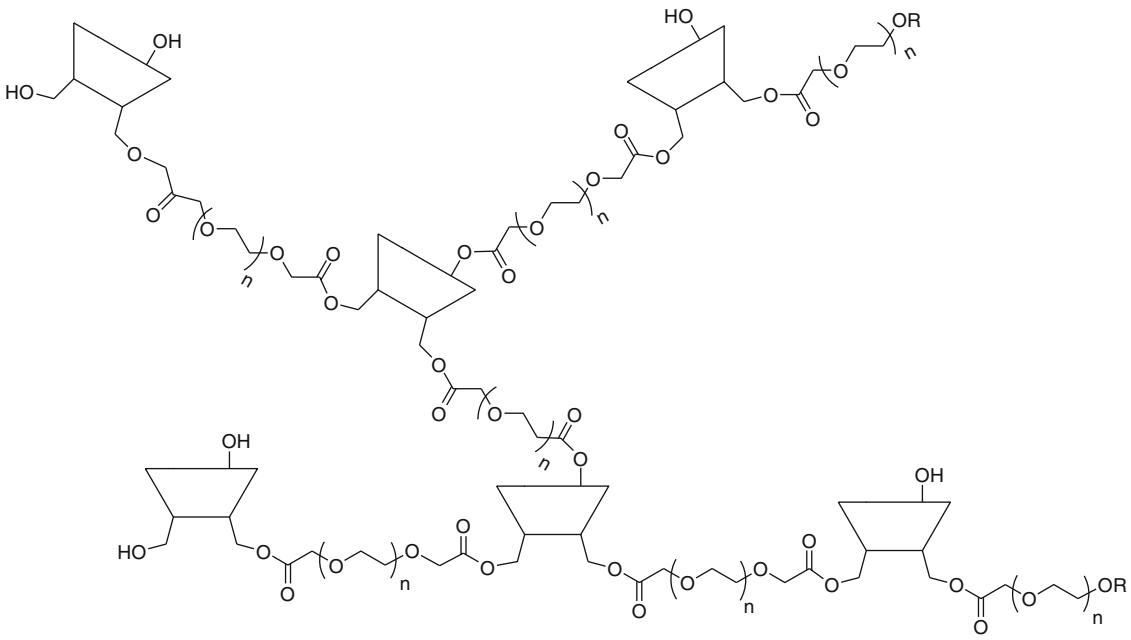


**Fig. 2** Schematic illustration of the PEG/βCD-polymers

6–13 g $L^{-1}$ and all dilutions were made by adding water directly into the viscometer (30 min between each dilution). ITC measurements were made using a MicroCal VP-ITC microcalorimeter. In each titration, injections of 5 µl of concentrated AdaAA, or AdaTMA, solutions ($10^{-2}$ mol $L^{-1}$ in phosphate buffer, pH 6.95) were added from the computer controlled 295 µl microsyringe at an interval of 180 s into the cell (volume = 1.4569 mL) containing the polymer solution ($10^{-3}$ mol $L^{-1}$ in βCD), while stirring at 450 rpm. The experiments were carried out at 25 °C. The raw experimental data were obtained as the amount of heat produced per second following each injection of adamantyl derivative as a function of time. Integration of the heat flow peaks by the instrument software (after taking the heat of dilution into account) gives the amount of heat produced per injection. The experimental data are fitted with a theoretical titration curve using the instrument software. The enthalpy change, ΔH, the binding constant, K, and the stoichiometry, n, are the adjustable parameters.

## Results and discussion

### Synthesis and characterization

A series of polymers with different PEG/βCD ratio were obtained by esterification of native βCD and PEG-diacylchloride prepared from commercially available PEG600-diacid. The PEG-diacyl chloride was prepared using an excess of oxalyl chloride and could be used directly without purification. The esterifications were made in DMF/pyridine at 80 °C for 24 h, using a catalytic amount of DMAP. Reaction times shorter than 12 h led to smaller size polymers with no obvious correlation between equivalence of PEG600-diacylchloride and molecular weight. This was also the case for synthesis without the presence of DMAP all indicating that the reaction is fairly slow. The polymers were purified extensively by dialysis against water using membranes with a molecular cut-off of 6000–8000 Da to ensure removal of monomers, oligomers, DMAP and residual solvents. Yields of the polymers are reported in Table 1 and vary from 71 to 82% independent of the molecular weight.

The chemical composition of the polymers has been determined by $^1$H NMR spectroscopy (Table 1). Due to overlap between the PEG signals and the βCD signals, the contribution of PEG is calculated from integrating the anomeric proton of βCD (5.1 ppm) and the combined signals of the remaining six protons of βCD and the protons of the PEG. Figure 3 shows the $^1$H NMR spectrum of PEG/CD-2.75. From NMR analysis, the PEG chain is found to have 48 protons equivalent of 11 ethylene glycol units and two carboxymethyl units on average, which is in well accordance with the molar mass stated by the supplier. Hence the integration of the two regions can be expressed in terms of molar composition as stated in Eq. 1.

$$\mathrm{Int}_1 = 7 \cdot \mathrm{n}_{\beta\mathrm{CD}}; \quad \mathrm{Int}_2 = 7 \cdot 6\mathrm{n}_{\beta\mathrm{CD}} + 48 \cdot \mathrm{n}_{\mathrm{PEG}} \qquad (1)$$

From this, the mass percentage of βCD is calculated using Eq. 2.

**Table 1** Yields, mass % of βCD, equivalency of PEG, molecular weight and polydispersity index of the polymers

| Name | Equivalency PEG/CD | | Yield (%) | Mass % of βCD | | Mw (g mol$^{-1)}$ | PDI |
|---|---|---|---|---|---|---|---|
| | Eq. calc. (mol/mol) | Obs. | | % calc. (g/g) | % obs. | | |
| PEG/CD-2 | 2.00 | 2.14 | 78 | 50.1 | 48.4 | 21600 | 1.5 |
| PEG/CD-2.25 | 2.25 | 2.31 | 82 | 47.1 | 46.5 | 24100 | 1.8 |
| PEG/CD-2.5 | 2.50 | 2.62 | 71 | 44.5 | 43.4 | 36800 | 2.5 |
| PEG/CD-2.75 | 2.75 | 2.88 | 79 | 42.2 | 41.1 | 39300 | 2.4 |
| PEG/CD-3 | 3.00 | 3.37 | 74 | 40.1 | 37.3 | 57900 | 2.0 |
| PEG/CD-3.5 | 3.5 | 4.05 | 78 | 36.4 | 33.1 | 86100 | 1.9 |

The theoretical molar ratios and mass % of βCD are calculated from the amounts of reactants applied. The chemical composition is deduced from NMR analysis

$$\text{Mass}\%\beta\text{CD} = \frac{n_{\beta CD} \cdot M_{\beta CD}}{n_{\beta CD} \cdot M_{\beta CD} + n_{PEG} \cdot M_{PEG}} \quad (2)$$

The amounts of βCD determined by NMR in the polymers are generally a few percent lower than the theoretical amounts, based on the amount of reactants added (Table 1), and the lowering being more pronounced in the polymers with high content of PEG. Loop formation where a PEG chain reacts with only one βCD is likely to occur to some extent, though this is not detectable by NMR analysis. The molecular weight of the polymers seems to have an almost linear correlation with the amount of PEG; the molecular weight range span from 21 × $10^3$ g mol$^{-1}$ to 86 × $10^3$ g mol$^{-1}$ with 2–3.5 equivalences of PEG, respectively. A representative SEC chromatogram of PEG/CD-3 is illustrated on Fig. 4 showing a relatively homogeneous molecular weight distribution and no low molecular weight peaks. The polydispersity index ranges from 1.5 to 2.5 (Table 1). Attempts to increase the molecular weights by using higher concentrations of reactants during the synthesis were unsuccessful. Concentrations of βCD higher than 80 g L$^{-1}$ led to immediate gel formation upon addition of PEG-diacyl chloride. Synthesis with PEG chains having lower molecular weight (PEG250-diacyl chloride) under the same conditions led to large fractions of insoluble polymers, which is assumed to be due to a higher degree of cross linking compared with the PEG600, though this has not been verified.

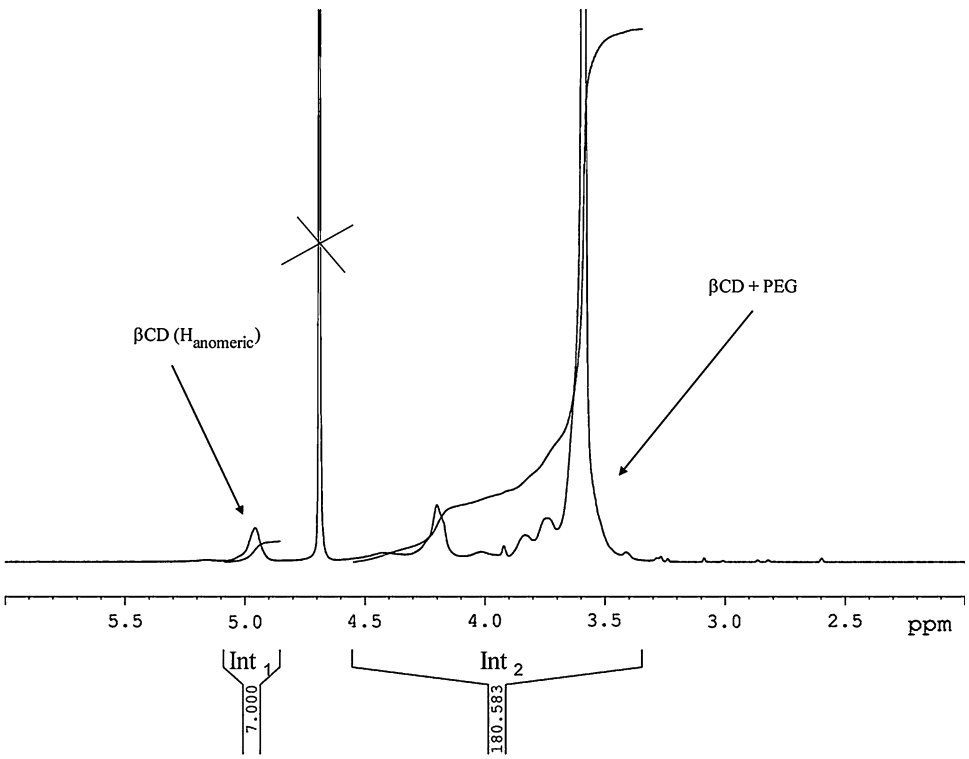


**Fig. 3** $^1$H NMR spectrum of PEG/CD-2.75 in $D_2O$

## Physico-chemical characterizations

### *Thermal properties*

The glass transition ($T_g$) of the polymers was measured by differential scanning calorimetry (DSC) and the results are reported in Table 2. Only the three polymers having the highest content of PEG show a glass transition. One should note that after freeze-drying, PEG/CD-3.5 turns into a "gum" at room temperature. The $T_g$ values slightly vary from −19.5 °C to −16.6 °C as the βCD content increases from 33 to 41%. These results are in agreement with $T_g$ values reported for a series of PEG/βCD networks with higher [PEG]/[βCD] molar ratio (comprised between 14 and 4) for which the $T_g$ values vary from −37 °C to −28 °C [16]. These results are not surprising since the βCD units introduce rigidity in the system containing flexible PEG spacers. Increasing content of βCD should thus increase the $T_g$. No $T_g$ is observed for the polymer PEG/βCD-2 with the higher βCD content. A similar behaviour has been observed in the case of copolymers from βCD/epichlorohydrin that usually have βCD content higher than 50% [19].

### *Viscometry*

The specific viscosity ($\eta_{spe}$) of the polymers was measured in water as a function of the concentration. The reduced viscosity ($\eta_{red}$) is obtained as $\eta_{red} = \eta_{spe}/c$, where c is the polymer concentration in g $L^{-1}$. Examples are shown in Fig. 5. As expected, $\eta_{red}$ decreases with decreasing the concentration, except in the case of PEG/CD-3.5, for which $\eta_{red}$ slightly increases. This behaviour is typical of a polyelectrolyte [20]. After the esterification, acidic functions may still be present at one end of the PEG chains, if both ends did not react with the βCD. Incomplete PEG reaction can thus lead to slightly charged polymers, the charges being due to the residual acid functions. Experimentally, only the sample PEG/CD-3.5 which has the larger ratio [PEG]/[βCD] showed a polyelectrolyte behaviour. This shows that the amount of residual acid functions probably increases with the [PEG]/[βCD] ratio. Adding salt in PEG/CD-3.5 solution (NaCl at 0.1 mol $L^{-1}$) leads to a charge screening, and therefore the usual behaviour of neutral polymer is recovered, that is decreasing of $\eta_{red}$ with decreasing the concentration (Fig. 5). Values of the intrinsic viscosity, [η], were obtained by double extrapolation of the reduced, $\eta_{red}$, and inherent, $\eta_{inh}$, viscosities to zero concentration in water (except PEG/CD-3.5, where [η] was determined in NaCl at 0.1 mol $L^{-1}$). The obtained values are reported in Table 2 (only the reduced viscosities are shown in Fig. 3). All the polymers show positive slopes for both the reduced and the inherent viscosities as a function of concentration. The positive slope of the inherent viscosity is unusual for a neutral polymer, and it may reflect the self-association of the copolymers in water even at low concentration. This self-association is also evidenced by the fact that the samples needed to equilibrate for at least half an hour

**Table 2** Glass temperature and intrinsic viscosity of several polymers

| Copolymer | $T_g$ (°C) | [η] (L/g) |
|---|---|---|
| PEG/CD-2 | * | 0.0053 |
| PEG/CD-2.75 | −16.6 | 0.0025 |
| PEG/CD-3 | −17.7 | 0.0072 |
| PEG/CD-3.5 | −19.5 | 0.0090** |

* Not observed

** In NaCl at 0.1 mol $L^{-1}$

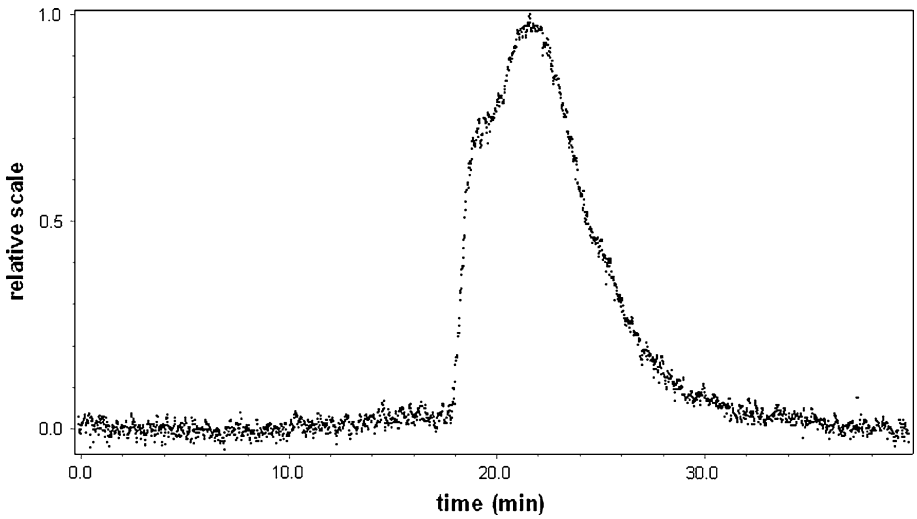


**Fig. 4** SEC chromatogram of PEG/CD-3 (obtained by LS detection)

between each dilution step, in order to obtain reproducible results. No definite trend can be established between [$\eta$] and the $\beta$CD content of the copolymers as there is first a decrease and then an increase of [$\eta$] as a function of the [PEG]/[$\beta$CD] molar ratio. This complex behaviour can be the result of two opposing effects. Increasing the [PEG]/[$\beta$CD] molar ratio should increase the functionality of the branching points in the polymers and thus increase its compacity which is directly probed by a reduction of [$\eta$] in neutral systems. Conversely, increasing the [PEG]/[$\beta$CD] molar ratio can lead to increasing amount of charges. These charges should induce a swelling of the polymer coils and thus an increase of [$\eta$]. The obtained values [$\eta$] are in the range of the one previously determined for p$\beta$CD ([$\eta$] = 0.0067 g $L^{-1}$ [21]), indicating similar compacities of both copolymers. Attempts on quantifying the charges by titration were unsuccessful (data not shown).

*Binding properties*

The ability of the polymers to form inclusion complexes was investigated by isothermal titration microcalorimetry (ITC) at 25 °C and in phosphate buffer (0.01 mol $L^{-1}$) at pH 6.95. The two chosen guests were 1-adamantane acetic acid (AdaAA) and 2-(1-adamantyl) ethyl trimethylammonium bromide (AdaTMA), bearing at pH 6.95 one negative or one positive charge, respectively. Figure 6 reports the enthalpograms obtained in the case of PEG/CD-2 titration by AdaAA and AdaTMA, respectively. The interactions between the species are strongly exothermic, as expected for a complex formation between $\beta$CD cavities and an adamantyl derivative. The experimental data were fitted by a theoretical curve according to the following relations (Eqs. 3, 4), where R and T are the gas constant and the temperature, respectively:

$$\mathrm{CD} + \mathrm{Ada} \rightleftarrows \mathrm{CD/Ada} \quad \mathrm{K} = \frac{[\mathrm{CD/Ada}]}{[\mathrm{CD}][\mathrm{Ada}]} \tag{3}$$

$$\Delta G = -RT \ \ln \ K = \Delta H - T\Delta S \tag{4}$$

The different thermodynamic parameters (enthalpy and entropy variations, $\Delta$H and $\Delta$S, binding constant, K, reaction stoichiometry, n) derived from these experiments are given in Table 3. For comparison, the data are also given for the titration of $\beta$CD and p$\beta$CD. For the different PEG/CD polymers, the values of n are close to 1.0 as expected for a 1:1 complex, and the binding constants are high, between $4.1 \times 10^4$ and $1.3 \times 10^5$ L $mol^{-1}$. For the same polymer, K is generally two times lower with AdaAA compared to AdaTMA. The adamantyl group and the charge have a larger separation in AdaTMA compared to AdaAA due to an additional carbon atom. This probably leads to a better inclusion of the adamantyl group inside the $\beta$CD cavity in the case of AdaTMA. On the other hand, the K values obtained with $\beta$CD and adamantyl derivatives are quite comparable to data reported in the literature ($\sim 10^5$ mol $L^{-1}$ [22–24]), and those of the PEG/CD polymers are lower than the one with $\beta$CD when the PEG content is high. Indeed, Table 3 shows that K decreases with increasing the PEG content. Higher PEG content should correspond to larger $\beta$CD substitution and thus to a possible decrease of the accessibility of the cavities, in agreement with the decreases in K values observed. It has been shown that PEG and $\beta$CD do not form strong complexes [25] as evidenced by their large miscibility in water. However, the occurrence of single crystals PEG/$\beta$CD in very specific conditions (large $\beta$CD/PEG ratio and low water content) show that there is an affinity between these two compounds [26]. Thus it could be speculated that partially reacted PEG chains would occupy some of the $\beta$CD cavities. The finding that n values are close to 1 for all the PEG/CD polymers proves that the affinities of adamantyl derivatives for $\beta$CD cavities of the polymers are much larger than that of PEG. It proves also that there is a negligible amount interlocked CD cavities. The association constants determined should reflect an overall mechanism of displacement of PEG segments and inclusion of the adamantyl groups and thus be slightly lower than the one expected for free CD cavities. For comparison, the K value obtained with p$\beta$CD is even lower than for the PEG/CD series and this can be attributed to the lower accessibility of the cavities due to a larger degree of substitution and higher molecular weight. The |$\Delta$H| values are high, around 30–34 kJ $mol^{-1}$ and the complex formation is enthalpy driven.

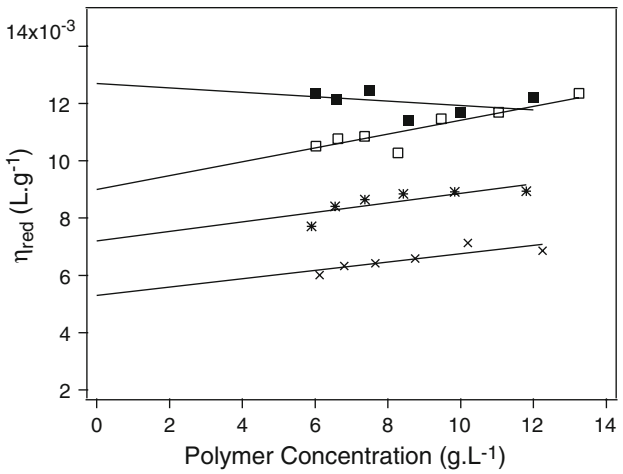


**Fig. 5** Reduced viscosity as a function of polymer concentration for PEG/CD-2 (*cross*), PEG/CD-2.75 (*asterisk*) and PEG/CD-3.5 (*filled square*) in water solution and for PEG/CD-3.5 (*open square*) in NaCl (0.01 mol $L^{-1}$) solution

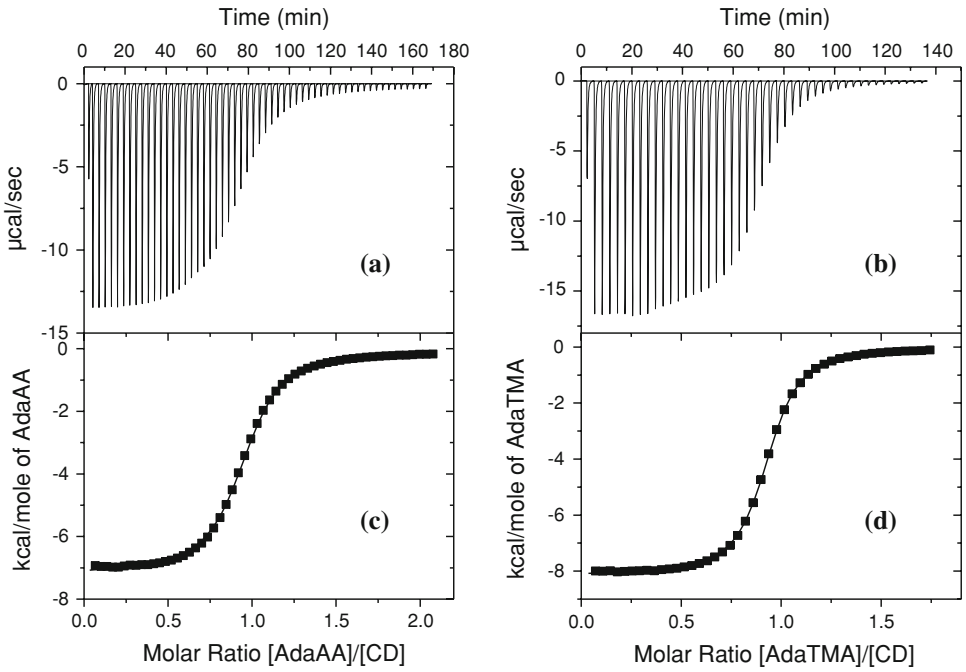


**Fig. 6** Titration of PEG/CD-2 ([CD] = $10^{-3}$ mol $L^{-1}$) by AdaAA (*left part*) and AdaTMA (*right part*) at 25 °C in phosphate buffer (0.01 mol $L^{-1}$) at pH 6.95; (**a**) and (**b**) heat flow as a function of time; (**c**) and (**d**) enthalpogram (integrated heat versus the molar ratio) with the best fit of the experimental points

Large negative enthalpy changes can partially be attributed to Van der Waals interactions caused by the precise matching in size and shape between the guest and the host, which is particularly the case of the adamantyl group and the $\beta$CD cavity [24].

The ITC experiments show a complexing ability of the PEG/CD polymers comparable to the one of native $\beta$CD. These polymers are well designed for loading and controlled release of drugs having large affinity for $\beta$CD. Moreover, the high affinity for adamantyl derivatives (4–10 times larger than p$\beta$CD) make the PEG/CD polymers very attractive candidates for DNA delivery by polyplex formation between DNA, cationic adamantyl connectors and $\beta$CD polymer as previously described [13].

## Conclusion

Novel water soluble $\beta$CD polymers prepared by polycondensation between difunctionalized poly(ethylene glycol) and $\beta$CD were synthesized. It has been shown that the polymers characteristics are strongly dependent on the PEG/CD ratio since the polymers molecular weight increased from $2 \times 10^4$ to $9 \times 10^4$ g $mol^{-1}$ when the equivalencies of PEG compared to $\beta$CD varied from 2.0 to 3.5. Simultaneously, the polymer microstructure was varied due to the increased number of PEG linked to a same CD, increasing the compacity of the structures. In these polymers, the ability of cyclodextrin cavities to make inclusion complexes with model guests has been probed by

**Table 3** Thermodynamic parameters for inclusion complex formation of AdaAA, and AdaTMA, with $\beta$CD and different $\beta$CD polymers, obtained at 25 °C from microcalorimetric titration ([CD] = $10^{-3}$ mol $L^{-1}$; [AdaAA] = [AdaTMA] = $10^{-2}$ mol $L^{-1}$) in phosphate buffer (0.01 mol $L^{-1}$) at pH 6.95

| Compound | AdaAA | | | | AdaTMA | | | |
|---|---|---|---|---|---|---|---|---|
| | n | K (mol $L^{-1}$) | ΔH (kJ $mol^{-1}$) | TΔS | n | K (mol $L^{-1}$) | ΔH (kJ $mol^{-1}$) | TΔS |
| PEG/CD-2 | 0.95 | $6.8 \times 10^4$ | −30.0 | −2.5 | 0.92 | $1.3 \times 10^5$ | −34.0 | −4.9 |
| PEG/CD-2.25 | 1.01 | $5.8 \times 10^4$ | −29.8 | −2.6 | 0.88 | $1.2 \times 10^5$ | −34.1 | −5.2 |
| PEG/CD-2.5 | 0.93 | $5.0 \times 10^4$ | −30.0 | −3.2 | 0.97 | $1.2 \times 10^5$ | −33.3 | −4.4 |
| PEG/CD-3 | 0.99 | $4.5 \times 10^4$ | −30.8 | −4.3 | 0.98 | $8.6 \times 10^4$ | −33.6 | −5.5 |
| PEG/CD-3.5 | 1.01 | $4.1 \times 10^4$ | −30.7 | −4.4 | 1.01 | $4.1 \times 10^4$ | −33.0 | −6.7 |
| $\beta$CD | 0.97 | $9.5 \times 10^4$ | −26.2 | 2.1 | 0.97 | $1.9 \times 10^5$ | −30.9 | −0.8 |
| p$\beta$CD | 0.95 | $1.6 \times 10^4$ | −22.3 | 1.6 | 0.85 | $1.3 \times 10^4$ | −24.9 | −1.5 |

Standard deviation of K and ΔH measurements is less than 2% in all experiments

ITC measurements. The large values of the inclusion constants proved the very good accessibility of the cyclodextrins in the polymers, though there was a slight decrease at larger PEG/CD ratio resulting from the larger substitution degree of the cyclodextrins. Biodegradability of these polymers, which is under current investigation, can lead to very promising drug delivery systems for biomedical applications.

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