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Tunability of polycaprolactone hydrophilicity by carboxymethyl cellulose loading

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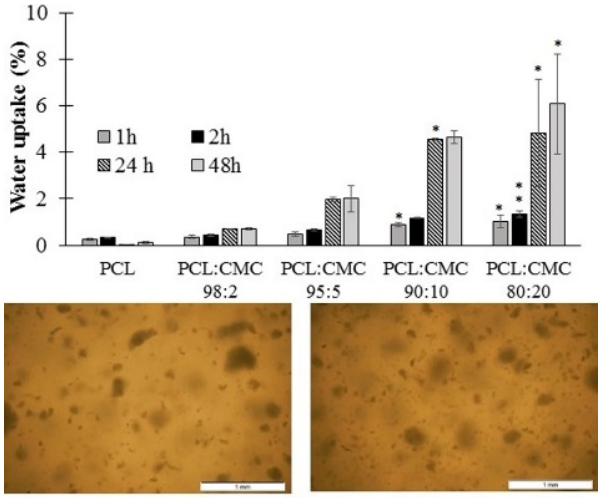
ABSTRACT

Carboxymethyl cellulose (CMC) is herein proposed as additive in polycaprolactone (PCL) matrices to obtain composites with tunable hydrophilicity. This composite material can be

obtained by compression moulding. The thermogravimetric degradation profile, the FTIR spectra, values of the water contact angle, water and phosphate buffered saline (PBS) uptake values and the results of a cytotoxicity assessment are presented herein. The concentrations of CMC in the groups of samples are 0, 2, 5, 10 and 20%. The water contact angle on the prewetted state decreases proportionally to the concentration of the additive. These results evidence the possibility of obtaining a polycaprolactone-based composite with tunable hydrophilicity. Besides, the biological assessment does not reveal any cytotoxic effects. Therefore, the addition of CMC entails an innovative strategy to control the water affinity of polycaprolactone in biomedical applications where such feature is required to improve diffusion of biological medium through, or accelerate degradation by hydrolysis.



Polycaprolactone:microcrystalline cellulose 95:5 (left) and 80:20

1. Introduction

Polycaprolactone (PCL) is a linear polyester with good biocompatibility, a relatively slow degradation rate (it remains up to 2 years without shape modifications *in vivo*) [1] and ease of processability.[2] These characteristics are suitable for the usage of this polymeric material in tissue engineering applications.[3, 4] However, surface cell attachment and

wettability of the structures are limited because of its hydrophobic character.[2, 5, 6] Surface modification has been proposed as a strategy to overcome this restriction. The procedures can be based on plasma treatment of the structure to introduce functional groups[7] or the coating of the surface with bioactive compounds, such as RGD peptides (peptides based on the sequence arginine-glycine-aspartic acid)[8], collagen[9] or gelatin[10].

However, surface treatments have the disadvantage of being effective for a short period of time: as long as the degradation process does not affect the outer layer of material. Alternatively, in this study the feasibility of obtaining bulk polycaprolactone-based hybrid material with tunable hydrophilicity is proposed. This tailored hydrophilicity can be achieved by introducing different amounts of a highly hydrophilic biocompatible material, as carboxymethyl cellulose (CMC).

CMC is a highly hydrophilic[11] polymer derived from cellulose. Its water affinity allowed Wang et al.[12] to develop a superabsorbent composite material based on the combination of CMC with graphene oxide. Besides, it has been proposed by many authors as a component of hybrid biomaterials to be used in biomedical applications.[13, 14]

Its proved biocompatibility and water affinity are two characteristics that make this compound a potential functional additive to be introduced in a polycaprolactone matrix to increase its hydrophilicity for biomedical applications. Herein, PCL has been loaded with CMC in a wide enough range of concentrations (2-20 wt%) to correlate the variation of the surface wettability (assessed by measurement of water contact angles) and equilibrium water uptake (through swelling and mass loss on drying in a thermogravimeter) with its nominal chemical composition and morphology (analyzed by microscopy and infrared spectra).

An increment of the hydrophilicity of the composite material would improve the diffusion of the biological medium and it would accelerate degradation by hydrolysis.

Therefore, obtaining structures with tunable hydrophilicity could be useful to modify their biological performance.

2. Experimental Section

2.1.Materials

Polycaprolactone (PCL) Capa ® 6800 with mean molecular weight 80,000 Da, melting point of 58-60°C and melt flow index of 4.03-2.01 g/10 min was kindly supplied by Perstorp. Sodium carboxymethyl cellulose (CMC) with mean molecular weight 90,000 Da and a substitution degree of 0.7 carboxymethyl groups per anhydroglucose unit was purchased from Sigma Aldrich. KCl (99%), Na_2HPO_4 (99-102%) and KH_2PO_4 (99%) were purchased from Panreac and NaCl (98%) from VWR.

Commercial L929 mouse fibroblast from connective, areolar and adipose tissue were purchased from Sigma Aldrich, expanded and used in their 10^{th} passage. Dulbecco's modified Eagle medium (DMEM), fetal bovine serum (FBS) and penicillin-streptomycin (P/S, 10000 U/mL) were purchased from Gibco. Quant-iT PicoGreen dsDNA Assay Kit was purchased from Thermo Fisher Scientific. Tris-HCl 1M Buffer pH 7.5 and EDTA 0.5M were purchased from Invitrogen. Triton X-100 was purchased from Sigma Aldrich.

2.2. Material compounding

PCL pellets were milled at 8000 rpm in an Ultra Centrifugal Mill ZM 200 (Retsch). This powder was mixed with the amount of powder of CMC needed to obtain PCL:CMC 98:2, 95:5, 90:10 and 80:20 (wt:wt) mixtures. As CMC is not a thermoplastic material, the amount of this additive must be low in order to be able to process the hybrid material by thermal techniques. After homogenization, the mixture was subjected to compression molding in a Collin P 200 P/M press. The cycle used consisted of a first step of heating at

20°C/min up to 85°C at constant pressure of 10 bar, keeping the temperature and pressure for 2 min and subsequent cooling until room temperature at 20°C/min.

2.3.Thermogravimetric and calorimetric analysis

The pellets of pure PCL and hybrid PCL:CMC materials (98:2, 95:5, 90:10 and 80:20) were subjected to thermogravimetric scans in a TGA/DSC 1 Mettler Toledo device. A cycle of heating up to 600°C at a heating rate of 20°C/min with an air flow of 10 ml/min was followed in each case, using aluminum crucibles. The experiments were carried out in triplicate to obtain the degradation profile of the hybrid materials. The same procedure was followed to analyze pure CMC powder. During the TGA testing it was possible to obtain the calorimetric data using the same thermal cycle. These data allowed determining the melting temperature of the hybrid materials and their melting enthalpy.

2.4. Infrared characterization

Fourier-transformed infrared (FTIR) spectra were obtained in the attenuated total reflectance (ATR) mode using a Perkin Elmer IR Spectrum Two with wavelengths from 4000 to 450 cm^{-1} at 8 cm^{-1} resolution. 12 scans per measurement were used to obtain the average spectra. For each sample, five measurements were carried out.

2.5. Morphology

The integration of the CMC particles in the polycaprolactone matrix was coarsely evaluated by microscopic observation. The device used was an Olympus BX51 optical microscope. The microscopic observation of the matrix allows evaluating whether the particles of the additive integrate homogenously within the PCL matrix or otherwise they tend to agglomerate.

2.6. In vitro swelling in Phosphate Buffered Saline (PBS) and water

Three replicates per composite were immersed in PBS prepared according to[15] (137 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4 and 1.8 mM KH_2PO_4) for 1 h, 2h, 24h and 48 h at 37°C. The samples were weighed dry, before their immersion in the solution. At withdrawal, they were dried with filter paper to remove any surface excess of liquid and weighed in their wet state. The PBS uptake was calculated according to:

$$PBS\ uptake\ (\%) = \frac{m_w - m_d}{m_d} \cdot 100$$

where m_w is the mass of the wet sample, and m_d is the initial mass of each sample after drying in a desiccator overnight. An analogous procedure with distilled water was followed to evaluate the water content of the materials after the same time periods. These periods were chosen in order to evaluate how long it takes to reach the equilibrium for swelling.

The water uptake values allowed establishing the time needed to reach the equilibrium in swelling. In order to obtain more accurate values of the water content in equilibrium, a thermogravimetric assessment of the desorption of water was carried out: three replicas of the samples were immersed in water up to this equilibrium time and next subjected to the previously described thermogravimetric cycle (Section 2.3.) in order to obtain the mass loss percentage on drying, attributed to water entrapped in the structure. The mass loss values at 150°C were analyzed in order to compare the amount of water that the samples are able to absorb during the swelling equilibrium time.

2.7. Water contact angle

The water contact angle (WCA) at the surface of the samples was determined at room temperature in an OCA-20 contact angle meter from DataPhysics Instruments, equipped with SCA20 software, by measuring the static contact angle of 8 µl water droplets onto the solid surfaces. Reported contact angles are the average of fifty measurements per sample.

The measurements were carried out both on dry and prewetted samples, as the results vary significantly from one state to the other. This methodology allow confirming if the previous hydration of the samples has an effect on their wettability, as described with other polymers, such as poly(glycerol sebacate)[16] or poly(hydroxyethyl acrylate)[17].

As carboxymethyl cellulose has a high water affinity, to measure the contact angle in the dry state it was necessary to dry the samples under vacuum between measurements, because they absorbed water from the ambient. To pre-wet samples, an immersion in water for 24 hours was imperative to ensure that they reached their equilibrium water content before measurement. After withdrawal, the surface was gently dried with laboratory paper and analyzed immediately.

2.8. In vitro biological development

Mice L929 fibroblasts were cultured on 7 mm diameter discs of each material in order to test the viability of the seeded cells after 1, 2 and 4 days of culture. The samples were first sanitized as described in [18, 19], by immersion in ethanol 70° for 2 hours, followed by rinses in ethanol 50°, ethanol 30° and three times in water (10 min/step) to gradually remove the absorbed ethanol. Afterwards, they were incubated in cell culture media (DMEM + 10% FBS + 1% P/S) overnight at 37°C. The discs were then placed on the bottom of the tissue culture plate wells and $2 \cdot 10^4$ cells were seeded on top of each sample. The viability of the cells was evaluated by the quantification of the L929 double-strand DNA, following the protocol of the Quant-iT PicoGreen dsDNA Assay Kit, after treating the cells with a lysis buffer (Tris-HCl pH 7.4 10 mM + Triton X-100 1% + EDTA 1mM) for 30 min at 4°C in an orbital shaker and freezing them at -80°C O/N. The amount of DNA contained in each L929 cell was based on referred literature[20]. The same procedure was followed on glass coverslips used as positive control of the viability assay. Glass coverslips were purchased from VWR. The test was

carried out with four replicas for each group (PCL, PCL:CMC 98:2, PCL:CMC 95:5, PCL:CMC 80:20 and glass coverslips used as control).

2.9. Statistical analysis

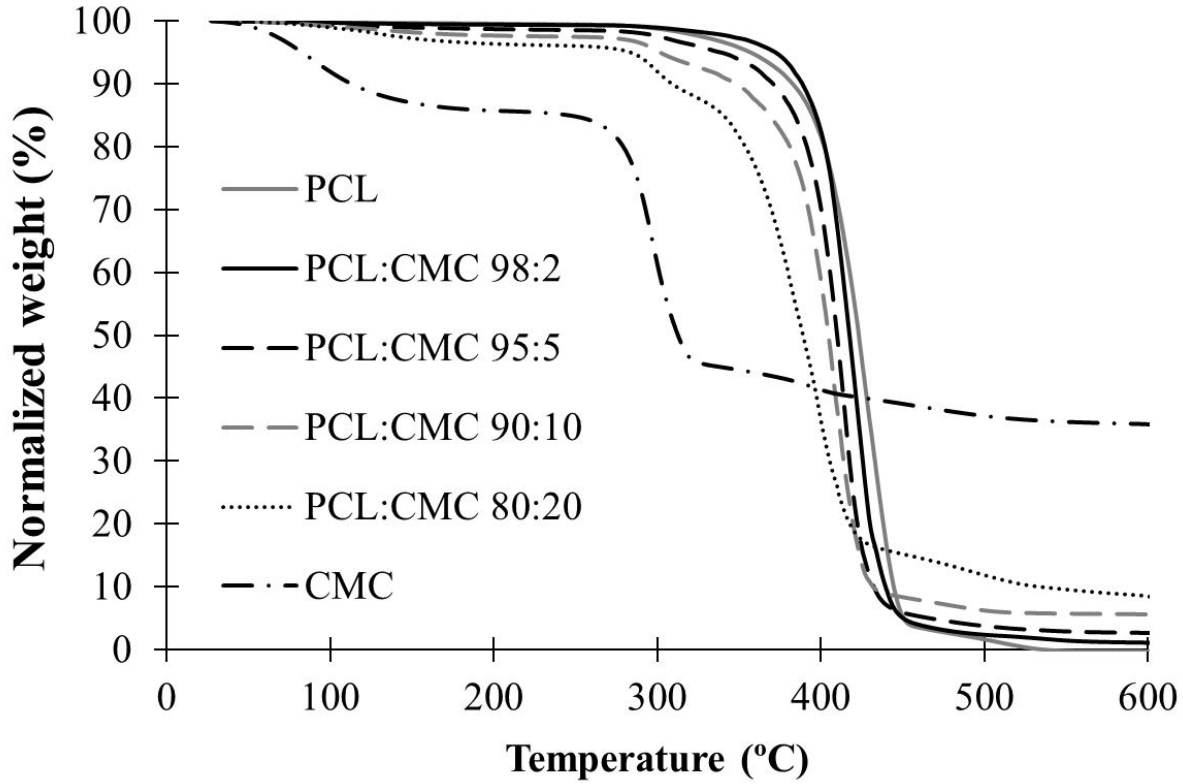
The data obtained during this study were analyzed using the Kruskal-Wallis test. The HSD Tukey's method was used for the multiple range test and the Mann-Whitney test was used when only two groups of data were compared ($p<0.05$ for significant and $p<0.01$ for highly significant statistical difference) using Matlab software. All the figures show the mean values of each group and their standard deviation are represented with error bars.

3. Results and Discussion

3.1.Thermogravimetric and calorimetric analyses

The thermal degradation of polycaprolactone occurs by specific chain end scission in a single thermal step[21, 22] at 430°C whilst the degradation of CMC occurs at 300°C (**Figure 1**). For PCL:CMC 98:2 and PCL:CMC 95:5 the amount of CMC is not high enough to distinguish its own degradation step in the thermogram from that of PCL (Figure 1). However, for PCL:CMC 90:10 and PCL:CMC 80:20, it is possible to observe two degradation steps: a first one related to the CMC degradation and a second one related to PCL. This behavior has been reported previously by Mir et al.[23] in the blend of CMC with polyethylene, another thermoplastic material.

Figure 1. Dynamic thermogravimetric curves of polycaprolactone, carboxymethyl cellulose and their composites.



The presence of carboxymethyl cellulose decreases the maximum degradation temperature from 429°C (for PCL) to 421°C for the 98:2 PCL:CMC blend, 415°C for 95:5 PCL:CMC, 408°C for 90:10 PCL:CMC and 394°C for PCL:CMC 80:20. The values of the melting enthalpy and temperature, presented in Table 1, seem to increase when a small fraction of CMC is introduced, but decrease as such fraction grows.

Table 1. Values of the maximum degradation rate temperature, melting temperature and enthalpy of fusion for polycaprolactone, carboxymethyl cellulose and their composites.

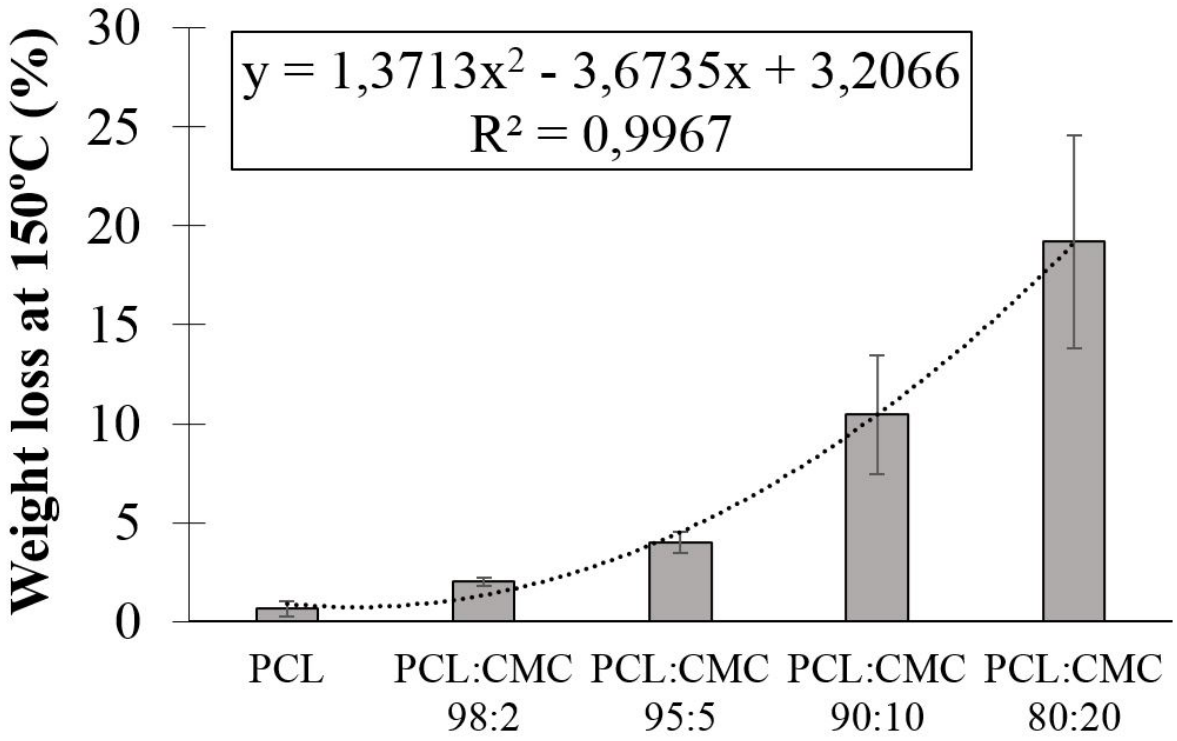
Material	**Maximum degradation rate temperature (°C)**	**Melting temperature (°C)**	**Enthalpy of fusion (J/g)**
PCL	429	63	23
PCL:CMC 98:2	421	69	29
PCL:CMC 95:5	415	68	27
PCL:CMC 90:10	411	68	25
PCL:CMC 80:20	394	64	18
CMC	295	NA	NA

The decrease of the maximum degradation rate temperature observed as the CMC fraction in the composites increases, has been previously reported for other cellulose-based fillers in polycaprolactone matrices, like agricultural waste [24] or sisal fiber.[25] On the other hand, this additive has a slight influence on the melting temperature of the hybrid material and on its melting enthalpy ($p>0.05$) (Table 1), suggesting that the introduction of CMC slightly favors the crystallization of PCL provided that its fraction in the composite is below 10%. This increase in crystallinity can be explained by the nucleation effect caused by the presence of the carboxymethyl cellulose particles. When the concentration of the additive is increased up to 10%, this nucleation effect is hindered because of the formation of aggregates described in section 3.3.

Despite of the decrease of the degradation temperature of the hybrids, as their melting temperature are in all combinations between 61 and 69°C (Table 1), there is a wide safe temperature window to process the proposed hybrid materials by thermal techniques.

Regarding the desorption of water during the thermal cycle, it is possible to identify the first mass loss in the thermograms (Figure 1), located between 90 and 150°C, with this process. The measurement of this mass loss allows a fine determination of the water content of the samples (**Figure 2**). It is possible to observe that the concentration (%wt) of the additive in the polycaprolactone matrix correlates with the weight loss at 150°C by a quadratic polynomial function (R^2= 0.9967) (Figure 2). This correlation is a clear indicator of the possibility of tuning the hydrophilicity of the blend by changing the amount of additive loaded in it.

Figure 2. Correlation of weight loss at 150ºC (measured by TGA) and the amount of carboxymethyl cellulose introduced in the polycaprolactone matrices.

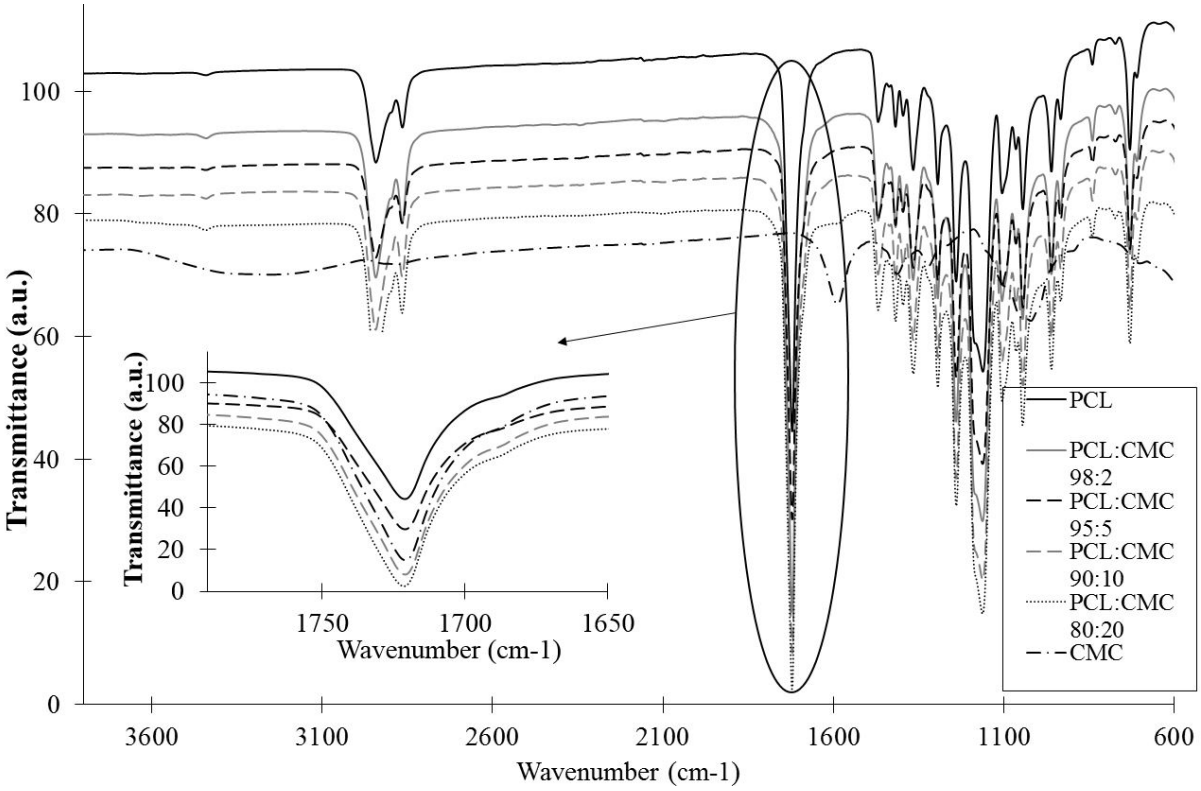


3.2.Infrared characterization of the hybrid material

The carboxymethyl cellulose spectrum (**Figure 3**) shows a signal around 1600 cm^{-1} characteristic of the carboxymethyl ether group.[26] The broad band between 3000 and 3500

cm^{-1} is explained by the presence of hydroxyl groups and the bands at 1415 and 1325 cm^{-1} correspond to CH_2 scissoring and OH bending vibration, respectively.

Figure 3. FTIR spectra of polycaprolactone, carboxymethyl cellulose and their composites. Enlargement: Carbonyl FTIR peak of polycaprolactone.



The spectra of all composites, as well as that of pure PCL, display the characteristic band around 1720 cm^{-1} attributed to the carbonyl stretching of the ester group[27, 28] from polycaprolactone and the peaks at 2946 and 2870 cm^{-1} corresponding to asymmetric and symmetric CH_2 stretching (Figure 3). [29]

The evaluation of the crystallization of polycaprolactone and its blends by the analysis of their infrared spectra has been proposed by different authors.[30, 31] In this study, the area of

the peaks related to the asymmetric stretching of CH_2 in the amorphous phase (2945 cm^{-1}) and to the symmetric stretching of C-O-C in the crystalline phase (1245 cm^{-1}) were measured aiming to evaluate by this technique whether the loading of carboxymethyl cellulose influences the crystallinity of the material. According to Phillipson,[32] the CH_2 asymmetric stretching peak is of medium intensity in the amorphous phase (very weak in the crystalline one), whereas the C-O-C symmetric stretching peak is of medium intensity in the crystalline phase (weak in the amorphous one). Thus, the areas of both peaks have been used herein to have an approximate indication of the PCL crystallinity. Table 2 shows the ratio between the area of the CH_2 peak and that of the C-O-C one. These results agree substantially with those obtained from calorimetric scans.

Table 2. Ratio of the FTIR peaks areas (CH_2 in the amorphous phase/C-O-C in the crystalline phase).

Material	**Ratio of areas (CH_2 peak/C-O-C peak)**
PCL	1.34±0.11
PCL:CMC 98:2	1.67±0.16
PCL:CMC 95:5	1.37±0.27
PCL:CMC 90:10	1.63±0.09
PCL:CMC 80:20	1.43±0.18

Regarding the structure of both components, hydrogen bonding between the hydroxyl groups in the carboxymethyl cellulose and the carbonyl group of the polycaprolactone could be expected. The presence of the hydrogen bonding would be confirmed by the characteristic

peak at 1710 cm^{-1} of the hydrogen-bonded carbonyl vibration[31] or by the shift of the carbonyl peak to lower values of the wavenumber.[33] However, neither the 1710 cm^{-1} peak nor the shift of the position of the carbonyl signal are noticeable in the spectra from the blends containing carboxymethyl cellulose (enlargement in Figure 2). Therefore, in view of the FTIR spectra obtained herein, it seems that there is no interaction between both components of the proposed composites. The absence of intermolecular interaction between them enhances the formation of larger aggregates as the concentration of CMC is increased.

3.3.Morphology

As shown in **Figure 4**, the CMC particles are evenly distributed in the polycaprolactone matrix and they form non-uniform aggregates of two distinct sizes: below 100 microns, and around 200-300 microns.

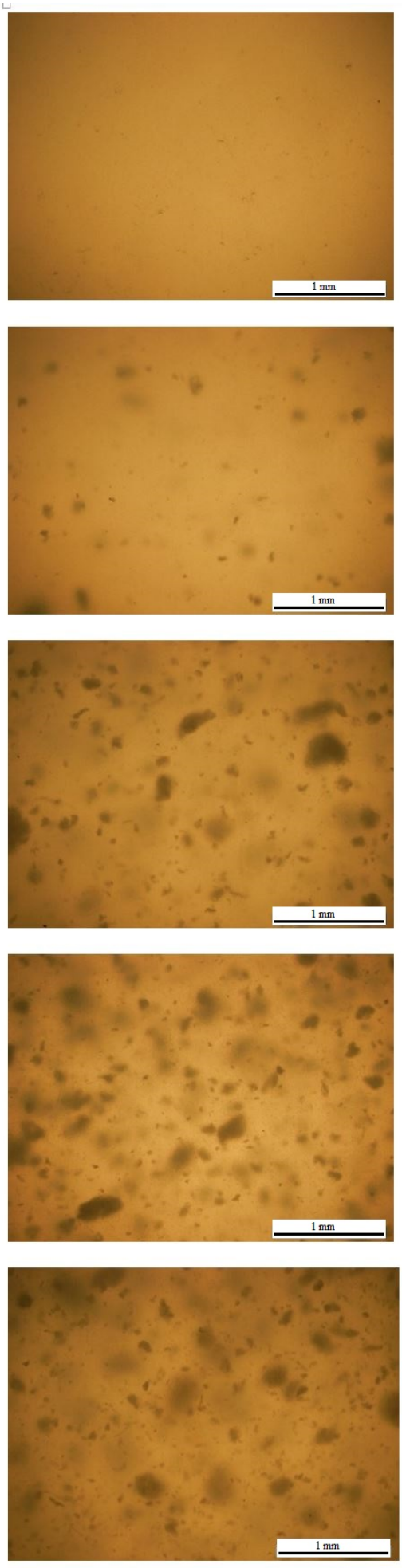


Figure 4. Optical microscopy images of the distribution of the CMC in the polycaprolactone matrices (from top to bottom: PCL, PCL:CMC 98:2, PCL:CMC 95:5, PCL:CMC 90:10, PCL:CMC 80:20). Scale bar: 1 mm.

3.4. In vitro swelling in Phosphate Buffered Saline (PBS) and water

Medium absorption is an adequate indicator of the hydrophilicity of a material.[34] From the results shown in **Figure 5** and **Figure 6** it is possible to confirm that the loading of carboxymethyl cellulose increases the hydrophilicity of the material even for short periods of immersion in water and PBS, as the values of PBS and water uptake are higher for the composites than for pure polycaprolactone. For example, the water uptake increases from 0.2% in pure PCL until 1.0% for PCL:CMC 80:20 in 1 hour, i.e., the addition of CMC in the composite allows to increase five times the amount of water the material is able to absorb in a short period of time.

Figure 5. PBS uptake for 1h, 2h, 24 h and 48h of immersion (*p<0.05; **p<0.01 compared to the equivalent group of pure PCL samples).

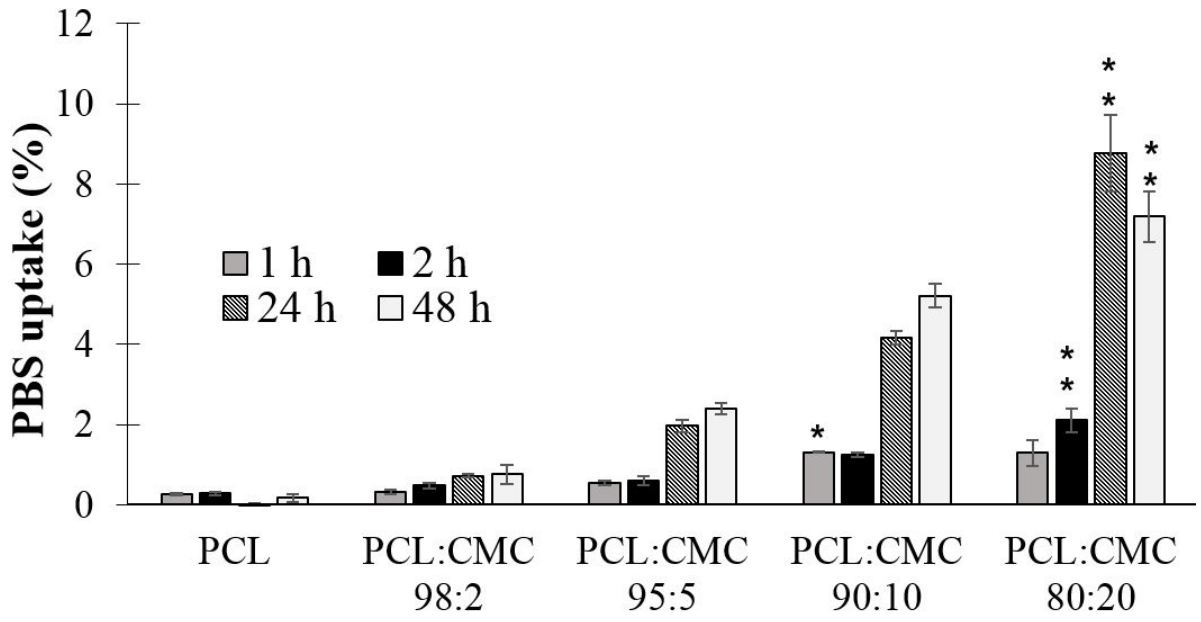
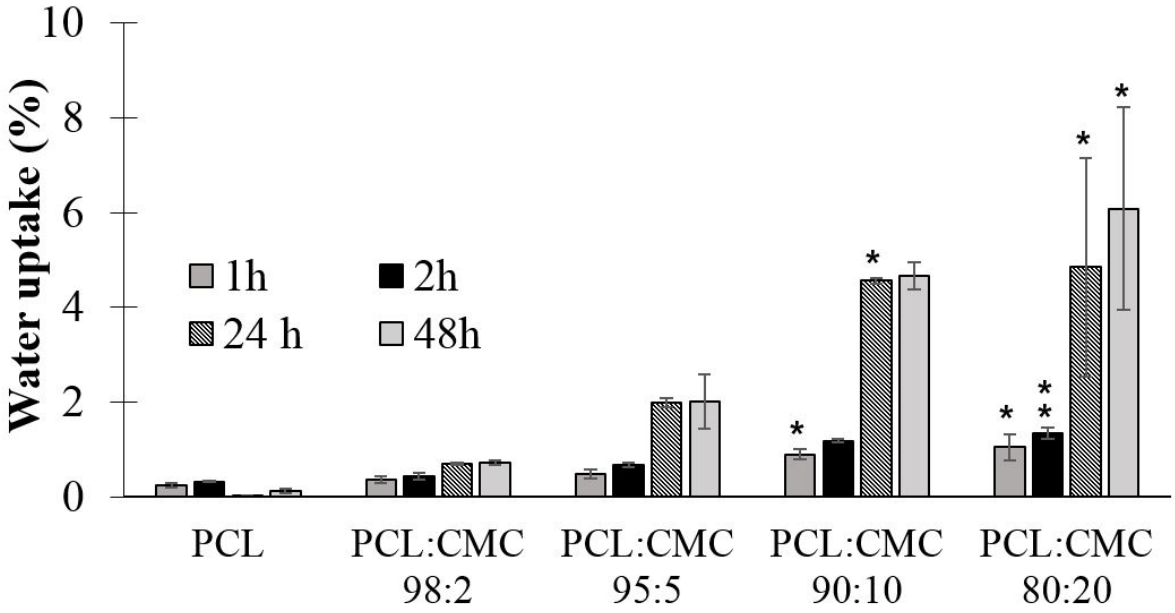


Figure 6. Water uptake for 1h, 2h, 24 h and 48h of immersion (*p<0.05; **p<0.01 compared to the equivalent group of pure PCL samples).



Regarding the time necessary to reach the swelling equilibrium, it is possible to observe that there is not a significant change in the PBS uptake nor in the water uptake between 24 h and 48 h. Therefore, it may be stated that 24 h is a long enough period for the samples to completely swell. The equilibrium swelling is five- to ten-fold greater in the composites with 10 and 20% of CMC, respectively, than in pure PCL.

On the other hand, although the type of fluid used (PBS or water) does not provide a significant statistical difference between groups, one can observe that there is an increment of the mean swelling value in PBS compared to water uptake (Figure 5 and Figure 6). This slight increase can be explained by the interaction of the carboxylate functional groups in the carboxymethyl cellulose structure with the ionic media.

The ability of the hybrid materials to swell in short periods entails an important difference against other strategies proposed in the literature to increase the water uptake

ability of polycaprolactone. For instance, Liu et al.[35] developed phosphate glass fiber reinforced polycaprolactone composites that showed increased water uptake after several days of immersion, but none the first day.

3.5.Water contact angle

Table 3. Water contact angle values in the dry and the prewetted state of the samples (*p<0.05; **p<0.01 compared to PCL values).

Material	**Water contact angle in dry state**	**Water contact angle in prewetted state**
PCL	86.6 ± 5.2 º	78.3 ± 4.8 º
PCL:CMC 98:2	86.5 ± 6.8 º	75.1 ± 5.0 º
PCL:CMC 95:5	92.6 ± 6.6 º	73.6 ± 4.6 º **
PCL:CMC 90:10	99.2 ± 6.3 º *	72.2 ± 5.2 º **
PCL:CMC 80:20	90.0 ± 6.2 º	67.0 ± 5.5 º **

Table 3 presents the average water contact angles of the different samples. Contrary to what one might think, the water contact angle of the samples in their dry state increases with the amount of carboxymethyl cellulose from 2% until 10%, suggesting that their wettability is lower. These results led us to perform the measurements on pre-wetted samples in order to check whether the behavior of the composites is affected by their previous hydration. In the pre-wetted state, the trend is indeed the opposite: an increment on the concentration of the additive implies a significant reduction of the water contact angle, i.e., greater surface wettability.

The increase of the water contact angle as CMC mass fraction increases, when measured on the dry samples. These results, which seem to contradict those described before related with the swelling in water or PBS, can be explained by intra- and intermolecular hydrogen-bonding interactions between polar terminal groups in the dry state, as stated in previous studies.[16, 17, 36, 37] In the prewetted state, the trend is the opposite: an increment on the concentration of the additive implies a significant reduction of the water contact angle, i.e., greater surface wettability. This effect has already been observed in other polymers, like poly(glycerol sebacate),[16] poly(hydroxyethyl acrylate)[17] and previously in poly(hydroxyethyl methacrylate),[36] which better expose hydroxyl (and carboxylic acid as well in the former) groups at the surface only when hydrated. In the work of Ratner,[37] this effect is named reversal surface structure, occurring when transferring this type of samples from air into a water environment.

Other authors have reported problems with the measurement of the contact angle with polycaprolactone-based samples treated to increase the hydrophilicity of the material, as the drop is rapidly absorbed by the sample when it is dry.[38] This fact is interpreted as enough evidence to show the increase of the water affinity of the surface. However, the measurement of the water contact angle in the wet state allows avoiding this obstacle to obtain quantitative comparison. In addition to this, the decrease in the WCA observed in the present work when adding CMC is only slightly lower than some reported results for plasma treatment (Table 4).[39] However, the main advantage of the incorporation of an additive in the polycaprolactone matrix is the possibility of changing the hydrophilicity of the bulk material instead of only that of its surface. Besides, the effect observed immediately after the plasma treatment evolves with time. Indeed, Moraczewski et al.[40] have reported that aged plasma treated polycaprolactone samples increase their contact angle between 20^0 and 40^0 after 9 weeks of aging.

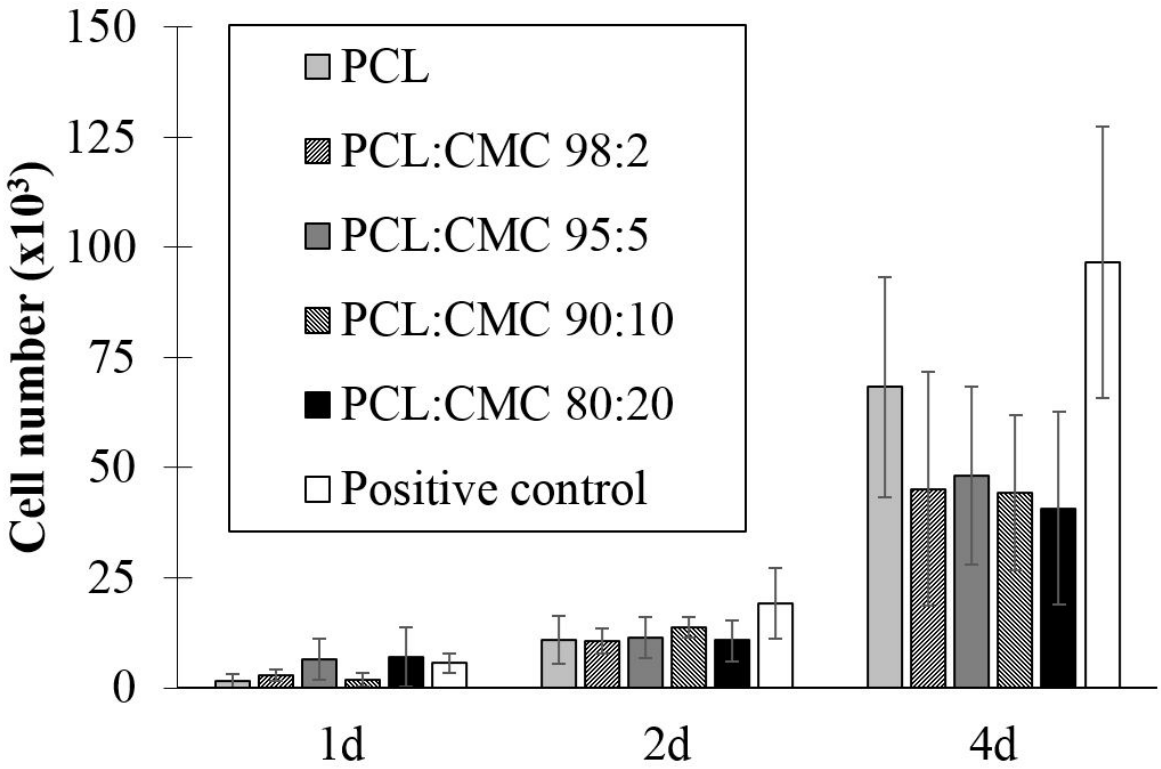
Table 4. Comparison of the decrease on the WCA of this study to the values obtained with plasma treatment of the surface.

Type treatment	**WCA**	**Decrease on the WCA**	**Reference**
Oxygen plasma	52º	21º	38
Argon plasma	42º	31º	38
Combination with CMC	67-75º	3-11º	This work

3.6. In vitro biological development

The population of cells is able to proliferate in all the groups at a similar rate. In fact, there is not a significant difference between the polycaprolactone samples and the composites (**Figure 7**).

Figure 7. Cell number throughout the fibroblasts culture on PCL and PCL:CMC samples after 1, 2 and 4 days (no significant differences were found among groups).



The combination of carboxymethyl cellulose with polycaprolactone has demonstrated to be non-cytotoxic for the proliferation of fibroblasts. Therefore, the hybrid materials are a suitable environment to support fibroblasts attachment and proliferation. The slight non-significant decrease in the cell density of more hydrophilic composites could find partial explanation on the poorer adsorption of adhesion-signaling extracellular proteins, although other factors such as the surface topography or distribution of chemical groups cannot be ruled out.

4. Conclusions

The incorporation of CMC in polycaprolactone matrices at different concentrations is a useful tool to modify the water affinity of the composite materials. This trend has been

confirmed by water contact angle measurements and the water and PBS and water uptake values.

The possibility of obtaining tunable hydrophilicity of polycaprolactone-based materials is especially interesting in the biomedical sector. In this sense, cytotoxicity tests carried out with fibroblasts have demonstrated the biocompatibility of the composite materials proposed.

Finally, the thermal analysis of the composite materials obtained demonstrated that it is a wide enough temperature window to process this set of materials by thermal techniques.

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Carboxymethyl cellulose loading can be used as a strategy to increase the hydrophilicity of polycaprolactone matrices. It is possible to tailor the water affinity of the matrix by modifying the content of this additive. Besides, the composites do not show a cytotoxic effect, so they are promising for biomedical applications.

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