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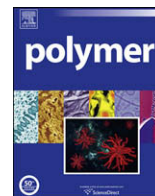Universidad de Talca
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Inclusion complexes containing poly(ε-caprolactone)diol and cyclodextrins. Experimental and theoretical studies

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ABSTRACT

Inclusion complexes (ICs) between poly(ε-caprolactone)diol (PEC) with α-cyclodextrin (α-CD) (α-CD–PEC) and γ-cyclodextrin (γ-CD) (γ-CD–PEC) were prepared and characterized by FT-IR, ^{1}H NMR, thermogravimetry, surface activity and wettability measurements. The thermal stabilities of the inclusion complexes are very similar. The thermal stability of PEC is better than ICs and CDs. Stable monolayers of PEC and α-CD–PEC and γ-CD–PEC complexes have been obtained at the air–water interface using the Langmuir Technique. The surface pressure–area isotherms (π–A) were found to be of different types, depending on the CD utilized. From the surface free energy values of PEC and ICs it was possible to conclude that ICs are more hydrophobic than cyclodextrins. PEC is the most hydrophobic. The surface parameters the minimum area A_0, the critical surface pressure π_c, and static elasticity ε_0 were also estimated for ICs and PEC. In order to describe the experimental results, molecular dynamic simulation (MDS) was performed. In addition, the physical properties that stabilize CD–CD, CD–polymer and CD–solvent interactions were elucidated by MDS. Theoretical results have demonstrated that complexes are stabilized by hydrophobic interactions between the cavity of CDs and the –$(CH_2)_5$-units of PEC, and also by hydrogen-bond formation between the hydroxyl groups situated along the rim of CD molecules threaded onto the PEC chain. CD–CD hydrogen-bond formation is maximized in 1:2 γ-CD–PEC complex and 1:1 α-CD–PEC complexes.

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1. Introduction

Cyclodextrins are cyclic oligosaccharides consisting of six (α-CD), seven (β-CD), eight (γ-CD), and more glucose units linked by α-1,4 bonds. They form inclusion complexes (ICs) with a wide range of low molecular weight compounds which have been prepared and characterized, it have been also reported ICs formation with various polymers [1,2], such as poly(ethylene glycol) (PEG), poly(propylene glycol) (PPG), poly(methyl vinyl ether) (PMVE) and poly(ethylene oxide) (PEO) [3–5]. Most of the polymers considered for this purpose are stable and is very difficult that they were used as biodegradable polymers. In the polymer field, biodegradable polymers have been studied extensively thinking in their contribution towards the formation of the complexes involves the threading of the CD along the polymeric chain. This process is driven by non-covalent attractive forces, therefore allowing the CD to slide along the polymeric backbone [6]. The formation of IC is

entropically unfavorable; therefore, the linear polymeric chain must fit into several CDs units to produce the final IC. The complex is thought to be promoted by hydrophobic interactions between the cavity of α-CD and the methylene units of PEC and also by hydrogen-bond formed between the hydroxyl groups situated along the rim of CD molecules threaded onto the PEC chain.

Inclusion complexes formation between α- and γ-CD with PEC, have been widely studied by Tonelli et al. [7–9]. Studies about the characterization using ^{1}H NMR and FT-IR spectroscopy, DSC and X-ray diffraction have been done [10,11]. These results have showed that the complexes are formed and no free crystalline PEC remains in the sample.

Because IC can be used for drug release and they can be present at biological interfaces, it is interesting and necessary to know the surface activity of these supramolecular systems and their surface free energies. The structural organization of IC should present a different behavior at the air–water interface in comparison to their respective precursor polymer. The determination of the surface free energy of the complexes is also of interest in different fields. The surface activity of the α-CD–PEC and γ-CD–PEC

complexes seems to have not been studied in comparative terms. This work is also focused on the driving force formation of IC containing α-CD, γ-CD and PEC, using theoretical tools.

2. Experimental section

2.1. Materials

α-CD and γ-CD (Sigma–Aldrich) and PEC-diol of $M_w = 2000$, were used as received. All solvents used were analytical grade. Water was purified by a Mili-Q-system.

2.2. Methods

2.2.1. Preparation of inclusion complexes
ICs were prepared following the procedure reported by Harada et al. [12], 20 mg of PEC was put into tubes heated above the melting temperature and satured aqueous solution of CD (α-CD 1.8×10^{-4} mmol in 1,2 mL and γ-CD 1.1×10^{-4} mmol in 0,6 mL) was added. The heterogeneous mixtures were ultrasonically agitated for 10 min on heating and then allowed to stand overnight at room temperature. The mixture became turbid and the complexes were obtained as white crystalline precipitates. They were collected by centrifugation, dried in a vacuum oven at 373 K, washed with water and dried under vacuum and then washed with THF and finally dried under vacuum. ICs were obtained as white powder.

The solubility of CDs and PEC in different solvents was determined at room temperature.

2.3. Spectroscopic characterization

2.3.1. Fourier transform infrared measurements
Infrared spectra of ICs were recorded on a Vector 22 Bruker TM FT-IR spectrophotometer. Samples were prepared directly in KBr pellets. The spectra were recorded with a resolution of 1 cm^{-1}, and 128 scans were accumulated. The spectra were analyzed through the computer system of the instrument.

2.3.2. Nuclear magnetic resonance (^1H NMR)
^1H NMR spectra of ICs were run on a Brucker AM 400 MHz spectrometer at room temperature in CDCl$_3$. TMS was used as internal standard.

2.4. Thermogravimetric and DSC measurements

Dynamic thermogravimetric measurements were performed using a Mettler TGA/SDTA 851^e thermobalance. The thermogravimetric results were processed by the Mettler calorimetric system using the STAR^e program. Samples were heated in Al$_2$O$_3$ pans. Measurements were carried out between 300 K and 1000 K at 20° min^{-1} under N$_2$.

The calorimetric measurements DSC reported were carried out at a 20 K/min heating rate in a Mettler 821 calorimetric system, using Start^e program system; the temperature scale was calibrated using indium. The typical amount of sample used was 20 mg.

2.5. Wettability measurement (contact angle)

The contact angle (CA) was determined by means of the technique of the sesil drop using a Dataphysics OCA 20. A syringe, connected to a capillary of Teflon of around 2 mm of internal diameter, was used to provide the liquid and to deposit the drop on the film. Measurements were done at room temperature and with liquids whose surface tensions are well known (diiodomethane and bromonaphthalene) [12,13]. This allows to determine the surface

free energy and the dispersion and polar contributions by means of the Owens, Wendt and Kaelble method [14,15].

2.6. Surface pressure–area isotherms (π–A)

The surface pressure–area isotherms for α-CD–PEC, γ-CD–PEC complexes and PEC were studied using the Langmuir Technique. The surface pressure–area isotherms (π–A) were performed with a surface balance of Langmuir Nima 611 at 298 K. The compression velocity was 10 cm^2/min. The subphase was water purified by a Mili-Q-system (18 MΩ cm). CHCl$_3$ and DMF were used as spreading solvents. Due to solubility reasons a binary spreading solvent DMF/CHCl$_3$ was also used at different ratios (v/v).

2.7. Molecular models

The structure of PEC containing eight monomers was constructed using Sybyl (Tripos, Inc., St. Louis, MO). The starting α-CD and γ-CD structures were taken from Protein Data Bank (PDB entry 1CXF for α-CD and 1D3C for γ-CD). These structures were fully minimized (CHARMM27 carbohydrate parameters were employed) and good agreement with the experimental geometry was obtained. Parameters for poly(ε-caprolactone) were adapted by analogy from others included in the CHARMM27 force field [16]. Optimized CDs and a monomer of PEC are shown in Fig. 1.

Three models were built for studying CD–polymer complexes by MDS:

PEC + 8 α-CDs (PEC–8 α-CD)
PEC + 8 γ-CDs (PEC–8 γ-CD)
2 PEC + 8 γ-CDs (2 PEC–8 γ-CD)

Models contain head-to-head and tail-to-tail orientation for all CDs. The ends of PEC were protected with phenyl substituents (Fig. 2A). For hydration of each model, a water box confined by periodic boundary conditions was added to the simulation systems. The water boxes for each model were generated by adding 20 Å from the last atom outward in all possible directions.

Three additional models were built for studying the complex formation by steered molecular dynamics (SMD):

PEC + α-CD (PEC–α-CD)
PEC + γ-CD (PEC–γ-CD)
2 PEC + γ-CD (2 PEC–γ-CD)

These models are represented in Fig. 2B. The polymer was oriented with its principal axis aligned with the z-axis. In these models, water boxes ensure the whole surface of the complex to be covered along the trajectory through the z-axis.

2.8. Molecular dynamic simulations

Explicit solvent MDS were carried out for studying the structural features of the CD–PEC complexes. All MDS were carried out using
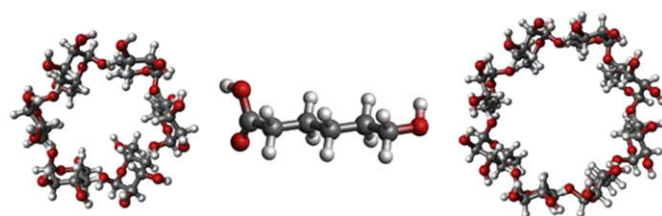

Fig. 1. Structures of α-cyclodextrin, ε-caprolactone and γ-cyclodextrin.
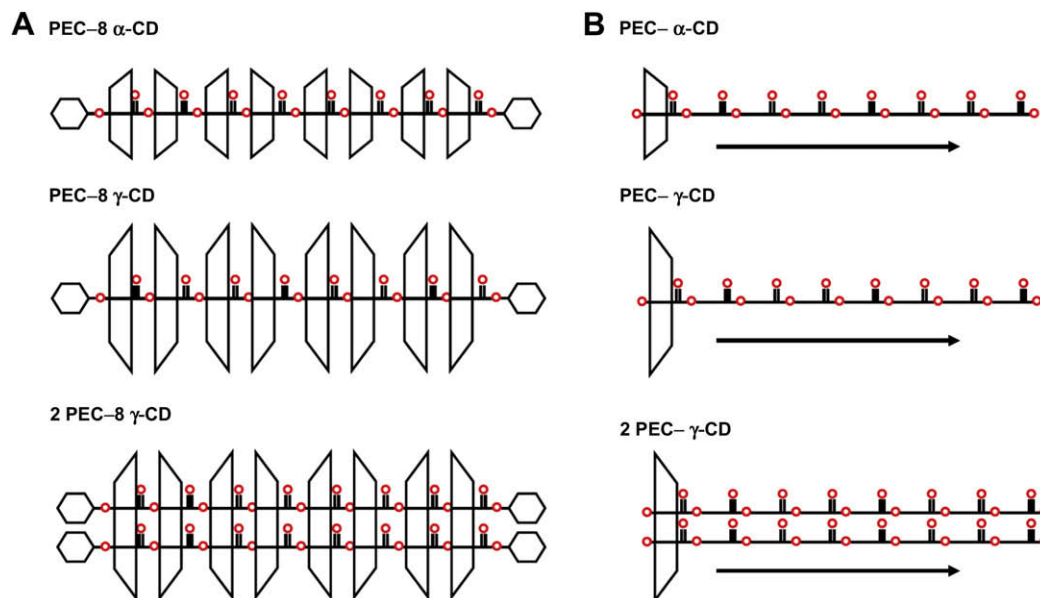
Fig. 2. Models for molecular dynamic simulations. a) MD and b) SMD.

the parallel MD program NAMD2 [17] and the CHARMM27 force field. Simulations were performed in the NPT ensemble; the non-bonded Coulomb and van der Waals interactions were calculated with a cut-off using a switching function starting at a distance of 10 Å and reaching zero at 12 Å. The TIP3P water model was employed for the solvent [18]. Periodic boundary conditions were applied with a flexible cell. The particle mesh Ewald (PME) method [19] was employed for computation of electrostatic forces. An integration time step of 1 fs was assumed, permitting a multiple time-stepping algorithm [20] to be employed in which interactions involving covalent bonds were updated every time step. In all simulations, Langevin dynamics were utilized to keep a constant temperature of 298 K; likewise, the hybrid Nosé-Hoover Langevin piston method was used to control a constant pressure of 1 atm [21].

The system was first equilibrated for 1 ns. The first and the last oxygen atoms of the first and the eighth monomers of PEC respectively were restrained with a 0.5 kcal/mol/Å² spring constant during relaxation. The outputs of the equilibrated phase were used as inputs for the main simulations. Then, simulations of 2.5 ns were performed without any constraints. All calculations were performed on a processors SGI Origin 300 server.

2.9. Steered molecular dynamics

MDS have been applied to CD–polymer complexes in several reports [22–27]. However, SMD simulations have not been used yet for studying these systems. Quite recently, SMD was used to investigate the energetic properties of formation of the inclusion complex between progesterone and β-CD [28]. In this report, the movement of the guest molecule through the β-CD's interior was adequately characterized.

To simulate the α-CD–PEC and γ-CD–PEC formations, external forces along the *z*-axis were applied to all atoms of CDs (models PEC–α-CD, PEC–γ-CD, and 2 PEC–γ-CD). The first and the last oxygen atoms of the first and the eighth monomers of PEC respectively were restrained with a 0.5 kcal/mol/Å² spring constant during this process. In each simulation, the pulling velocity was 10 Å/ns, slower than those used in some previous SMD studies in biological systems [29–31]. During each SMD trajectory, the force

was only applied along the pulling direction. CDs were free from constraint in the plane perpendicular to the pulling direction. The trajectories were saved for every 5 ps, and steering forces were recorded for every 0.5 ps. Each trajectory was repeated for four times.

## 3. Results and discussion

3.1. Spectroscopic characterization

The characterization of the inclusion complexes with PEC was done using FT-IR and ^{1}H NMR spectroscopy. The ICs formed for α-CD and γ-CD with PEC, have been previously characterized by these techniques [9]. The host–guest stoichiometric ratios are 1:1 for PEC–α-CD IC and 2:1 for PEC–γ-CD IC, this observation has been reported in previous works [7–9,32]. The spectra obtained indicate that the complexes are formed and they were in agreement with those obtained by Tonelli and Harada [33].

3.2. Solubility

PEC and CDs are soluble in chloroform and water respectively. ICs are not soluble in chloroform neither in water but are soluble in DMF and also DMSO. PEC, α-CD–PEC and γ-CD–PEC do not have a common solvent, for this reason a spreading binary solvent DMF/CHCl₃ (v/v) was used to obtain a suitable spreading solvent to use in the Langmuir technique. The spreading solvent must be immiscible with water and volatile.

3.3. Thermal analysis

In order to know the thermal properties of the α-CD, γ-CD, and ICs a thermal analysis was performed. From the degradation profiles it was determined the temperatures of initial thermal decomposition T_{ID} and the temperature to which a 50% of loss weight is registered T_{50}, for PEC, α-CD and the corresponding ICs. Fig. 3 shows the thermogravimetric curves for PEC, α-CD–PEC and γ-CD–PEC complexes, α-CD and γ-CD represented as the first derivative of the weight loss with temperature (dm/dT). This kind of representation is a better way to enhance the thermogravimetric
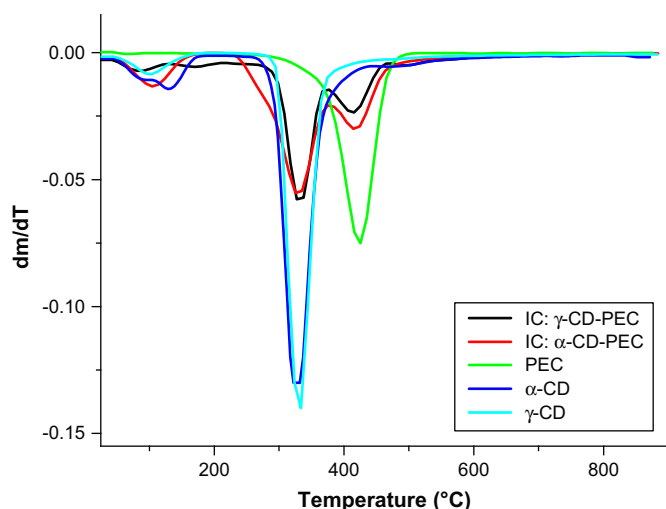
Fig. 3. First derivative of the weight loss of the thermogravimetric profiles dm/dT against temperature: α-CD–PEC and γ-CD–PEC complexes, PEC and α-CD and γ-CD.

Fig. 4. Surface pressure–area isotherms for a) γ-CD–PEC, b) PEC and c) α-CD–PEC.

behavior to observe the degradation temperature than the diagrams of pure weight loss versus temperature. The thermal stability of ICs of α-CD–PEC or γ-CD–PEC is very similar. The main observation on these systems is that decomposition of PEC takes place at higher temperatures than those for the degradation of the CDs (α or γ).

These thermogravimetric profiles follow a single one-stage decomposition process for pure compounds (polymers and CDs). However, for ICs two stage decomposition profiles are found, one corresponds to the decomposition of CDs and the other to PEC decomposition.

In order to provide some characterization of the physical structures of the Langmuir layers, it was estimated the crystallinity degree of the samples of γ-CD, PEC and IC (γ-CD–PEC).

It was observed that the crystallinity degree of PEC decreases from 10% to 1%, when this polymer is incorporated inside the γ-CD. From this preliminary result it is possible to conclude that the single or double threaded PEC chains should be in the form of somewhat flexible pseudo-rotaxane without crystallinity. Further works are in progress about this aspect. It is important to consider that this behavior is in solid state in 3D. However, this situation was extrapolated to a pseudo-solid state (2D) of the monolayer at high pression and low surface area.

3.4. Surface energy

To get information about the degree of hydrophobicity of ICs, PEC, α-CD and γ-CD, the total surface free energy (SE) was estimated by measurement of contact angles (CAs) of bromonaphthalene and

diiodomethane on the system surfaces. The dispersion force and polar contributions to SE, γ^D and γ^P, respectively, were calculated by using the Owens and Wendt and Kaelble methods [14,15]. The measurements of CA on a given system solid surface is one of the most practical ways to obtain surface free energies. Table 1 summarizes the results obtained by wettability measurements for the systems studied. From the SE values in Table 1 for ICs, PEC and CDs it can be concluded that the complexes present a degree of hydrophobicity higher than PEC, α-CD and γ-CD. PEC is the most hydrophobic.

The influence of the type of CD used to form the ICs was also studied. The IC of γ-CD–PEC is less hydrophobic than IC of α-CD–PEC for the same molecular weight of PEC. These results are consequent because γ-CD possesses more hydroxyl groups in comparison to α-CD. This situation confers it a more hydrophilic character to IC of γ-CD–PEC, although it is balanced by the two polymeric chains of PEC in their cavity.

3.5. Surface pressure-area isotherms

Surface area isotherms recorded for spread IC monolayers α-CD–PEC and γ-CD–PEC and PEC are presented in Fig. 4. α-CD and γ-CD do not present surface activity. The obtained isotherms are of two types, γ-CD–PEC (a) is the expanded type [34] i.e. surface pressure increases gradually upon monolayer compression and the compressibility is higher than α-CD–PEC (c). The PEC isotherm is of the condensed type (b). Table 2 summarizes the main surface parameters for the ICs and PEC. In Fig. 4 the surface pressure isotherms for IC of α-CD–PEC and PEC are of the condensed type, whereas the surface pressure isotherm for IC of γ-CD–PEC shows one isotherm of the expanded type. The explanation for this particular behavior could be the presence of two PEC chains inside of γ-CD. From Table 2 it is possible to observe that the minimum
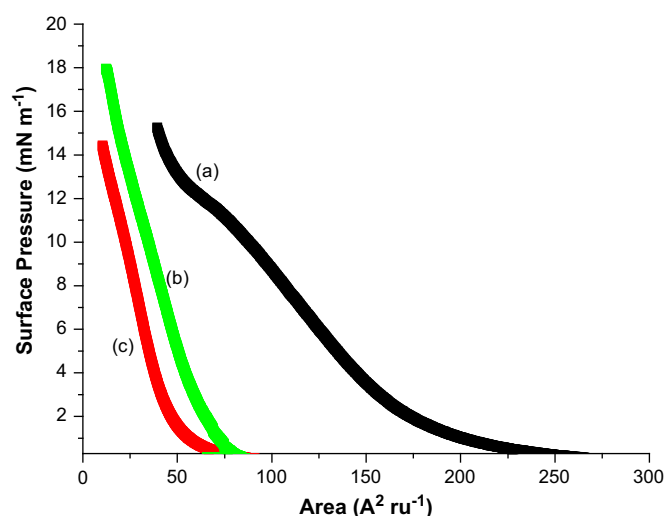
Table 1
Static contact angle (CA), total surface energy (SE), dispersion force (γ^D), and polar contribution (γ^P) of α-CD–PEC complex, γ-CD–PEC complex, α-CD, γ-CD and PEC.

Systems	Contact angle CA (degrees) [a]	Contact angle CA (degrees) [b]	SE (mN m^{-1})	γ^D mN m^{-1}	γ^P (mN m^{-1})
γ-CD–PEC	46.1 ± 0.6	27.2 ± 0.7	40.0 ± 0.4	39.6 ± 0.4	0.4 ± 0.4
α-CD–PEC	42.6 ± 0.5	32.7 ± 0.8	38.2 ± 0.7	37.6 ± 0.7	0.5 ± 0.7
α-CD	48.7 ± 0.7	21.2 ± 1.1	44.5 ± 0.9	41.5 ± 0.9	3.1 ± 0.9
γ-CD	48.4 ± 0.7	15.7 ± 0.9	47.3 ± 0.8	42.8 ± 0.8	4.5 ± 0.8
PEC	48.3 ± 0.4	43.4 ± 0.6	34.7 ± 0.5	33.1 ± 0.5	1.6 ± 0.5

[a] From diiodomethane.
[b] From bromonaphthalene.

Table 2
Minimum area A_0 per repeating unit (ru) values and collapse pressure π_c values for surface pressure isotherms of ICs: α-CD–PEC and γ-CD–PEC and PEC.

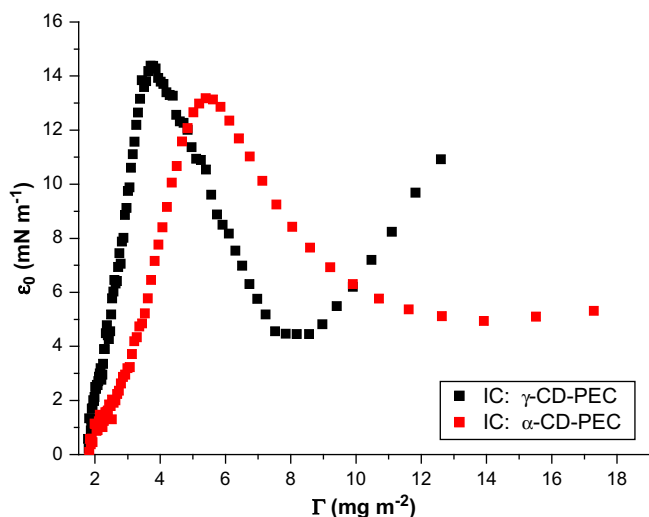| System	A_0^2 ru^{-1} ± 2 at $\pi = 0$	π_c (mNm^{-1})
α-CD–PEC	50	14.4
γ-CD–PEC	175	15.3
PEC	66	18.1

Fig. 5. Static elasticity modulus in function of the surface concentration Γ, $(\varepsilon_0$–$\Gamma)$ calculated from π–A isotherms for ICs: α-CD–PEC and γ-CD–PEC.

Fig. 7. Snapshot of the complexes obtained by MD study for (A) 1:1 α-CD–PEC complex, (B) 1:1 γ-CD–PEC, and (C) 1:2 γ-CD–PEC complexes.

area A_0 value of the IC of α-CD–PEC is smaller than the A_0 value of IC of γ-CD–PEC and PEC. They achieve very similar collapsed pressure.

To gain a deeper insight into the inclusion complex formation between α-CD and γ-CD and PEC and to understand the organization of these systems at the air–water interface, molecular dynamic simulations were carried out. It is known that the nature of the monolayer partially depends on the strength of interfacial interactions with substrate molecule and that of polymer or polymer complex intersegmental interaction [35]. Therefore, the viscoelastic properties of polymeric monolayers could also be dependent on these interactions. From the experimental π–A or π–Γ curves, it was possible to calculate the classical static elasticity modulus ε_0, which only accounts for hydrostatic compression:

$$\varepsilon_0 = -A(\mathrm{d}\pi/\mathrm{d}A)_T = \Gamma(\mathrm{d}\pi/\mathrm{d}\Gamma)_T \qquad (1)$$

Γ is the surface concentration.

The data from static elasticity ε_0 for ICs are shown in Fig. 5. The maximum ε_0 values were found in the diluted region. This is the normal behavior. It is known that the maximum ε_0 values are in the case of the polymeric systems in the diluted and semidiluted region [36] since the chains are independent or are in mutual
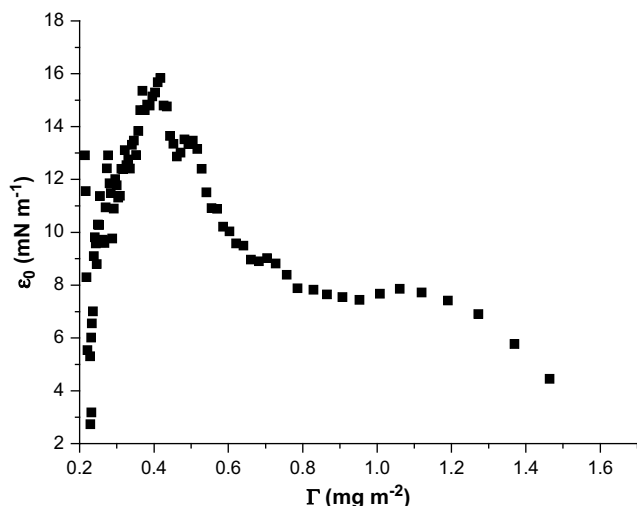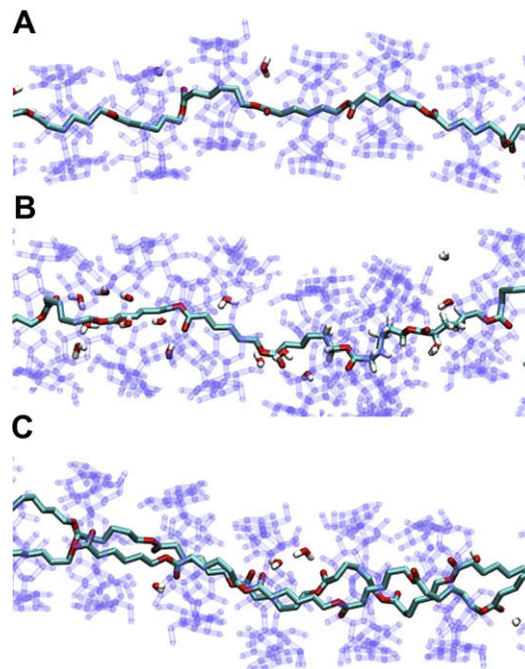
contact, but responding almost in individual form front to the deformation.

The plot of compressibility modulus or static elasticity, ε_0, calculated from the surface pressure isotherms is provided in Figs. 5 and 6. In the case of IC of α-CD–PEC and γ-CD–PEC (Fig. 5), the maxima are located in the concentrated region, where the contact between chains of ICs is very close, responding to the deformation like a polymeric lattice.

Fig. 6 shows, that the greatest increase in elasticity for PEC occurs within the semidiluted regime.

3.6. Molecular dynamic simulations

One of the most striking features of the complexation properties of host–guest systems, including polymeric guests, is geometrical
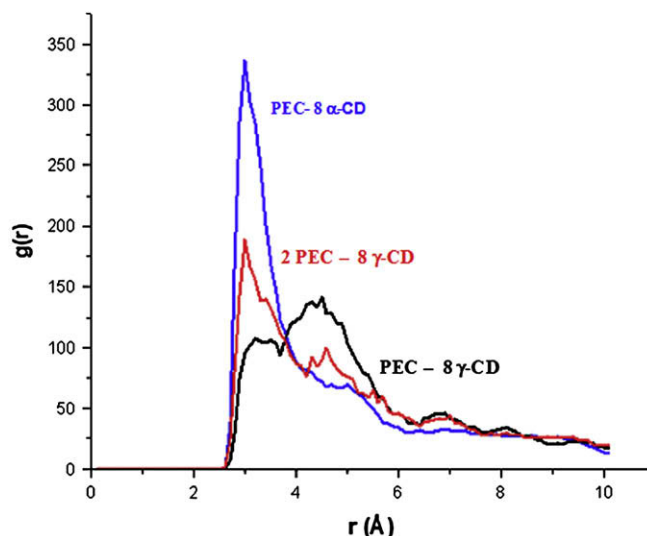

Fig. 6. Static elasticity, ε_0 versus surface concentration Γ plot for PEC.
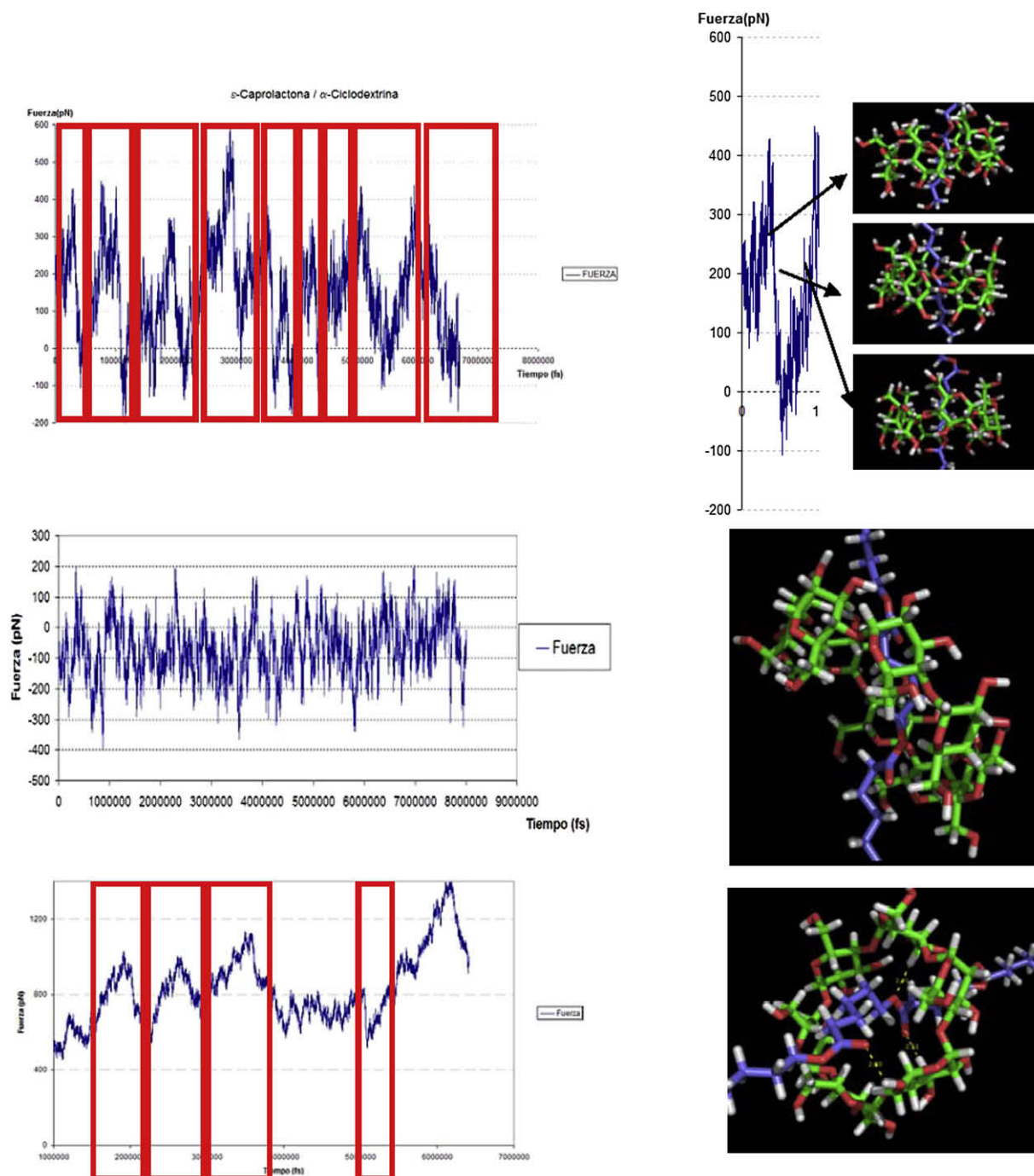

Fig. 8. Secondary OH radial distribution functions from MDS.

Fig. 9. Force profiles in pulling CDs for (A) 1:1 α-CD–PEC complex, (B) 1:1 γ-CD–PEC, and (C) 1:2 γ-CD–PEC complexes.

complementarity between the diameter of the inner CD cavities and cross-sectional diameters of the polymer chain. In this sense, the underlying assumption in this study is that the structural features of the 1:2 γ-CD–PEC complex are similar to those with 1:1 α-CD–PEC. An important property of polymer–CD inclusion complexes is the strict regularity in the arrangement of CDs along the chain that favors the formation of crystalline compounds. Head-to-head and tail-to-tail arrangement of successive CDs in the complex favor intermolecular H-bonding between CD units.

Fig. 7 shows the most probable conformations of the inclusion complexes in water according to MDS. The MD trajectory of the complexes confirms that each CD includes one monomer and H-

bonds contribute to maintain the head-to-head and tail-to-tail arrangement. In 1:1 α-CD–PEC and 1:2 γ-CD–PEC complexes (Fig. 7A and C), the accommodation of the guest inside the cavity optimizes these H-bond interactions. However, in the 1:1 γ-CD–PEC complex, CDs cannot keep the head-to-head and tail-to-tail arrangement since there is a space between the host and guest, and CDs bend down to optimize van der Waals interactions. In addition, this disarrangement causes some water molecules to fill these spaces (Fig. 7B).

In the 1:1 γ-CD–PEC complex, the accommodation of the guest inside the cavity reduces the number of H-bonds. To seek such information the Radial Distribution Function (RDF) was calculated.

The RDF was established between secondary OH of neighbouring cyclodextrins. Fig. 8 shows the radial distribution functions derived from MDS. The plot for α-CD–PEC complex shows a sharp peak centered at 3.0 Å. This unique peak indicates that OHs are well distributed in a head-to-head arrangement. The plot for 1:2 γ-CD–PEC complex shows the same sharp peak centered at 3.0 Å, but a less intense broad peak appears above 4 Å. This broad peak occurs when CDs bend down to optimize van der Waals interactions. Finally, the plot for the 1:1 γ-CD–PEC complex shows the same peaks, but the broad peak above 4 Å is more intense. In this sense, our MD study suggests that the head-to-head arrangement is not stable for this complex.

3.7. Steered molecular dynamics

Fig. 9 shows force profiles for pulling α-CD surrounding the PEC chain (model PEC–α-CD), and γ-CD surrounding one and two PEC chains (models PEC–γ-CD and 2 PEC–γ-CD). The forces fluctuate, indicating that the thermal fluctuation of CDs is larger than the perturbation from the pulling force. The process is therefore near equilibrium. In general, increased force appears when the polymer encounters stability due to van der Waals interactions with the CD cavity. The system must pass over an energy barrier while breaking this interaction, but the force decreases as the guest leaves this energy barrier (Fig. 9A). According to this, the inclusion of PEC inside the CD should occur in small steps where the guest is stabilized in each step. During the movement of the CDs surrounding the PEC chain, van der Waals interactions are established between each monomer and the hydrophobic interior of the host, while CD's hydroxyls interact with carbonyl groups of PEC forming H-bonds. Stable conformations optimize these interactions; therefore, in each step CD includes a PEC's monomer, and the transition from the previous to the following monomer requires passing an energy barrier. Force profiles for α-CD surrounding the PEC chain and γ-CD surrounding two PEC chains reiterate a pattern due to this process (Fig. 9A and C); however, in the force profile for γ-CD surrounding one PEC chain this pattern was not observed (Fig. 9B). Due to this, it can be concluded that the complex between γ-CD and one PEC is not favored, since interactions between a monomer and the hydrophobic cavity of γ-CD are not optimal. On the other hand, these interactions are well established when one PEC chain is included inside of a α-CD, and a similar behavior can be found when two PEC chains are included inside of a γ-CD.

4. Conclusions

The Inclusion Complexes (ICs) between poly(ε-caprolactone) (PEC) and α-cyclodextrin (α-CD) and γ-cyclodextrin (γ-CD) were prepared. ICs were analyzed by thermal analysis, DSC, surface activity at the air–water interface and wettability measurements. Molecular Dynamic Simulation (MDS) was also performed. The PEC shows a thermal stability greater than the α-CD–PEC complex, γ-CD–PEC complex and α-CD and γ-CD. PEC and ICs form stable monolayers at the air–water interface. CDs do not present surface activity. The surface pressure–area isotherms (π–A) are strongly influenced by the nature of the cyclodextrin used. The π–A isotherms of IC with α-CD are the condensed type and the IC with γ-CD shows an expanded type isotherm. The surface free energy (SE) values and the MDS studies, show that PEC is more hydrophobic than the respective ICs, α-CD–PEC and that γ-CD–PEC. CDs are less hydrophobic than ICs and PEC. Finally, MDS provided information about the specific interactions that favor the formation of 1:2 γ-CD–PEC and 1:1 α-CD–PEC.

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