RESEARCH ARTICLE

Synthesis of ureasil-polyether film forming materials by using environmentally friendly solvent

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Abstract

Organic inorganic hybrids present several advantages as drug release systems, such as: high flexibility, high mechanical and thermal resistance, transparency, and low water solubility. These hybrids are synthesized through a chemical route named sol-gel that usually uses as solvente tetrahydrofuran (THF). **Objetives:** To develop film formers from hybrid materials replacing THF with ethanol, a less toxic solvent for skin application and for the environment. **Methods:** Four polymers were used: two based on polyethylene oxide (PEO) with molecular weight of 500 and 1900 g mol-1 and two based on polypropylene oxide (PPO), with molecular weight of 400 and 2000 g mol-1. The structural analysis was performed by FTIR, 1H-NMR and 29Si-NMR, and the thermal-mechanical analysis by DSC and TG-DTA. **Results:** The results of the thermo-mechanical analysis revealed that the solvent replacement did not affect the thermal stability and flexibility of the di-ureasil hybrid. **Conclusions:** Structural characterization confirmed the formation of hybrids both in THF and in ethanol. Therefore, ethanol is an excellent solvent for the synthesis of these hybrid matrices, since it allows obtaining the same material without changing its characteristics, with some advantages, however, over THF. Furthermore, this paper describes the efficiency of ethanol as a solvent, which is environmentally friendly, to replace THF in the physical-chemical characteristics of these filming former materials.

Keywords: Organic-inorganic hybrids, sol-gel process, film formers, structural analysis, thermal analysis, ethanol, mechanical analysis.

1. INTRODUCTION

The interest in different fields in new technologies for controlled release has been increasing in recent years, as these systems have advantages over conventional[1-4] ones, such as reduced toxicity, prolonged time in the bloodstream, gradual and controlled release of the drug, safe and adequate administration, targeting to specific organs, and the ability to incorporate hydrophilic and lipophilic substances[5,6].

Some modifications at the nanometric structure of polymeric materials offer optimization of structural, optical and mechanical characteristics with great application for controlled release of drugs. Among the new class of nanostructured polymers, one can highlight the organic-inorganic hybrid materials[7], in particular, di-ureasil hybrids, which are biocompatible, transparent and flexible, and present better mechanical properties than pure polyethers[8]. The transparency is a feature desired in some pharmaceuticals and cosmetics systems, as it increases patient acceptability and allows the physician to monitor the healing process.

These hybrids are synthesized and processed through the chemical route known as sol-gel[9-12]. During the synthesis of precursors, the usually employed solvent is tetrahydrofuran (THF), which is widely used industrially. Several human studies show that THF is readily absorbed from the respiratory tract. Moreover, this solvent is absorbed through the skin and the THF vapors may cause irritation of mucous membranes, respiratory system and skin[13,14]. Ong et al.[15] reported that occupational exposures (inhalation and dermal) to THF resulted in measurable blood and urine THF levels. As a result of its industrial uses, THF may enter the environment through industrial waste streams and if it is accidentally released in soil or water, precipitating some volatilization to the atmosphere. In addition, THF is more expensive than ethanol and, in Brazil, THF is controlled by the Federal Police, which complicates its use on an industrial scale, as well as its acquisition.

Therefore, in this work, we show that ethanol, an environmentally friendly solvent, can be successfully employed in replacing THF in the synthesis of ureasil-polyether film forming hybrids.

## 2. MATERIALS AND METHODS

2.1 Materials

3-(Trithoxysilyl)Propyl Isocyanate (ICPTES), 95%, Sigma-Aldrich, [O,O'-bis(2- aminopropyl)polypropyleneglycol-block-polyethyleneglycol-block-polypropylene glycol] (PEO, Mw= 500 and 1900 g.mol^{-1}) and [Poly(propylene glycol)bis(2-aminopropyl ether)] (PPO, Mw= 400 and 2000 g.mol^{-1}), Sigma Aldrich were used without prior purifications. The solvents Tetrahydrofuran 99.9%, Sigma Aldrich and ethanol 99.5%, Synth were used to promote hybrid precursor molecule formation. An aqueous solution of HCl 37%, Synth, was used to catalyze the hydrolysis and condensation reactions..

2.2 Synthesis of the polyether-ureasil precursors (hybrid precursors)

The preparation of the di-ureasil hybrids precursors involved the formation of a covalent urea linkage between the terminal aminopropyl groups of the functionalized PEO or PPO and the isocyanate group of the ICPTES (Step 1 of the Scheme 1). In a typical procedure, the functionalized PEO or PPO was dissolved in THF or ethanol (amounts described in Table 1) and added to a three-necked round-bottomed flask equipped with a mechanical stirrer, and reflux condenser. Then, ICPTES was introduced with a molar ratio of 1:2, and the mixtures were stirred and refluxed for 24 h. The solvent (THF and ethanol) was eliminated by evaporation under vacuum at 80°C (±10ºC), leading to the formation of the hybrid precursors. The nomenclatures U-PEO500, U-PEO1900, U-PPO400 and U-PPO2000 were adopted to identify the final precursors prepared using ethanol (ET) or THF as solvents.

Table 1. Amount of reagents used in the synthesis of hybrid matrices.

Hybrid matrices	ICPTES (mL)	NH$_2$-PEO-NH$_2$ or NH$_2$-PPO-NH$_2$ (g)	THF/Ethanol (mL)
U-PEO 500	19.6	25	100
U-PEO 1900	6.3	25	40
U-PPO 400	34.3	25	80
U-PPO 2000	6.0	25	40
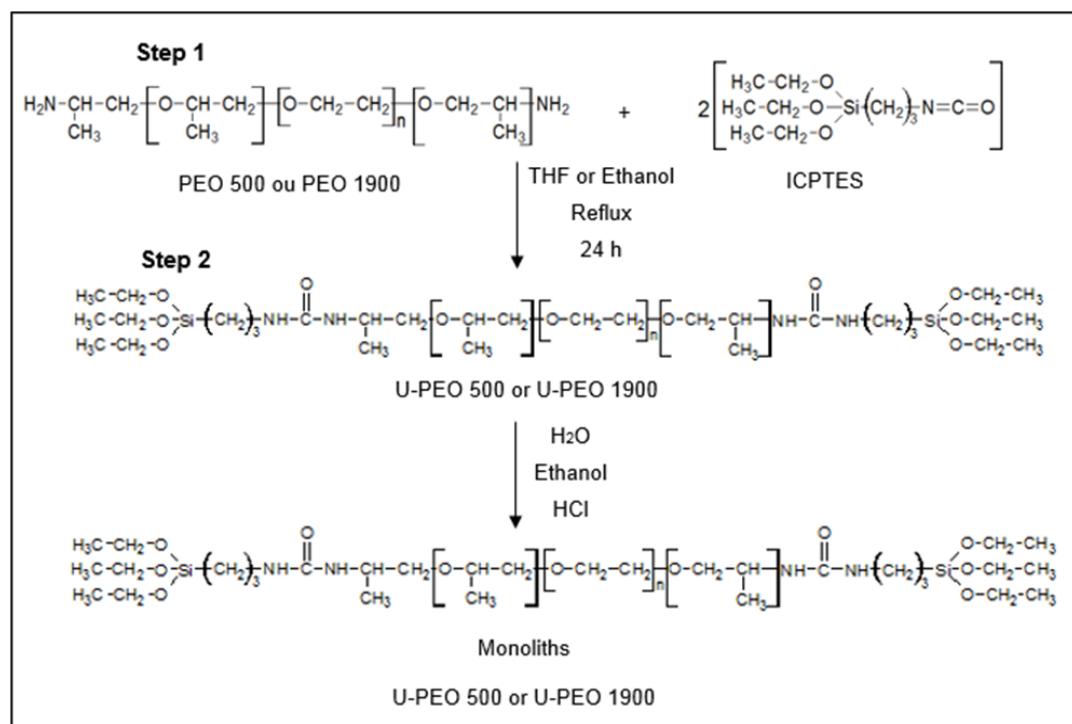
Scheme 1. Schematic representation of the synthesis of U-PEO500 and U-PEO1900 hybrids monoliths. (A similar process was adopted for the synthesis of U-PPO400 and U-PPO2000 hybrid monoliths).

2.3 Preparation of the monoliths

The second step (Step 2 of Scheme 1) comprised the hydrolysis of $Si(OCH_2CH_3)_3$ to generate silanol moieties, followed by condensation reactions to form di-ureasil hybrid monoliths. The hydrolysis reaction was initialized by adding 500µL of ethanol, 50µL of water and 36µL of HCl as catalyst to 0.75g of the di-ureasil precursors. Finally, monoliths were obtained after drying under vacuum at 70°C for 24 h.

2.4 Characterizations of hybrid precursors and monoliths

FTIR spectra of hybrid precursors and monoliths were registered from their thin film cast onto NaCl windows and KBr pellets, respectively, using a Perkin Elmer Spectrum 2000 in transmittance mode. The analysis was done in the 4000-370 cm^{-1} region and at resolution of 1 cm^{-1}.

The ^{1}H-NMR spectra of functionalized POE and PPO and hybrid precursors were recorded in a Varian (500 MHz) using CDCl$_3$ as solvent. The spectra ^{29}Si-NMR of monoliths were recorded in a Varian (300 MHz). The following parameters were fixed: spectral width of 100 kHz; pulse of 101.2º; relaxation of 30s and line broadening in 50Hz.

The monoliths were also characterized by TG and DSC. TG were performed using a TA-SDT Q600 instrument and the samples were heated to 980ºC with a heating rate of 5ºC/min under nitrogen flow. The glass transition, melt temperatures and transition enthalpies of hybrid monoliths were measured using the TA-DSC Q100 equipment with the temperature ranging from -90°C to 350°C and heating rate of 10°C/min under nitrogen atmosphere.

The DMA technique was used to determine the mechanical strength of the hybrid matrix. The measurements were performed using a TA-DMA 2980, operating at room temperature, with a variation ramp force of 1N/min to 18N, static force of 0.02 N, compression load mode and samples in a cylindrical shape with 6.25mm diameter.

3 RESULTS AND DISCUSSION

### 3.1 Synthesis and characterization of hybrid precursors

Figure 1 shows the FTIR spectra of di-ureasil precursors prepared as previously described. The absorption band of isocyanate groups (N=C=O) of ICPTES at around 2274 cm^{-1} disappeared, indicating that this group reacted completely with N-H groups of functionalized PEO and PPO to form urea bridges in both solvents. The presence of urea linkages (- NHC(=O)NH-) in all precursors was confirmed by bands in the amide I and II region. The amide I region in the FTIR spectra of all di-ureasil precursors showed a weak band at 1720 cm^{-1} assigned to free carbonyl band and an intense band with maximum range from 1630 to 1660 cm^{-1} associated with the hydrogen-bonded carbonyl band. Indeed, a strong band in the amide II region of these spectra at about 1560 cm^{-1} ascribed to N-H in-plane blending and C-N stretching. In addition, two broad bands appeared at about 3330 and 3530 cm^{-1}, which were attributed to "free" and hydrogen-bonded stretching vibration of N-H groups of urea, respectively. The last band was less intense than the first one for all precursors with the exception of those prepared using Jeffamine ED2003. Bands attributed to ethoxysilane groups (Si-OCH$_2$CH$_3$) are characterized by strong doublets at 1100-1075cm^{-1} and less intense bands at around 1170 and 950 cm^{-1}. Unfortunately, these bands appear in the same region of C-C and C-O stretching and CH$_2$ angular deformation of functionalized PEO and PPO backbones and then the presence of ethoxysilane groups in the di-ureasil precursors cannot be confirmed in their FTIR spectra.
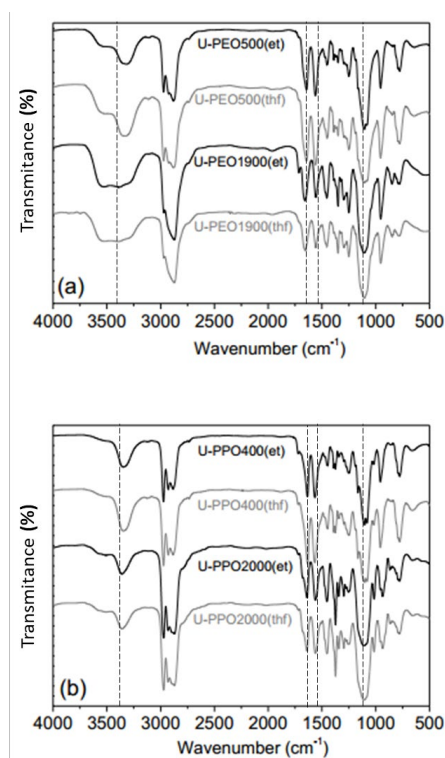

Figure 1. FTIR spectra of di-ureasil precursors prepared by using THF and ethanol as solvent (a) U-PEO and (b) U-PPO.

The molecular structures of di-ureasil precursors are also confirmed by the ^{1}H NMR technique. Figures 2 and 3 show the ^{1}H NMR spectra of U-PEO and U-PPO precursors, respectively, prepared with different molecular weight using THF and ethanol solvents. The signals of functionalized PEO and PPO backbone can be assigned as follows: methyl groups

(- O-CH(-CH$_3$)-CH$_2$-) at 1.05 ppm, methylene groups (-O-CH(-CH$_3$)-CH$_2$-) at 3.31-3.49 ppm and methyne groups (-O-CH(-CH$_3$)-CH$_2$-) at 3.0 ppm attributed to propylene units present in backbone of all PEO and PPO, and methylene groups (-O-CH$_2$-CH$_2$-) at 3.56 ppm from ethylene units present in backbone of the functionalized PEO. The presence of ethoxysilane groups was confirmed by the intense signals at 1.18 ppm (-Si-O-CH$_2$CH$_3$) and 3.65 ppm (-Si-O-CH$_2$CH$_3$), showing that hydrolysis of these groups did not occur during the reaction. Furthermore, the methylene groups linked next to silicon atoms (–Si-CH$_2$-CH$_2$-) appear at 0.55 and 0.77 for U- PEO and UPPO, respectively. The next methylene groups (–Si-CH$_2$-CH$_2$-) showed a signal at 1.50 ppm for all precursors. However, the signal of methylene groups linked next to urea bridges are covered by methylene groups of propylene units at around 3.0 ppm.
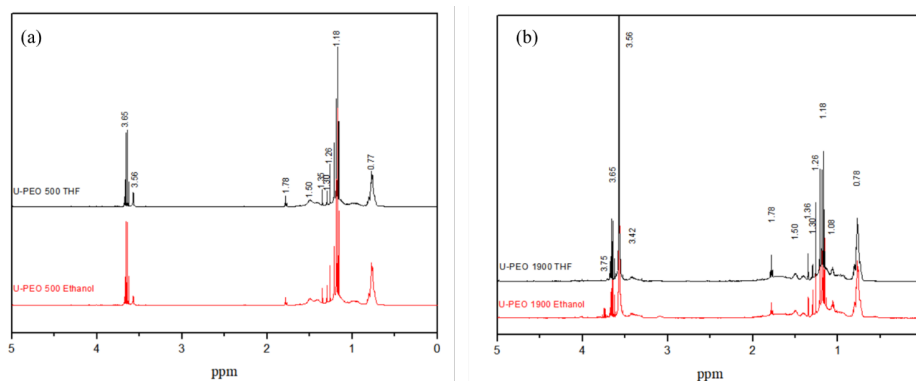
Figure 2. ^{1}H NMR spectra of U-PEO500 (a) and U-POE1900(b) hybrid precursors prepared with THF and ethanol solvents.
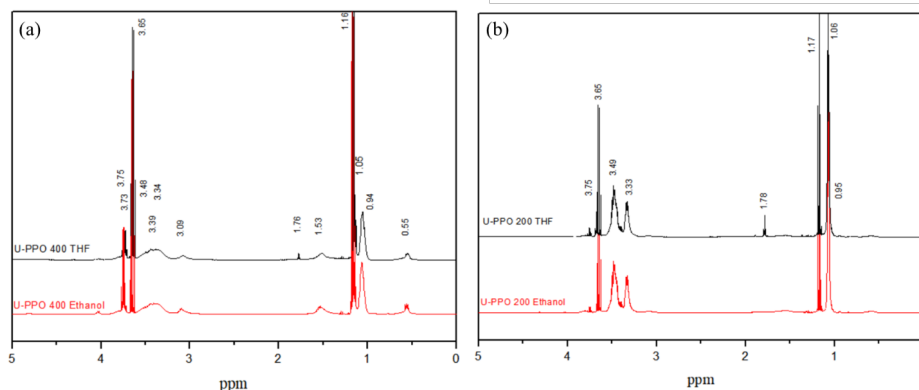

Figure 3. ^{1}H NMR spectra of U-PPO400 (a) and U-PPO2000(b) hybrid precursors prepared with THF and ethanol solvents.

3.2 Characterizations of monoliths

3.2.1 Structural characterization

Figure 4 shows the hybrid monoliths prepared using all di-ureasil precursors. The transparency of these monoliths is a result of the nanostructural uniformity of the network produced by the organic-inorganic hybrid approach. FTIR spectra of these monoliths are presented in Figure 5a and b.
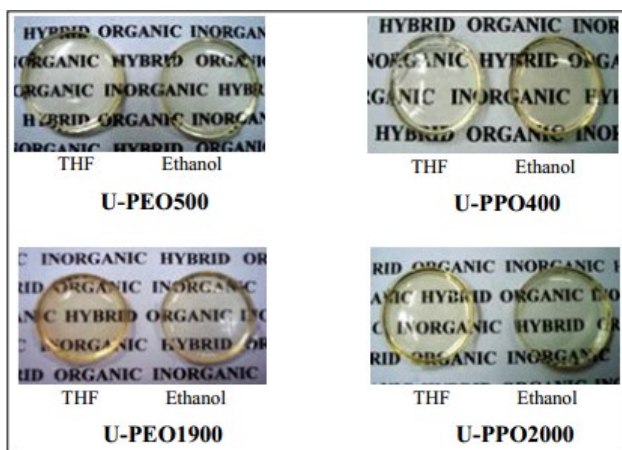
Figure 4. Images of hybrids monoliths prepared using di-ureasil precursors synthesized in THF and ethanol.
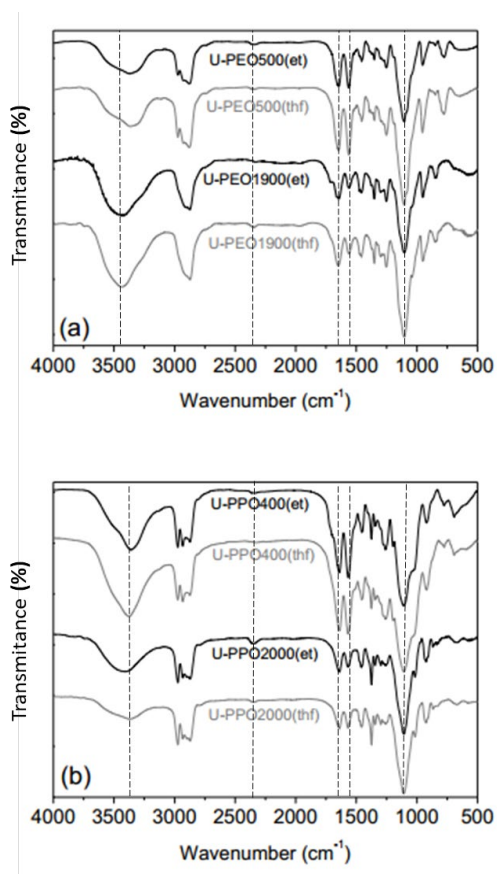

Figure 5. FTIR spectra of monoliths prepared from di-ureasil precursors (a) U-PEO and (b) U-PPO with THF and ethanol.

The use of different solvents and functionalized polymers to synthetize the di-ureasil precursors did not influenced on FTIR spectra of their respective monoliths. The most intense bands in these spectra appeared at about 1100 cm^{-1} and it was attributed to the C-O stretching of oxyethylene units. The presence of urea linkages in these monoliths are confirmed by bands at amide I and II regions. The band at 1640 cm^{-1} in all spectra is attributed to amide I mode (C=O and C-N stretch and C-C-N deformation vibrations) associated to more ordered hydrogen-bonded aggregated (e.g., urea/urea association). However, the spectrum of U- PEO1900(et) showed other amide I components at 1715 cm^{-1} that are assigned to the

absorption of hydrogen-bonded C=O in disordered aggregates. Amide II band appears at 1560 cm^{-1}, and the N-H stretching of urea linkage is centered at about 3450 – 3360 cm^{-1} in these FTIR spectra. The shift of the N-H stretching band can be attributed to intermolecular hydrogen bonding. In addition, the intensities of amide I and II in relation to C-O stretching band of oxyethylene units are affected by average molecular weights of functionalized polymers. The amide I and II bands of U-PEO500 and U-PPO400 are more intense than those of U-PEO1900 and U-PPO2000 due to the presence of more oxyethylene units in the backbone of the last two.

Figure 6 presents ^{29}Si NMR spectrum of monoliths, in which it was possible to observe the presence of peaks between -59 and -67 ppm, which are assigned to the species T_2 (RSi(OSi)$_2$(OH)) and T_3 (RSi(OSi)$_3$, respectively[16]. Table 2 shows that the hybrid matrices presented a high degree of polycondensation (above 85%), revealing the existence of few terminal OH groups in the structure of these materials. This fact has also been shown in previous works, with U-PEO500 and U-PEO1900 being synthesized with THF from basic or acid catalysis[9,11].
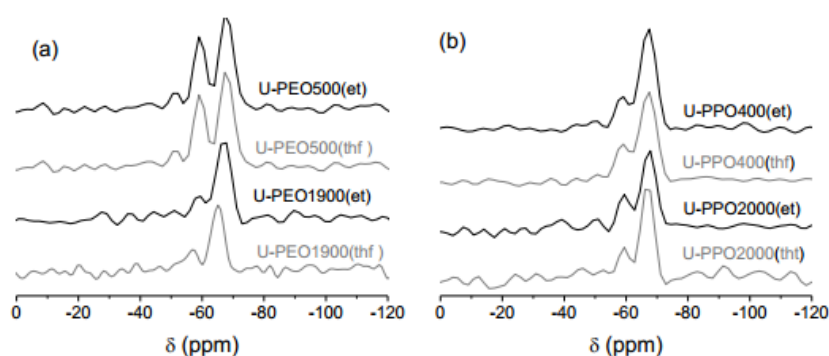
Figure 6. ^{29}Si NMR spectrum of monoliths from di-ureasil precursors (a) U-PEO and (b) U-PPO with THF and ethanol.

Table 2. Area under peaks of different T^n species of ^{29}Si NMR of monoliths and degree of polycondensation.

Hybrid	Solvent	T^2 area %	T^3 area %	Degree of Polycondensation (%)
U-PEO500	THF	34	65	88
	Ethanol	41	59	86
U-PEO1900	THF	27	72	90
	Ethanol	17	82	94
U-PPO400	THF	27	73	91
	Ethanol	22	78	92
U-PPO2000	THF	24	76	92
	Ethanol	26	73	90

3.2.2 Thermal analysis

Figure 7 shows the DSC curves for di-ureasil monoliths prepared as previously described. The DSC data for U-PEO1900 showed an endothermic peak between 25-27ºC related to the melting of the crystalline phase present in the materials. In these polymers, the appearance of regions or crystalline domains surrounded by an amorphous disordered phase and characterizing the formation of a semi-crystalline polymer is well related in the scientific literature[8,9,11]. The negative glass transition temperature for all U-PEO and U-PPO monoliths is related to the high flexibility of di-ureasil polymers, as has been previously reported in the

literature[8,11]. U-PPO400 both in THF and in ethanol, however, showed less negative values (- 10 with THF and -8 for ethanol) indicating that this matrix has a higher stiffness. This can be explained by the fact that these matrices have a larger number of Si-O-Si bonds due to both the low molecular weight of the polymeric chains and the high degree of polycondensation (see Figure 6), increasing the ratio ureasil groups/polymers[11]. This fact, associated with the methyl group present in the polymer chain of these matrices, contributed to the increased rigidity of the polymeric matrixes. This great rigidity for U-PPO 400 monoliths was also observed macroscopically and by the DMA data shown by Figure 7. Observed values of glass transition temperature (Tg), melting point (Tm) and enthalpy change (ΔH) obtained from DSC curves for the hybrids di-ureasil synthesized with THF and ethanol are presented in Table 3.
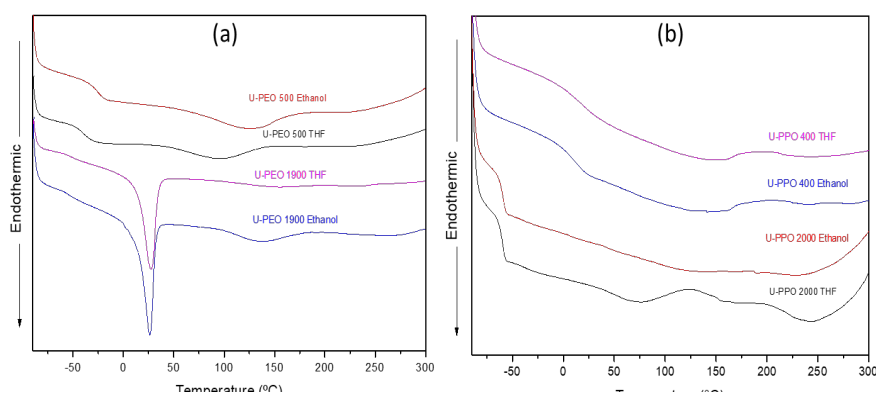
Figure 7. DSC curves of monoliths from di-ureasil precursors (a) U-PEO and (b) U-PPO with THF and ethanol.

Table 3. Data obtained from DSC curves for the hybrid ureasil PEO and PPO with THF and ethanol.

|	PEO 1900		PEO 500		PPO 2000		PPO 400	
	THF	ET	THF	ET	THF	ET	THF	ET
Tg (ºC)	-60	-61	-46	-42	-62	-63	-10	-8
Mp (ºC)	26.47	25.87	-	-	-	-	-	-
ΔH (J/g)	62.40	76.50	-	-	-		-	-

3.2.3 Mechanical analysis

The DMA data indicated that, after the application of a large force (18N = 0.6 MPa), the samples were not damaged.

Figure 8 shows the comparative deformation curves for U-PPO400, U-PPO200, U-PEO500 and U-PEO1900, all synthesized in THF and ethanol.

Regardless of the solvent used, the values do not change. However, when we comparing the values between the different U-PPO or U-PEO groups, the degree of deformation was as follows: U-PPO400 (≈15%) < up U-PEO1900 (≈22%) < up U-PEO500 (≈28%) and U-PPO2000 around 40%. These data corroborate the DSC results, according to which U-PPO400 showed higher Tg, revealing that these matrices are more rigid and therefore more resistant to deformation. Those are followed by the low and high molecular weight U-POE, which presented intermediate Tg values (between -46 ºC and -61 ºC). Finally, the lowest Tg values were from the hybrid matrices ureasil-POP 2000, indicating that these matrices are more flexible and more easily deformable.
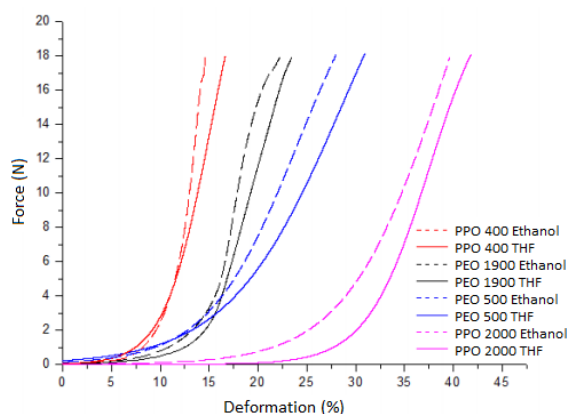
Figure 8. Strain curves as a function of force to hybrid matrices PEO and PPO.

4 CONCLUSIONS

This worked allowed to observe that the use of ethanol, instead of THF, to synthesize di-ureasil hybrids did not affect the structural characteristics, as well as the thermal and mechanical properties. Therefore, it is possible to obtain the same material while maintaining its desirable characteristics such as transparency, mechanical strength and low water solubility, but using a cheaper, more accessible and less toxic solvent.

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Authors' contributions

J.F. Mendes. – First author, Substantial contributions to the acquisition, analysis and interpretation of data; J.A. Oshiro-Jr. – Co-author, Substantial contributions to the conception and design of the work, analysis and interpretation of data; C.G. da Silva – Co-author, Substantial contributions to the analysis and interpretation of data and drafting the work or revising it critically for important intellectual content; L.A. Chiavacci. – Corresponding Author, Substantial contributions to the conception and design of the work, to the acquisition, analysis and interpretation of data and drafting the work or revising it critically for important intellectual content.