J Incl Phenom Macrocycl Chem (2013) 75:341–349
DOI 10.1007/s10847-012-0246-1

ORIGINAL ARTICLE

Novel method for preparation of cyclodextrin polymers: physico-chemical characterization and cytotoxicity

Mohamed Skiba · Malika Lahiani-Skiba

Received: 10 November 2011 / Accepted: 27 August 2012 / Published online: 8 September 2012

Abstract The objective of this work was to optimize the synthesis procedure of soluble cyclodextrin polymers developed by Weltrowski et al. The use of the parameters indicated by the latter in our laboratory led to a lower result, which did not exceed 15 % (w/w). The new method resulted simultaneously in two fractions, a water soluble one and an insoluble one with a yield of 40 and 85 % (w/w), respectively. Only soluble cyclodextrin polymers were characterized along with the cytotoxicity study. The optimized soluble polymers were characterized by Fourier-Transform Infrared Spectrophotometer, Thermogravimetric Analyzer, Differential Scanning Calorimetry, Powder X-Ray Diffraction Analysis and Size Exclusion Chromatography. In vitro cytotoxicity against peritoneal macrophage cells of female CD1 mice showed that soluble poly-α-CD and poly-γ-CD were less cytotoxic than soluble poly-β-CD at small dose and the opposite was true at higher dose. In conclusion, temperature and time could be used to optimize the yield of polymer cyclodextrins, which will have a broad use in the drug delivery system.

Keywords Synthesis · Direct melt polycondensation · Characterization · Polymer of cyclodextrin · Cytotoxicity

Introduction

Cyclodextrin (CD) α, β, and γ are well known cyclic oligosaccharides with the ability to form complexes with specific drug molecules via non-covalent interactions in their hydrophobic cavities. The hydrophobic internal cavity and the hydrophilic external part of the cyclodextrin structure have antagonist characteristics that provide CD their original and interesting structures. This characteristic makes them invaluable in the fields of pharmaceutics and drug delivery. The most common pharmaceutical applications of CD and their chemical derivatives are to enhance the aqueous solubility of the complexed species, to improve aqueous stability, to prevent photostability degradation of pharmaceutical active ingredient, to improve bioavailability of complexed drugs and eventually to reduce side effects, and to improve the release of poorly soluble drugs [1–4]. However, the natural CDs, in particular β-CD, are of limited aqueous solubility (e.g., solubility β-CD in pure water at ∼25 °C is 18.5 mg/mL) meaning that complexes resulting from interaction of lipophiles with these CDs may also be poorly soluble resulting in precipitation of the solid CD complexes from water and other aqueous systems [4, 5]. In addition, the chemical substitution of molecules on the hydroxyl group located on the outer surface of cyclodextrin led to minimum improvement of the aqueous solubility [6]. Thus, the development of new polymer of cyclodextrin is needed in order to overcome the abovementioned limitations.

As the twenty-first century begins, we are witnessing a great shift in medical practice. Whereas the use of polymers in new drug delivery and biomedical materials applications received a great attention among which we found soluble based cyclodextrin polymers synthesized by an esterification reaction, which took place between the hydroxyl group of cyclodextrin and the carboxylic group of citric acid in the presence of sodium phosphate dibasic at controlled temperature [7]. Also, the hydrogel polymer of cyclodextrins (α, β, and γ) crosslinked either by lysine triisocyanate or hexamethylene diisocyanate that were able to trap antibiotics in their hydrophobic pocket through a host–guest complexation

M. Skiba (✉) · M. Lahiani-Skiba
Pharmacy Galenic Laboratory, UFR Medicine and Pharmacy, University of Rouen, 22 BD Gambetta, 76183 Rouen, France
e-mail: mohamed.skiba@univ-rouen.fr

[8]. Since these polymers are interconnected by covalent crosslinks, they cannot dissolve and can only swell to the extent allowed by the crosslink density [9]. The outcome of the work [8] was very promising in providing long-term sustained release of antibiotics such as rifampin, novobiocin, and vancomycin using affinity-based delivery for an anti-infectious drug delivery system but the loading rate of antibiotics did not exceed 3.5 % along with a low release from the inner cavity of cyclodextrin [8]. Therefore, optimizing the procedure was needed but due to the organic solvents and linkers used, we directed our attention into an alternative method of based cyclodextrins polymers with a no use of organic solvent. Thus, we choose to modify the method developed by Weltrowski et al. using aqueous solution of citric acid as crosslink agent and sodium phosphate dibasic as catalyst (0.1 M of Na_2HPO_4, 0.05 M cyclodextrin (α, β, or γ) and 0.15 M citric acid). However, the use of the parameters indicated by Weltrowski et al. [7] in our laboratory led to a lower result, which did not exceed 15 % (w/w).

In this study a new process was developed [10], starting from cylodextrins (α, β or γ), citric acid and sodium phosphate dibasic as catalyst, soluble polymers was directly synthesized by direct melt polycondensation. The soluble polymers were characterized by Fourier-Transform Infrared Spectrophotometer, Thermogravemitric Analyzer, Differential Scanning Calorimetry, Powder X-Ray Diffraction Analysis, Size Exclusion Chromatography coupled with Multi-Angle Laser-Light Scattering.

In addition, in vitro cytotoxicity of the aforementioned soluble polymers was measured on peritoneal macrophage cells harvested from female CD1 mice by a colorimetric assay using tetrazolium salt MTT.

Experimental

Methods

Native cyclodextrins (α and γ) were obtained from Wacker, France. β-cyclodextrin was obtained from Roquette, France. Citric acid and sodium phosphate dibasic were purchased from Sigma Aldrich, France. Fetal bovine serum, RPMI 1640 medium and Nunc 96-well plates were obtained from ATGC, France. Penicillin and Streptomycin were purchased from Eurobio, France. Spectrum/Por® membrane MWCO: 12-14000 was obtained from Spectrum Labs, USA.

Synthesis of poly-α-CD, poly-β-CD and poly-γ-CD

Poly-α-CD, poly-β-CD and poly-γ-CD were synthesized by direct melt copolycondensation, according to the method reported by skiba [10]. Briefly, a mixture of known amount (w/w) of cyclodextrins (α, β or γ), citric acid and sodium phosphate dibasic was transferred into a reactor which was maintained at temperature ranging between 140 and 150 °C for fixed time. The obtained solid form was dissolved in water and dialyzed using polyether sulfate membrane filter with molecular weight cut off of 10,000 Da. After the dialysis, the resulted solution was spray dried using BUCHI Mini Sprayer Dryer B-290. The insoluble polymer was washed with methanol and dried at 60 °C.

The mass of the polymer soluble and insoluble was dependent on the parameters of the synthesis such as temperature, pressure and mass of the molecule.

Characterization

Infrared (IR) spectroscopy was carried out using a Perkin Elmer Spectrum™ One Fourier-Transform Infrared (FTIR) Spectrophotometer. Sample was used as it is. Scans were run from 4,000 to 600 cm^{-1} a resolution spectral of 4 cm^{-1} and 20 scans.

TGA measurements have been performed by a TGA 4000 thermogravimetric analyzer (TA instrument, PerkinElmer, USA) at heating rate of 0.5 °C/min and 10 °C/min and the samples were scanned between 20–160 °C and 20–500 °C, respectively. The technique is used to determine thermal stability of polymers and the upper limit of thermal stability is usually taken as the weight loss of the sample begins. In addition, optimized polymer cyclodextrins were subjected to DSC using a differential scanning calorimetry (Perkin-Elmer 6 DSC, USA). Samples (5 mg) were hermetically sealed in a flat-bottomed aluminium pan and heated from 30 to 300 °C at a flow rate of 10 °C/min against an empty aluminum pan as a reference. Also, each polymer was subjected to Powder X-Ray Diffraction analysis, a powder of poly-CD soluble fraction was analyzed using a Bruker D8 Advance, instrument at controlled temperature. Samples were prepared in disc forms with 10 mm diameter and 2 mm thickness. The tube was operated at 45 keV and 40 mA with Cu Kα radiation. The measurement step was 1.07° after each 4 s with an incidence angle of 2θ ranging between 10 and 50 °C.

The molecular weight was determined by Size Exclusion Chromatography coupled with Multiangle Laser-light Scattering (SEC/MALLS) instrument equipped with a degazer (ERC-413), pump (Flom Intelligent Pump, Japon) at a flow rate of 0.6 mL/min with water as eluent, a filter with pore size of 0.45 μm, an injector (100 μL), a guard column (OHpak SBG, Showa Denko) and two columns (OHpak SB-804 HQ and SB-806 HQ).

In vitro cytotoxicity (MTT assay)

Elicited mouse peritoneal macrophages were harvested from 20–25 g female CD1 mice (Charles River, Saint-Aubain-Les-Elbeuf, France). 3 days after intraperitoneal injection of

1.5 mL of thioglycolate broth; by irrigating the peritoneal cavity with 6 mL of ice-cold medium (RPMI 1640 Glutamax) supplemented with fetal calf serum (FCS) (10 % V/V). 5 mL of medium containing cells was recovered. The cell suspensions were pooled and washed twice with complete medium (RPMI 1640 medium, supplemented with 10 % FCS: penicillin 100 UI/mL and streptomycin, 100 UI/mL). After counting viable cells in the presence of trypan blue, the macrophage suspension was diluted to the desired concentration of 10^6 cells/mL in complete medium, and plated in flat-bottomed 96-well plates at 100 µL/well. The cells were allowed to adhere for 3 h at 37 °C in a humidified 95 % air-5 % CO_2 atmosphere. After adherence, the medium in 96-well plates containing mouse peritoneal macrophages was removed and replaced by a medium containing different concentration of either poly-α-CD or poly-β-CD or poly-γ-CD ranging from 0.25 to 25 µg/mL. The plates were incubated for 4, 24 and 48 h at 37 °C in a humidified 5 % CO_2 incubator. Control cells were incubated with culture medium alone. Cell viability was determined by a colorimetric assay using tetrazolium salt MTT [11].

Results and discussion

Optimization of cyclodextrin polymers

Two fractions were obtained after washing and dialysis: (i) soluble fraction and (ii) insoluble fraction. The synthesis of polymers was evaluated by the mass index of fraction soluble and insoluble and by correlating time and temperature. After 30 min of reaction, the yield of soluble polymer was low and did not exceed 15 % (w/w) at 120 and 150 °C, respectively (Fig. 1a). However, a small fraction of insoluble polymer was observed at 150 °C and kept increasing up to 65 % (w/w) at 170 °C. After 60 min of polymerization, the highest fraction of soluble polymer was obtained at 150 °C with a mass yield of 40 % (w/w) while the yield of the insoluble fraction was 10 and 62 % (w/w) at 150 and 170 °C, respectively (Fig. 1b). After 120 min of polymerization, the insoluble fraction was dominant even though at low temperature leading to a maximum yield of 85 % (w/w) at 170 °C (Fig. 1c). The temperature and time let to the removal of the water formed by the condensation reaction between the anhydride groups and the hydroxyl functions of cyclodextrins. Consequently, these factors moved the esterification equilibrium in the direction of the ester formation and explained the improvement of the yield of the reaction.

In addition, the total mass of soluble and insoluble fractions (% yield) was plotted versus the temperature and the reaction time. Figure 1d illustrated the major effect of the aforementioned parameters on the percent yield, especially at low temperature (120 °C) where 80 % (w/w) yield was attained after 120 min of polymerization. Therefore, a total of 99 % yield could be reach collectively between soluble and insoluble fractions.

Furthermore, we tried to synthesize the insoluble fraction based on the soluble fraction obtained during the first

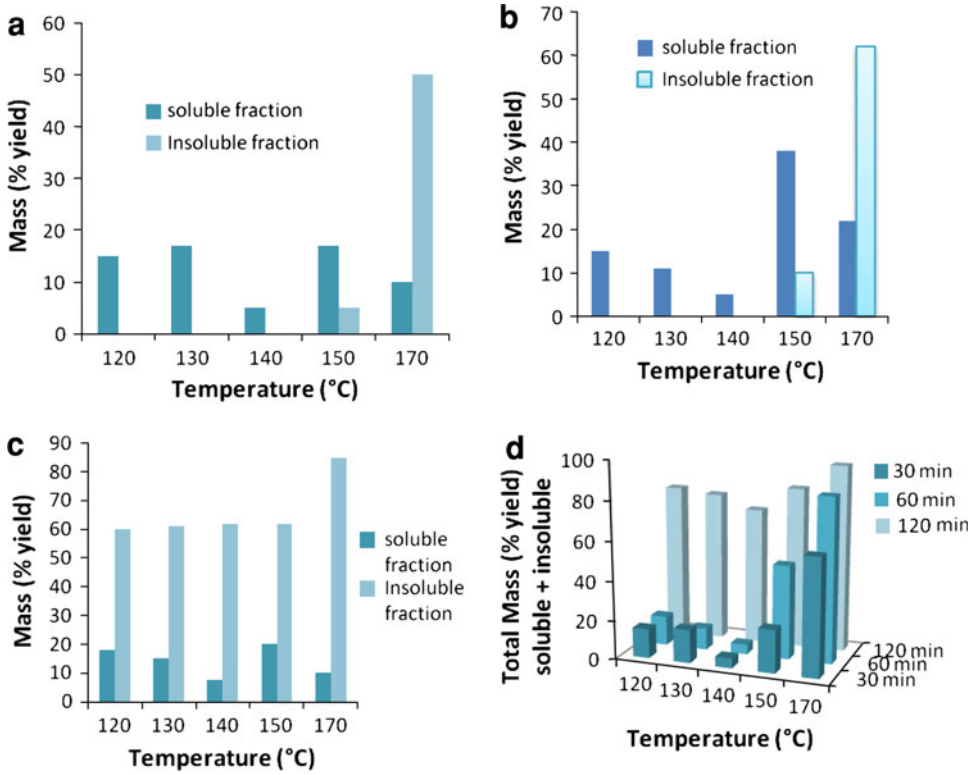

Fig. 1 Effect of temperature and time of on the percent yield of Poly-β-CD **a** 30 min, **b** 60 min, **c** 120 min and **d** total mass of soluble and insoluble polymer

Table 1 Quantity transformed of soluble fraction to insoluble polymer after 120 min of polymerisation

Temperature (°C)	% soluble fraction	% insoluble fraction	Transformation (%)	Loss (%)
120	18	16	88.5	11.1
130	15	13	86.7	13.3
140	7.5	6	80	20
150	20	18	90	10
170	10	9.5	95	5

polymerization by keeping the same conditions including the ratio of cyclodextrin to citric acid (1/3), temperature and time (2 h) because we assumed the formation of the former was primarily dependent on the latter. Therefore, the latter assumption was tested by taking the soluble fraction obtained during the first condensation and polymerized for 2 h under vacuum at 120, 130, 140, 150 and 170 °C. After washing with water and methanol, the insoluble fraction was dried and the yield was calculated. The results are tabulated in Table 1 and it was obvious that the fraction soluble was mandatory for the formation of the insoluble fraction polymer.

Physico-chemical characterization of cyclodextrin polymers

Poly-CDs were characterized by FTIR which is shown in Fig. 2. An ester peak derived from an esterification reaction between the hydroxyl group of cyclodextrin and the carboxylic group of citric acid at 1,723 cm^{-1} was clearly noticeable which its intensity changed with the temperature (Fig. 3). For instance at 150 °C and 1 h of condensation, the intensity of the ester peak was 27.2 % with a yield of 40 % (w/w), however at 140 °C, the intensity was only 12.6 % with 5 % yield, which indicated that the intensity of the ester peak is mass dependent.

TGA analysis showed the dehydration of natural forms of cyclodextrins, namely α, β and γ and the copolymers. On one hand, four different dehydrations stages were identified as illustrated in Fig. 4, which presents a TGA run performed at 0.5 °C/min and scanned at temperature ranging from 20 to 160 °C. The first stage involves the loss of the surface water with a final temperature scattered around 46 °C. The mass loss relevant to the second stage and its final temperature (∼58 °C) was heating rate dependent. However, the third stage shows a steady mass loss despite the increasing heating rate with a final temperature set at approximately 78 °C. The mass loss in stages 2 and 3 correspond to the water present in the interstices. The same explanation could be attributed to stage 4 and for the following continuous mass loss, which they follow the same heating rate dependence discussed in stages 2 and 3, respectively. Stage 4 characterized the water present inside the α-CD cavity. These finding were in agreement with the ones reported by [12]. On the other hand, α-CD-polymer shows one step of dehydration and this is due to the water loss during the lyophilization process.

The thermogravimetric of the natural cyclodextrins α, β and γ carried out at 10 °C/min and scanned at temperature between 20 and 500 °C showed a common profile (Fig. 5) consisting of three stages. The first stage presents the loss of absorbed water and water of crystallisation, which occurs at temperature around 100 °C. The second stage occurs at temperature between 300–370, 305–385, and 297–350 °C for α-CD, β-CD and γ-CD, respectively. This

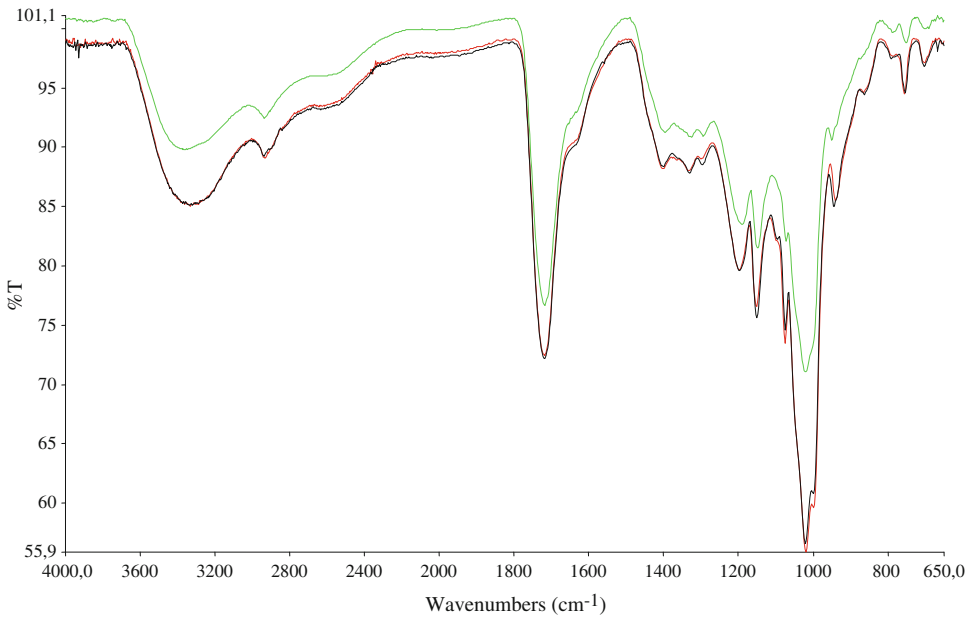

Fig. 2 FTIR spectra from top to the bottom crosslinked poly-α-CD, crosslinked poly-β-CD, and crosslinked poly-γ-CD at 150 °C

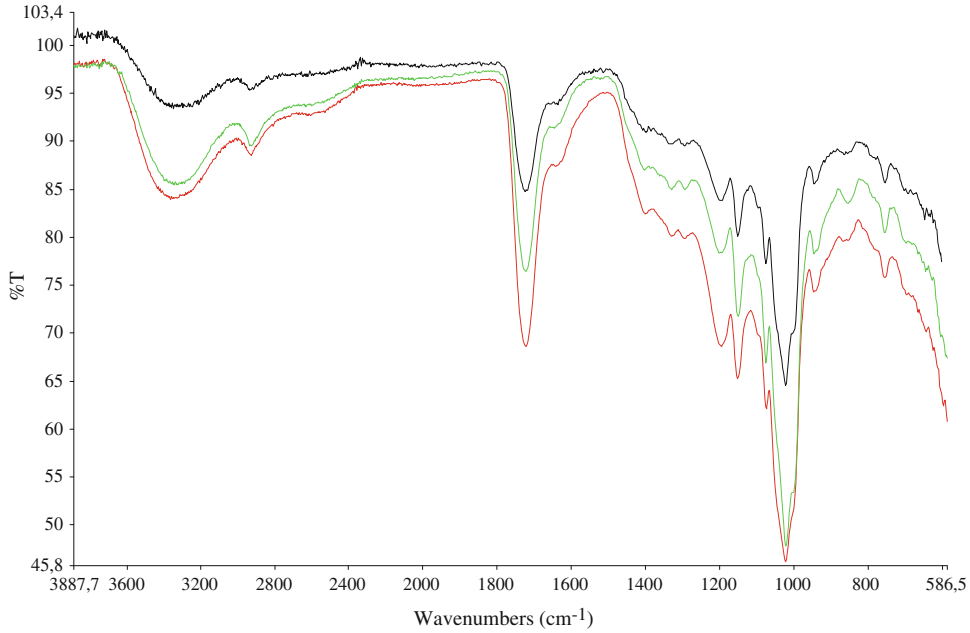

Fig. 3 FT-IR spectra from top to the bottom crosslinked poly-β-CD at 140, 120 and 150 °C

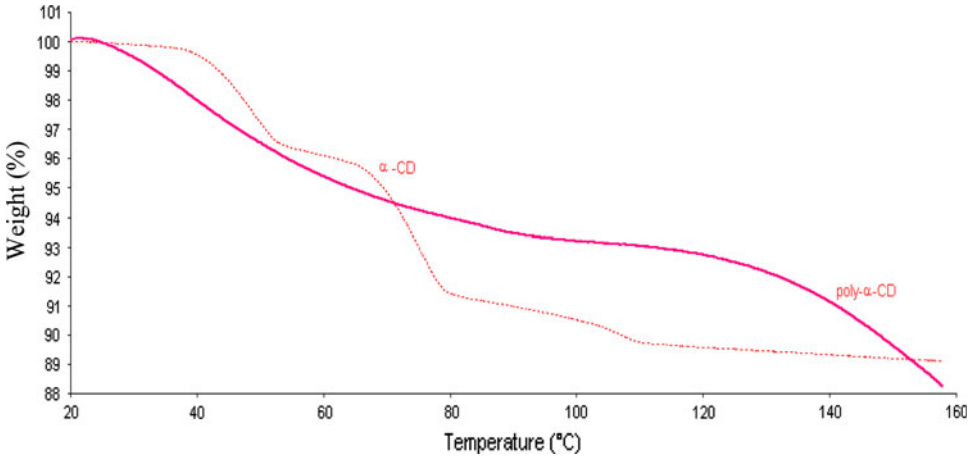

Fig. 4 TGA of α-CD and soluble poly-α-CD at 0.5 °C/min

stage was associated with a weight loss of approximately 80 % due to a start of melting and decomposition of glucose unit in α-CD, β-CD and γ-CD with the formation of a residue "char". The third stage shows a slow thermal degradation of the char at temperature greater than 400 °C. However, in case of soluble poly-α-CD, poly-β-CD and poly-γ-CD, the thermograms are different with the first mass loss occurred at around the same temperature but the second mass loss is at lower temperature of 187–350 °C, 244–340 °C and 90–335 °C poly-α, poly-β and poly-γ-CD, respectively. The causal link of latter results is due to the modification of the cyclodextrin unit with the resulting loss of its crystalline nature. Subsequent loss occurs due to the decomposition of the glucose and ester bond. Similar results were reported by Trotta et al. and Shown and Murthy [13, 14]. In addition, there is a noticeable effect of the cyclodextrin structure on thermal stability which increases in the following order of poly-β-CD < poly-α-CD < poly-γ-CD. These results are justified by powder X-ray diffractometry (XRD) as presented in Fig. 6, which reports a decrease in polymer crystallinity and gain of an amorphous form in poly-α-CD, poly-γ-CD and poly -β-CD which explain the order of solubility of the three form of cyclodextrins in water at approximately 25 °C (β-CD = 18.5 g/lL < α-CD = 145 g/L < γ-CD = 232 g/L)

DSC is an extremely useful technique for measuring glass transition temperature (T_g), crystalline melting point (T_m), and heat of fusion (ΔH_f). The thermograms of citric acid (CA)-β-CD binary systems at 120, 140 and 170 °C are shown in Fig. 7a. The glass transition temperature and crystalline melting point (T_g/T_m) were 55/121, 54/135 and 56 °C/154 °C for poly-β-CD at 120 °C, 140 °C and 170 °C, respectively indicating the same intermolecular forces and chain stiffness but with different number of ester bonds. In addition, the enthalpy values associated with the binary system melting were molecular weight of the

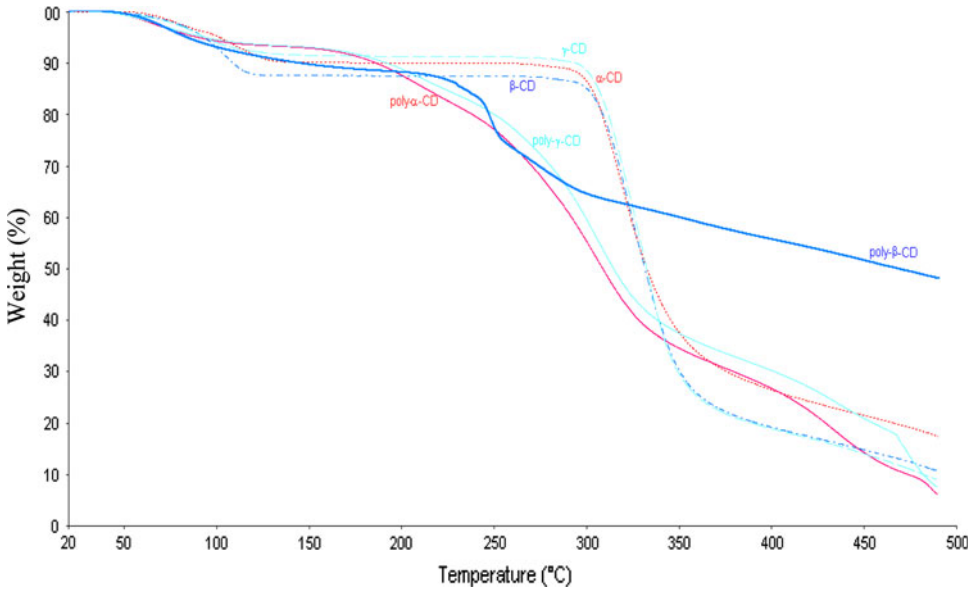

Fig. 5 TGA of α-CD, β-CD, γ-CD, soluble-poly-α-CD, soluble-poly-β-CD and soluble-poly-γ-CD at 10 °C/min

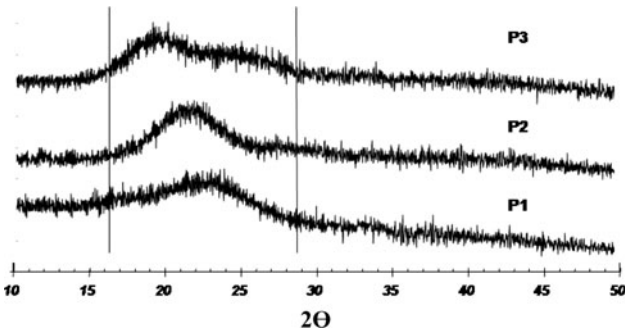

Fig. 6 Diffractograms poly-α-CD (P1), poly-β-CD (P2) and poly-γ-CD (P3) at 150 °C

polymer dependent and the observed results are summarized in Table 2. Moreover, a linear relationship was observed between the temperature of synthesis and crystalline melting point which is a clear indication of the formation of the polymer cyclodextrin crosslinked with citric acid.

Furthermore, the thermograms of poly-α-CD, poly-β-CD and poly-γ-CD synthesized at 150 °C were shown in Fig. 7b. At this optimum temperature, the yield of soluble fraction was at its maximum. Nevertheless, comparing the results from Fig. 7b, the order of the crystalline melting point (T_m) was as follows: poly-α-CD = 203.6 °C > poly-γ-CD = 179.6 °C > poly-β-CD = 175.1 °C indicating an increase in intermolecular forces (ionic) and hydrogen bonds within α-CD polymer. It was clear that the temperature of synthesis had a direct effect on the molecular weight of the polymer and the density of the ester bonds. Consequently, cohesion forces, hydrogen bonds, ionic and polar forces had been increased.

XRD analysis was performed to confirm the results of the DSC study. The diffractograms obtained for soluble poly-α-CD (P1), poly-β-CD (P2) and poly-γ-CD (P3) synthesized at the optimum temperature of 150 °C for 1 h are shown in Fig. 6, it is known that XRD is a powerful technique for identification of crystalline and non-crystalline phases. This technique was therefore used to establish the possible differences in the crystal form.

On the other hand, a total drug amorphization was observed in the XRD profile where only broad peak corresponding to the diffraction. These results confirmed that the partial or complete loss of drug crystallinity was not merely a thermal artifact caused during the DSC heating cycle and so conversion to an amorphous form was strongly suggested through the poly-CD formation.

Using SEC/MALLS, two types of polymers were characterized of soluble polymers synthesized at 140 °C for 30 min by Weltrowski et al. method (type 1) and at 150 °C for 60 min per our method (type 2). Poly-α-CD-type 1, Poly-β-CD-type 1 and Poly-γ-CD-type 1 were characterized and showed two kind of populations. The first population was eluted between 18 and 20 mL with small molecular weight and a second population after 21 mL which was probably due to native cyclodextrins (Table 3). These results indicated that the molecular weight of poly-CD- type2 synthetized by our method was greater than the Poly-CD-type 1 (Weltrowski et al. [7]).

The polydispersity index was calculated to measure the distribution of the polymer. Table 3 illustrates the light scattering and the refractive index of poly-α-CD (type 2) in which the molecular weight is plotted versus elution volumes (mL). Three populations were observed. First, a population eluted between 13 and 16 mL characterized by a strong light scattering and a weak refractive index

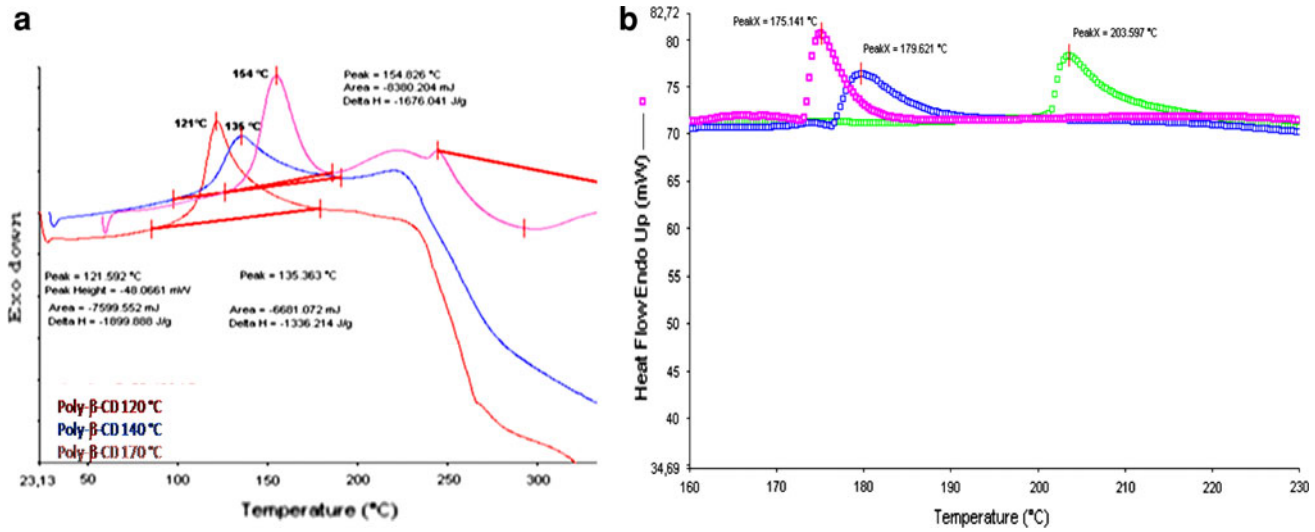

Fig. 7 Thermograms: **a**) poly-β-CD at 120, 140 and 170 °C; **b**) poly-α-CD (*green*), poly-β-CD (*purple*) and poly-γ-CD (*blue*) synthesized at 150 °C

Table 2 Thermotropic parameters of poly-β-CD at 120, 140 and 170 °C

Temperature (°)	T_g (°)	T_m (°)	ΔH_f (J/g)	Area (mJ)
120	55	121	1899.88	7599.55
140	54	135	1336.21	6601.07
170	56	154	1676.04	8380.20

Table 3 Weight average molecular weight, number average molecular weight and polydispersity index of based cyclodextrin polymers

	Weltrowski et al. type 1 at 140 °C and 30 min			Skiba-type 2 at 150 °C and 60 min		
	M_w (g/mol)	M_n (g/mol)	PDI	M_w (g/mol)	M_n (g/mol)	PDI
Poly-α-CD	25,000	7,000	3.6	240,000	30,000	8
Poly-β-CD	28,000	8,800	3.2	272,000	44,200	6.2
Poly-γ-CD	46,000	8,200	5.6	310,000	43,000	7.2

indicating the presence of polymers with high molecular weight. Second, a population eluted between 17 and 20 mL with a weak light scattering but a strong refractive index leaning to a high concentration of polymers but with molecular weight smaller than the first population. Third, a population detected after 21 mL with a small concentration and molecular weight which was probably due to the presence of a native cyclodextrin. The latter assumption was confirmed by injecting α-CD alone and the Table 3 showed a single population eluted after 21 mL with a small molecular weight. In addition, Poly-γ-CD and Poly-β-CD were characterized and Table 3 illustrates the elution of Poly-γ-CD type 2, which has the same profile and type of population as Poly-α-CD (type 2).

The number average molecular weight (M_n) and the weight average molecular weight (M_w) poly-CD type 1 and 2 were determined along with polydispersity index (PDI) and the data are summarized in Table 3. The molecular weight and the molecular weight distribution are very important because there is a definite relationship between the polymer molecular weight and the polymer properties. As the molecular weight rises, the mechanical properties of the polymer rise as well (e.g., formation of cross-linked polymeric network and the increased crosslink degree will have impact on the drug release).

Under Weltrowski conditions, at 140 °C and for 30 min of polymerization the number average molecular weight ranged between 7,000 and 8,800 g/mol for type 1 poly-CD. However and under our conditions at 150 °C and 60 min of direct melt copolycondensation, the number average molecular weight of type 2 poly-CD was twice higher than the one observed in type 1. Consequently, temperature and time have a major effect on the molecular weight of the poly-CD. Therefore, these results confirmed the ones obtained by FTIR, TGA and DSC. As indicated by the polydispersity index values, type 2 poly-CDs are polydispersed and the polymer molecules within a polymer mass have different molecular weights. In addition, Fig. 8 illustrates a comparison between the data of weight average molecular weight generated by the new process and the ones obtained by Weltrowski et al. and Martel et al. [7, 15]. It is clear that we were able to increase the M_w approximately by three fold.

In vitro cytotoxicity of murine peritoneal macrophages

The cytotoxicity of the macrophage cells increased with poly-α-CD, poly-β-CD and poly-γ CD concentration with

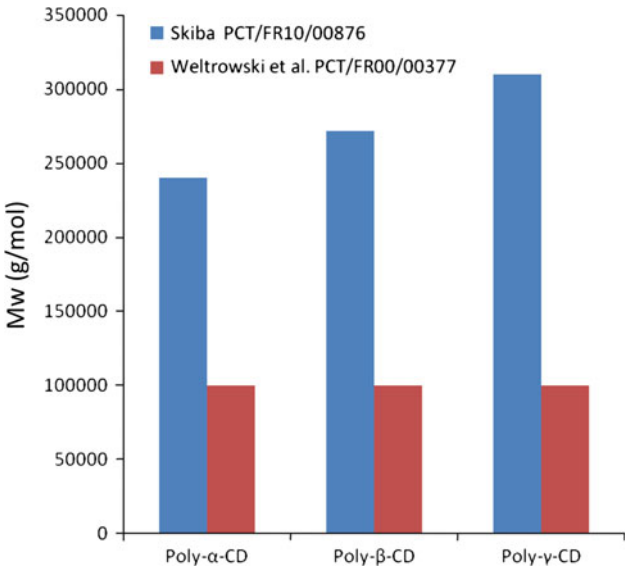

Fig. 8 Molecular weight comparison between the optimized poly-CD and the reference ones. Elution of polymer based cyclodextrin by SEC/MALLS. **a** poly-α-CD (type 2), **b** α-CD, **c** poly-γ-CD type 2 and **d** poly-α-CD-type 1, poly-β-CD-type 1 and poly-γ-CD-type 1

the time of incubation as illustrated by Fig. 9. At 4 h and 0.25 µg/mL, the cytotoxicity of poly-β-CD was two folds higher than poly-α and poly-γ-CD but at higher dose (25 µg/mL) the reverse was observed. As the concentration increased above or equal to 2.5 µg/mL along with incubation time a kill rate of more than 50 % was observed.

Conclusion

The cyclodextrin polymers obtained by Woltrowski et al. could be optimized by direct melt copolycondensation. A maximum yield of 40 % (w/w) of soluble polymer was obtained at 150 °C after 1 h of polymerization while more than 85 % (w/w) of insoluble polymer resulted after 2 h at 170 °C and 99 % (w/w) yield were obtained jointly between the soluble and the insoluble polymers. The aforementioned polymers were characterized by FTIR, TGA, DSC, and XRD which confirmed the ester bond, glass transition temperature, crystalline melting point and the amorphous form of the crosslinked cyclodextrin polymer, respectively. Moreover, the weight average molecular weight was calculated by the SEC/MALLS and the data found were threefold higher than the ones obtained by Weltrowski et al. In addition, the cytotoxicity data of poly-CD on macrophage cells at 4, 24 and 48 h suggested that poly-α-CD and poly-γ-CD were less toxic than poly-β-CD at small dose with short incubation time while the opposite was true at higher dose and longer incubation time. It was clearly demonstrated that the temperature and time of the reaction played a major role in the highly observed yield of

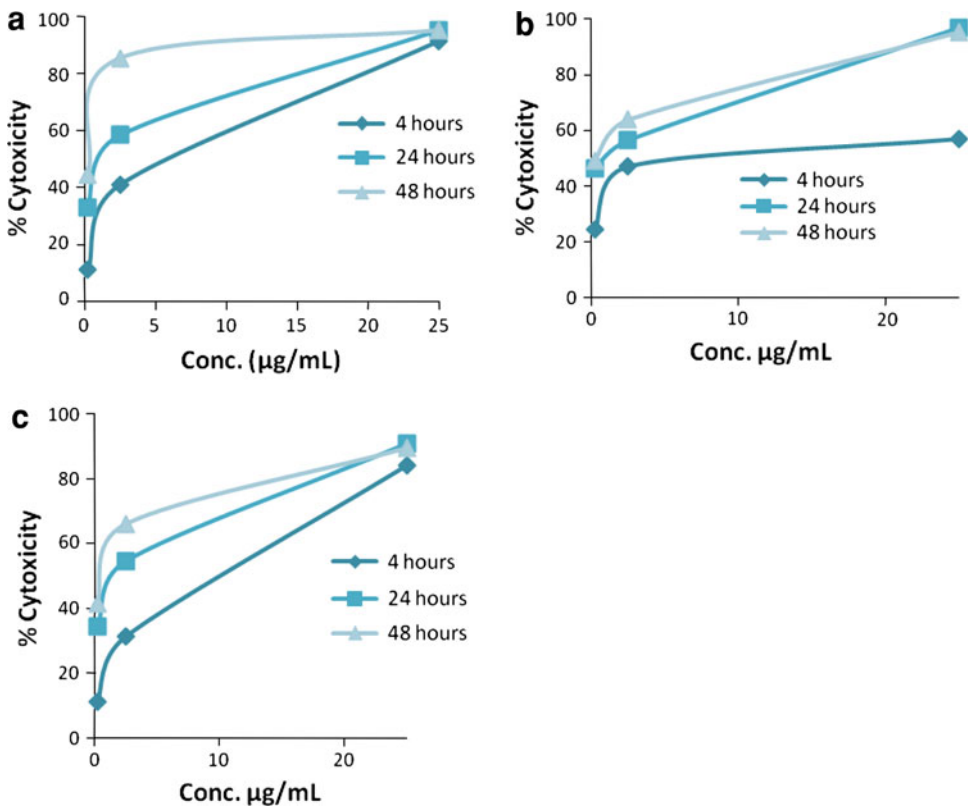

Fig. 9 Effect of soluble based cyclodextrin polymers on the viability of the macrophage cells **a** poly-α-CD, **b** poly-β-CD and **c** poly-γ-CD

the cyclodextrin polymers obtained by direct melt co-polycondensation. Given the ease of the manufacture and the relative chemical stability of the ester bond these polymers may have broad use in the drug delivery specifically and in the pharmaceutical formulation in general.

References

1. Lahiani-Skiba, M., Youm, I., Bounoure, F., Skiba, M.: Improvement in the water solubility and stability of 4ASA by the use of cyclodextrins. J. Incl. Phenom. Macrocycl. Chem. **69**, 327–331 (2011)
2. Sughir, A., Lahiani Skiba, M., Oulyadi, H., Skiba, M.: 2-HPbeta-cyclodextrin: a new Tool for the improvement of chemical stability of tiagabine HCl. Lett. Drug Des. Discov. **6**(3), 236–241 (2009)
3. Dutet, J., Lahiani Skiba, M., Didier, L., Jezequel, S., Bounoure, F., Barbot, C., Arnaud, P., Skiba, M.: Nimesulide/cyclodextrin/PEG 6000 ternary complexes: physico-chemical characterization, dissolution studies and bioavailability in rats. J. Incl. Phenom. Macrocycl. Chem. **57**, 203–209 (2007)
4. Brewster, M.E., Loftsson, T.: Cyclodextrins as pharmaceutical solubilizers. Adv. Drug Deliv. Rev. **59**, 645–666 (2007)
5. Loftsson, T., Jarho, P., Másson, M., Järvinen, T.: Cyclodextrins in drug delivery. Expert Opin. Drug Deliv. **2**, 335–351 (2005)
6. Khan, A.R., et al.: Methods for selective modifications of cyclodextrins. Chem. Rev. **98**(5), 1977–1996 (1998)
7. Weltrowski, M., Morcellet, M., Martel, B.: Procédé de fabrication de polymères solubles et insolubles à base de cyclodextrine(s) et/ou de dérivés de cyclodextrine(s) et polymères solubles à base de cyclodextrine(s) et/ou de dérivés de cyclodextrine(s). US 6,660,804 B1, 2003
8. Thatiparti, T., Von Recum, H.A.: Cyclodextrin complexation for affinity-based antibiotic delivery. Macromol. Biosci. **10**(1), 82–99 (2010)
9. Robinson, J.R., Lee, V.H.L.: Controlled drug delivery: fundamentals and applications second edition, revised and expanded. Drug Pharm. Sci. **29**, 167–193 (1987)
10. Skiba, M.: PCT/FR 10/00876, 2010.
11. Denizot, F., Lang, R.: Rapid colorimetric assay for cell growth and survival. Modifications to the tetrazolium dye procedure giving improved sensitivity and reliability. J. Immunol. Methods **89**, 271–277 (1996)
12. Berbenni, V., Marini, A., Bruni, G.: Thermogravimetric study of the dehydration process of α-cyclodextrin: comparison between conventional and high-resolution TGA. Thermochim. Acta **322**, 137–151 (1998)
13. Trotta, F., Zanetti, M., Camino, G.: Thermal degradation of cyclodextrins. Polym. Degrad. Stab. **69**, 373–379 (2000)
14. Shown, I., Murthy, C.N.: Grafting of cotton fiber by water-soluble cyclodextrin-based polymer. J. Appl. Polym. Sci. **111**, 2056–2061 (2009)
15. Martel, B., Ruffin, D., Meltrowski, M., Lekchiri, Y., Morcellet, M.: Water-soluble polymers and gels from the polycondensation between cyclodextrins and poly(carboxylic acid)s: a study of the preparation parameters. J. Appl. Polym. Sci. **97**(2), 433–442 (2005)