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Research Article

Synthesis and characterization of a novel amphiphilic block copolymer as a potential drug carrier

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Abstract

This paper presents the synthesis procedure of a novel amphiphilic block-copolymer poly (ethylene glycol)-b-poly (lactic acid) (PEG-b-PLA) and its various characterization techniques in order to explore the applicability of this copolymer as an agent of encapsulation for hydrophobic drugs. The synthesis consists of ring-opening polymerization (ROP) of L-lactide with stannous octoate ($Sn(Oct)_2$) as a catalyst and methoxy poly(ethylene glycol) mPEG as an initiator. The copolymer is characterized and confirmed by ^{1}H-NMR spectroscopy, Gel Permeation Chromatography (GPC), and Fourier Transform Infrared spectroscopy (FT-IR). The thermal properties of the synthesized copolymer are determined by Differential Scanning Calorimeter (DSC). The nanoscale size (100-130 nm) and its distribution is verified by Dynamic Light Scattering (DLS) and the critical micelle concentration (CMC) is determined by fluorescence spectrophotometry. The UV measurements show that the polymer has high encapsulation efficiency (72%) and is able to enhance (28 times) the solubility of a hydrophobic drug, namely Ibuprofen, in an aqueous medium. The results of this study reveal that the novel copolymer could be a potential candidate for hydrophobic drug delivery systems.
Keywords: Block-copolymer; Drug carrier; Ibuprofen; PEG, PLA, ROP

1. Introduction

Throughout history, humans have found several means to introduce medications into the body. This process has evolved from primitive extracts as chewing leaves or roots of medicinal plants and inhalants to more reliable methods such as tablets, capsules, and injections. The limitation of the latter method is that the concentration of the injected substance should be extremely diluted in the bloodstream. This is due to the fact that it acts on most tissues of the body and may be toxic to some of them. The problem could be solved by controlled drug delivery.

For decades, controlled drug delivery technology has drawn great interest and has been widely investigated. This is due to the numerous advantages offered by this technique compared to the conventional drug delivery routes, as for instance: (i) the protection of a drug against in vivo degradation and thus improving the drug bioavailability and pharmacokinetic profile, (ii) the reduction of toxicity risks when the drug is directly injected in the blood stream, (iii) the opportunity for using new drugs currently excluded from clinical use due to challenges including low solubility, (iv) the ability to overcome the barriers and physical properties of some tissues in the body (for example blood-brain barrier and cancer tumors), (v) the control of the drug concentration, the location of where the drug is delivered, and the duration of exposure, (vi) the improvement of the patient compliance and convenience by avoiding repetitive injections or perfusion pumps [1].

The thermoplastic aliphatic poly (esters), poly (lactic acid) (PLA), has been investigated worldwide due to several benefits that this polymer possesses. First, PLA is derived from renewable resources. Thus, it is biodegradable, recyclable, and compostable. These eco-friendly features make PLA an attractive biopolymer. Second, PLA is biocompatible. In fact, when PLA is degraded, it produces lactic acid which is a metabolite that can

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be eliminated from the human body via the Kreb's cycle. Furthermore, the Food and Drug Administration (FDA) in USA has approved PLA for direct contacting with biological fluids [2]. However, PLA also has several limitations. First, it is highly hydrophobic. This results in low cell affinity and can cause an inflammatory response upon direct contact with biological fluids. Second, PLA degrades at a relatively slow rate through the hydrolysis of ester groups. The degradation rate is usually considered as a significant criterion for biomedical applications. On one hand, a slow degradation rate leads to a long life time inside the body. There have been reports of a second surgery almost 3 years after implantation to remove a PLA-based implant. On the other hand, the slow degradation rate can cause serious problems when disposing consumer commodities [2].

The most common strategy to overcome PLA limitations is to prepare block copolymers. Block copolymers are macromolecules composed of linear or nonlinear arrangements of chemically different polymeric chains called blocks. On one hand, the properties of PLA can be significantly improved when copolymerization of lactic acid takes place with other groups such as hydroxyl acid, amino acid or polymers as poly(ethylene glycol). On other hand, several new copolymers in different macromolecular architectures can be obtained. The introduction of Poly (ethylene glycol) (PEG) used as macro-initiator to prepare block copolymers with lactic acid is a mean to give the nanoparticle the amphiphilic characteristics. PEG presents unique physicochemical and biological properties including high hydrophilicity, flexibility, biocompatibility, resistance to immunological recognition, and can be eliminated from an animal's body when the molar mass is below 30,000[3]. Through copolymerization of PEG with PLA, the resulting copolymers lead to enhanced drug loading, reduced burst effect, and extended in vivo residence time of drugs. These effects are due to enhanced hydrophilicity, degradation rate, and crystallization. On other hand, PEG-PLA copolymers exhibit reduced acidity of degradation products as compared to PLA as these products enter the tricarboxylic acid cycle or be eliminated by the kidneys. Moreover, due to their nano-scale particle size, the PLA-PEG nanoparticles can accumulate in inflammation or target locations to enhance drug efficacy and reduce toxicity[4][5].

Ring-Opening Polymerization (ROP) was selected as the method of choice in the present research due to its advantages: First, since this is not a condensation polymerization there is no need for the removal of water. Second, high molar mass with low polydispersity index can be achieved [6][7].

The aim of this paper is to synthesize a new amphiphilic polymer and test its capabilities to form micelles to be used as agents of drug delivery systems.

2. Materials and Methods

2.1 Materials

Schlenk reaction and storage tubes with capacities of 50 mL and 100 mL are purchased from Sigma-Aldrich and used for synthesis. Poly (ethylene glycol) methyl ether (mPEG average Mn 2,000), L-Lactide: (3S)-cis-3,6-Dimethyl-1,4-dioxane-2,5-dione 98%, and Stannous octoate: Tin(II) 2-ethylhexanoate ~95% are also obtained from Sigma-Aldrich. Silicon Oil is obtained from Himedia and used as an Oil bath. All the solvents used during this study are purchased from different providers, as listed below, and used without further purification: Toluene 99% (Surechem products LTD), Dichloromethane 99.9% (Prolabo BDH- VWR), Tetrahydrofuran 99.8% (Lab- scan analytical sciences), Diethyl ether 100.0% (Prolabo BDH- VWR), Chloroform-d $CDCl_3$ 99.8 atom% D (Sigma-Aldrich).

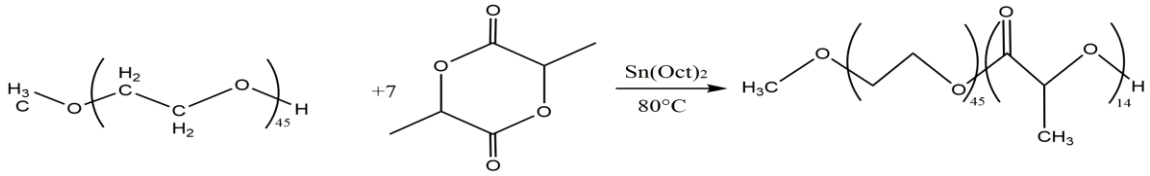

Figure 1: Synthesis of PEG-b-PLA

2.2 Synthesis of PEG-b-PLA

PEG-PLA diblock copolymers are synthesized by ring-opening polymerization based on the method used by [6]. Prior to the synthesis, Toluene is dried through a silica column. Typically, in a 100 mL oven dried Schlenk tube, 2 g of m-PEG with 2.16 g of L-lactide are mixed in 20 mL anhydrous toluene with 120 µL of 0.1% $Sn(Oct)_2$ stock solution used as a catalyst(Figure 1). The tube is fitted with a rubber septum. The mixture is degased by freeze-pump-thaw cycling method. After repeating this process three times, the Schlenk is placed in an oil bath at T

= 80 °C and the mixture is stirred under argon. A series of four copolymers are synthesized using the same procedure described above. The only varying factor is the polymerization time which is 1 hour, 2 hours, 4 hours, and 6 hours respectively. After the time needed for reflux elapses, the Schlenk is removed from the oil bath to cool and then quenched with HCl solution (1M, MeOH). 30 mg of the mixture are recuperated in order to find the percent monomer conversion by ^{1}H-NMR. The polymer is dissolved by the addition of some drops of Tetrahydrofuran (THF) and precipitated into an excess of cold diethyl ether. The solution of diethyl ether is able to purify the copolymer by removing any low molecular weight impurities. The solution is then filtered over fritted funnel and the polymer recuperated and kept in a desiccator under vacuum.

2.3 NMR Study

^{1}H-NMR spectra are recorded on a Bruker spectrometer (AMX II 300) operating at 300 MHz with a BBI probe. The data are obtained with the Bruker Topspin software (version 2.1). Five hundred microliters of each solution are introduced into a standard 5 mm NMR tube and the experiments are realized at 300 K. The deuterated chloroform $CDCl_3$ is used as a solvent. Chemical shifts are referenced to the peak of residual non-deuterated solvents.

2.4 Gel Permeation Chromatography (GPC)

GPC is performed at room temperature using a Viscotek GPCmax system equipped with a Viscotek guard column (10 × 4.6 mm) and two Viscotek columns LT 5000L mixed medium (300 × 7.8 mm), with a Viscotek VE 3580 refractometric detector and a Viscotek VE 3210 UV/vis detector. The calibration curve is established with polystyrene standards from Polymer Laboratories. THF is used as solvent with a flow rate of 1 mL.min^{-1}.

2.5 FT-IR

FT-IR spectra are performed on Frontier Infrared Spectrometer (PerkinElmer,USA) between 4000 and 450 cm^{-1}. First, KBr pellets are prepared for each polymer sample. The solid sample is taken on a microspatula, grinded in a mortar, and then mixed with about 0.25-0.50 teaspoon of dried KBr. The mixture is thoroughly grinded in a mortar with the pestle. Second, the mixture is placed in a pellet die, placed in a press, and pressed at 5000-10000 psi. Finally, the pressed disc is carefully removed from die and placed in the FT-IR sample holder. The pellet should be nearly clear if properly made [8].

2.6 Thermal Analysis

The thermal behaviors of the four synthesized copolymers are investigated by DSC. Data is collected by LabSys evo (Setaram, France) instrument under nitrogen flow. The heating rate is 10 °C/min starting from room temperature to 300 °C. Briefly, 10-15 mg of the samples are placed in the instrument crucible next to a blank crucible as a reference. The collected thermograms allow us to deduce two major properties of the copolymers: First the melting behavior of each copolymer by determining the melting temperature (T_m) and second the range in temperature at which the copolymers degrade [2][9].

2.7 Dynamic Light Scattering

The particle sizes and its distribution of the prepared block copolymers are determined at 25°C with a Partica Laser scattering (LA-950V2, Horiba, Japan) equipped with a He-Ne laser (λ = 632.8 nm). Samples are introduced directly into the sample bath [10].

2.8 Fluorescence Spectroscopy

The amphiphilic copolymers self-assemble into micelles in aqueous solution. The formation of these micelles is confirmed and their critical micelle concentration (CMC) is determined by fluorescence spectroscopy, using pyrene as a hydrophobic fluorescent probe. An aliquot of pyrene solution (6×10^{-6} M in acetone, 1 mL) is added into a series of vials, and the acetone is completely evaporated. Then, each vial is filled with 10 mL of aqueous solutions containing different concentrations of copolymer-4h (copolymerization time is 4 hours). The final pyrene concentration in each vial is 6×10^{-7} M, equal to the saturation solubility of pyrene in water at 22 °C. Fluorescence measurements are performed on a F-7000 fluorescence spectrophotometer (Hitachi, Japan) equipped with a Xenon light source. The emission and excitation slit widths are 3 nm and 5 nm, respectively. The samples are excited at 340 nm and emission spectra are recorded from 330 to 440 nm. The emission fluorescence values I_{375} and I_{395}, respectively at 375 and 395 nm, are used for the determining of CMC value. The I_{395}/I_{375} ratio is plotted against the logarithm of the polymer concentration. The CMC is taken as the intersection of regression lines calculated from the linear portions of the plot [6].

2.9 UV Measurements

The drug loading of Ibuprofen-loaded copolymers is determined by UV spectrophotometry. The UV absorption spectra are recorded using Shimadzu UV-1800 Spectrophotometer. 100 mg of each drug is stirred in 10 mL of a 2mg/mL polymer solution. The obtained drug-loaded nanoparticles are filtered using a 0.45 micron disc to remove any free drug. Then, the Ibuprofen content is determined by UV/Vis spectrometry by measuring the absorbance at 264 nm. The concentration of encapsulated Ibuprofen is determined using a standard calibration curve by plotting the absorbance versus the concentrations of Ibuprofen.

UV spectrophotometry is also used to determine the Encapsulation Efficiency of the copolymer. Briefly, a solution containing 2 mg/mL of the copolymer C with 2.5 mg/mL of Ibuprofen is digested in 1 N NaOH for 1 hour. After filtering the solution by 0.45 micron disc, the encapsulated Ibuprofen concentration was measured by spectrophotometry at 264 nm in order to calculate the Encapsulation Efficiency [9].

3. Results and Discussion

3.1 ^{1}H-NMR

^{1}H-NMR spectra are recorded for each synthesized block copolymer before and after precipitation. The recordings before the precipitation aim to determine the conversion percent. The ^{1}H-NMR spectrum observed in Figure 2 shows a peak at 5.125 ppm corresponding to CH of PLA polymer synthesized in 4 hours (Polymer C) [6][10].

In addition to the detected peaks of the polymer and the solvent, the CH of L-lactide monomers can be observed at 5.01 ppm[6][10]. Figure 3 shows the part of the spectrum recorded for polymer C where the peaks of polymer and monomer are integrated in order to calculate the conversion percent.

Thus, the conversion percent can be calculated using (3.1):

$$\%\ conversion = \frac{I_P - I_M}{I_P + I_M} \times 100 \qquad \text{(Equation 1)}$$

where

I_P is the integration of polymer peak determined by NMR,

I_M is the integration of monomer peak determined by NMR.

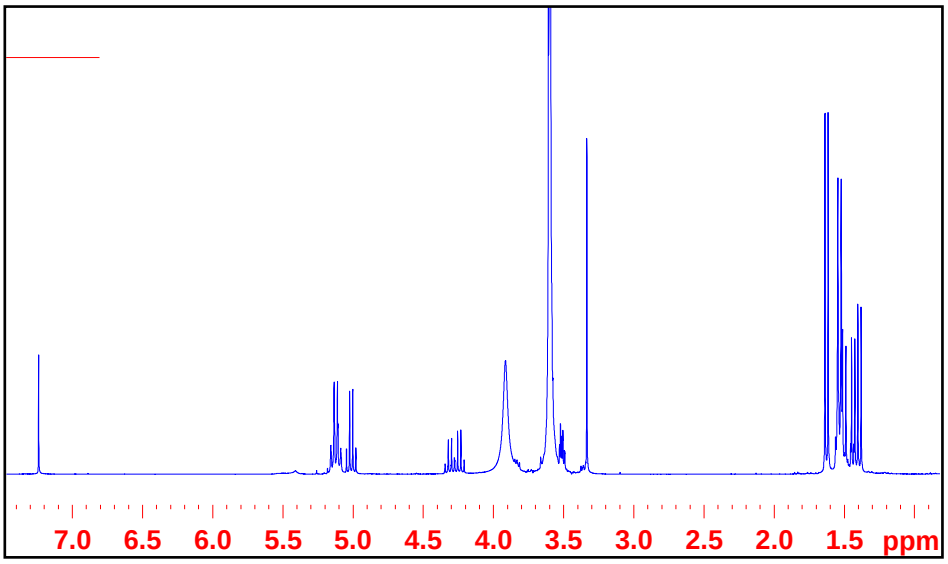

Figure 2: ^{1}H-NMR spectrum of polymer C- 4 hour

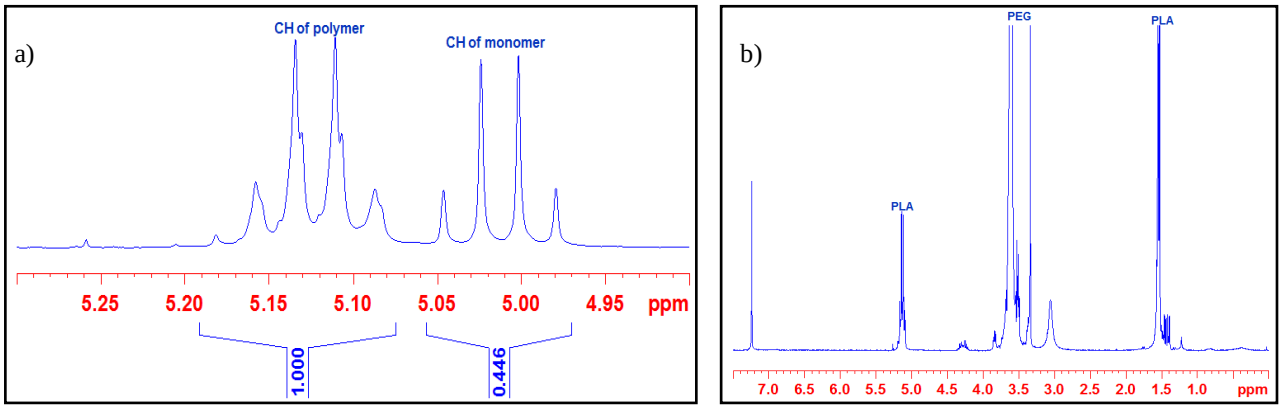

Figure 3: a) Integration of ^{1}H-NMR peaks of polymer C- 4 hours; b) ^{1}H-NMR spectrum of polymer C- 4 hours after precipitation

Second, the ^{1}H-NMR spectra are recorded for the solid polymers after precipitation and drying. The peaks corresponding to L-lactide monomers disappear as shown in Figure 3.3. Thus, the molar mass (Mn) and degree of polymerization (DP) can be calculated from the relative intensity of ^{1}H-NMR signals using (equation 2) and (equation 3) respectively.

$$M_n = M_{intiator} + (2 \times I_{CH}) \times M_{Lactideunit} \quad \text{(Equation 2)}$$

where

Mn is the molar mass of the polymer,

$M_{initiator}$ is the molar mass of PEG unit considered as the initiator = 44 g/mol,

I_{CH} is the integration of CH peaks in PLA polymer,

$M_{Lactide\ unit}$ is the molar mass of L-lactide unit = 72 g/mol.

$$DP = \frac{Mn}{M_0} \quad \text{(Equation 3)}$$

where

DP is the degree of polymerization of PLA,

Mn is the molar mass of PLA,

M_0 is the molar mass of L-Lactide unit.

Table 1 reports the molar mass and conversion percent calculated for each of the four synthesized copolymers.

Table 1: Conversion rates and molar masses of the four synthesized polymers determined by NMR

Copolymer	Polymerization time (hours)	m obtained (g)	Conversion percent	Mn by NMR (g.mol^{-1})
A	1 hour	2.168	38 %	2504
B	2 hours	2.107	48 %	2648
C	4 hours	2.755	73 %	3368
D	6 hours	1.937	100 %	2792

^{1}H-NMR confirms that as the polymerization time increases, the percent of unreactive L-lactide monomers left in the reaction medium decreases, and thus the conversion percent increases[6][10]. Therefore, the optimum polymerization time for this copolymer is 6 hours having a 100 % conversion rate. Additionally, the ^{1}H-NMR technique confirms the purification of the polymer after its precipitation in the diethyl ether. In fact, the comparison of the spectra before and after precipitation shows the disappearance of the L-lactide monomers from the reaction medium. The molecular weight of the resulting copolymer is also determined by ^{1}H-NMR and is equal to 3000 g.mol^{-1}. Therefore, by determining the degree of polymerization of each block, the synthesized diblock can be named: $mPEG_{45}$- PLA_{14}.

3.2 GPC

GPC results are obtained in order to determine the average molecular weight, its distribution, and the Polydispersity Index (PDI) for the polymers. Figure 4 shows the chromatogram obtained for Polymer D (synthesized in 6 hours). Mw and Mn can be deduced after the calibration of the GPC. Therefore, PDI is calculated using (equation 4):

$$PDI = \frac{M_w}{M_n} \qquad \text{(Equation 4)}$$

Where

PDI is the Polydispersity Index of the polymer,

Mn is the number-average molecular mass of the polymer,

Mw is the mass-average molecular mass of the polymer.

Table 2 reports all average molecular weights and the PDI calculated for each of the four synthesized copolymers.

Table 2: Average molecular weights and PDI of the four synthesized polymers determined by GPC

Copolymer	Polymerization time (hours)	Mn by GPC ($g.mol^{-1}$)	Mw by GPC ($g.mol^{-1}$)	PDI
A	1 hour	2601	2789	1.072
B	2 hours	2619	2807	1.072
C	4 hours	2592	2726	1.052
D	6 hours	2594	2789	1.076

The molecular weight data obtained from GPC are in good agreement with the results obtained from ^{1}H-NMR. These data indicate the feasibility of a well-controlled synthesis of the block copolymer with a good control of molar mass and low dispersity (PDI < 1.2).

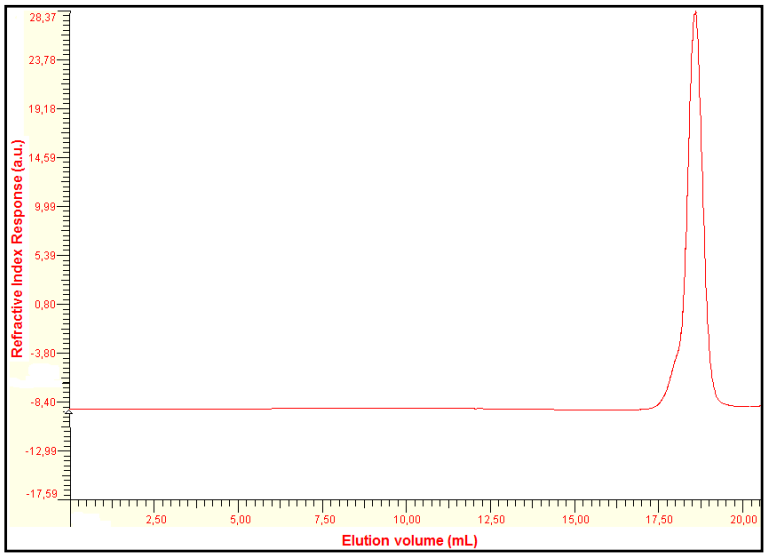

Figure 4: GPC chromatogram of polymer D - 6 hours

3.3 FT-IR

The FT-IR spectra for the PEG-PLA are obtained in order to verify the functional groups formed after the copolymerization. Figure 5 shows all the spectra obtained for the four copolymers synthesized each in a different duration. This figure shows that all the polymers have the same peaks at the same wavenumber but with different intensities.

On other hand, Figure 6 represents the FT-IR spectrum obtained for polymer D, synthesized in 6 hours. The band at 3500 cm^{-1} corresponds to the O-H group. The band at 2996 cm^{-1} is due to the C-H stretching vibration of -CH3 group. The peak at 1752 cm^{-1} is assigned to the stretching vibration of ester carbonyl group formed between the PEG block and PLA block [11]. Furthermore, the characteristic -C-O-C- stretching vibration from PEG block is detected at 1109 cm^{-1}.

FT-IR spectra are mainly useful in verifying the formation of an ester group between the PEG and PLA blocks. Hence, the three techniques (NMR, GPC, and FT-IR) provide a solid justification of the successful synthesis of the diblock copolymer.

3.4 DSC

DSC is used in order to detect the effect of molecular structure of the polymer and the time of polymerization on the thermal properties of the nanoparticles. DSC is also used to investigate any possible interaction between the drugs and the polymers. The melting temperature (Tm) is determined when the heat flow is endothermic. Figure 7 shows that all polymers have approximately the same Tm = 58.9 ^{o}C.

On other hand, TGA is used to investigate the thermal stability of the copolymers. The weight loss is measured in terms of temperature change. Figure 8 shows that the degradation of all copolymers starts approximately at 195 ^{o}C and completes at 305 ^{o}C.

The thermal properties of the synthesized copolymers, determined by DSC and TGA, confirm the formation of a block copolymer. First, the increase of the melting point of PEG (51.6 ^{o}C) by 7 ^{o}C confirms that PLA block is introduced to the polymer structure. Second, the temperature range at which the copolymer is degraded (195 – 305 ^{o}C) verifies the formation of PLA. In fact, pure PEG is usually degraded starting 400 ^{o}C [8][9]. Thus, the first weight loss step is attributed to the decomposition of PLA segment and the second step to the decomposition of PEG segment. Consequently, the formation of PEG-PLA diblock estimated from DSC and TGA results are in good agreement with those deduced from NMR and FTIR.

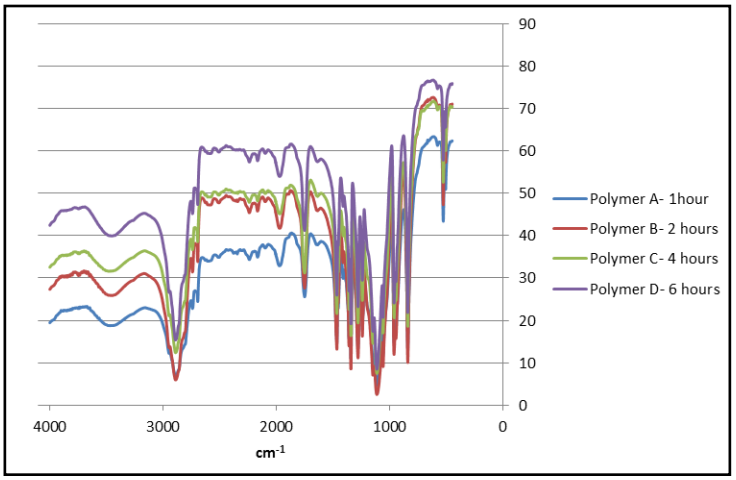

Figure 5: FT-IR spectra of the four copolymers

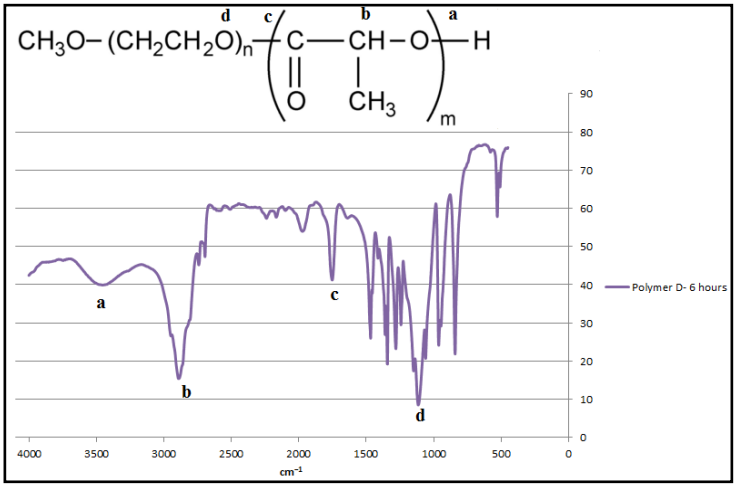

Figure 6: FT-IR spectrum of Polymer D - 6 hours

3.5 DLS

The DLS measurements are conducted in order to detect the diameter of the copolymer particles. Figure 9 shows that the size of the polymer D, synthesized in 6 hours, is between 100 and 130 nm. This range applies for all the polymers synthesized in our experiments.

3.6 Fluorescence

The formation of micelles is evaluated by measuring the critical micelle concentration (CMC) using fluorescence spectroscopy. The CMC is determined by plotting the intensity ratio I_{395}/I_{375} against the logarithm of the polymer concentration. A negligible change in intensity ratio is found at low concentrations. At a certain polymer concentration, the intensity ratio increases dramatically. The CMC value is found as the intersection of regression lines calculated from the two linear portions of the plot.

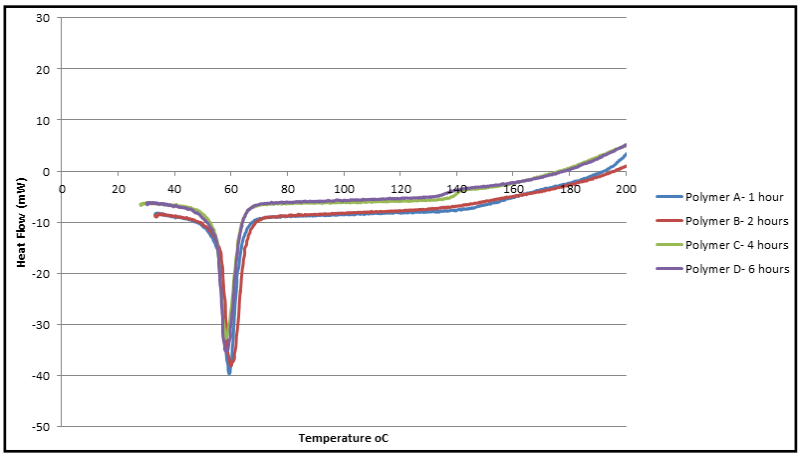

Figure 7: DSC measurements

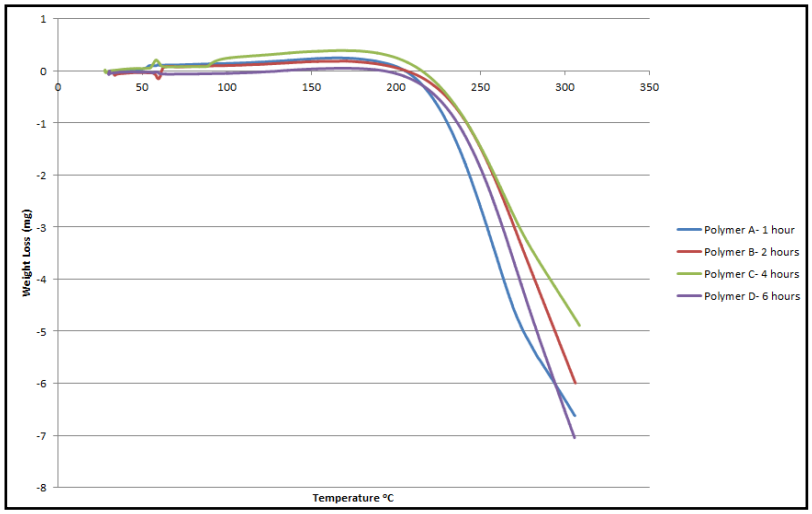

Figure 8: TGA measurements

Figure 10 shows the CMC value determined for the polymer C, synthesized in 4 hours.

The critical micelle concentration (CMC) determined by fluorescence spectroscopy is dependent on different factors such as the composition and the hydrophilic to hydrophobic ratio. The drastic change in intensity ratio corresponds indeed to the incorporation of pyrene into the hydrophobic core of the micelles. Starting this concentration, the copolymer forms micelles in aqueous media allowing the hydrophobic drug to be encapsulated inside the hydrophobic core. However, a lower CMC value represents relatively higher stability[12]. On contrary, the value obtained in this study (0.285 mg/mL) is higher than expected but confirms the formation of a diblock with a more important hydrophilic character since it has a larger PEG segment than PLA. Thus, in further studies, the PLA segment can be enlarged by changing the reaction conditions in order to have a better CMC and consequently a better stability of the copolymer.

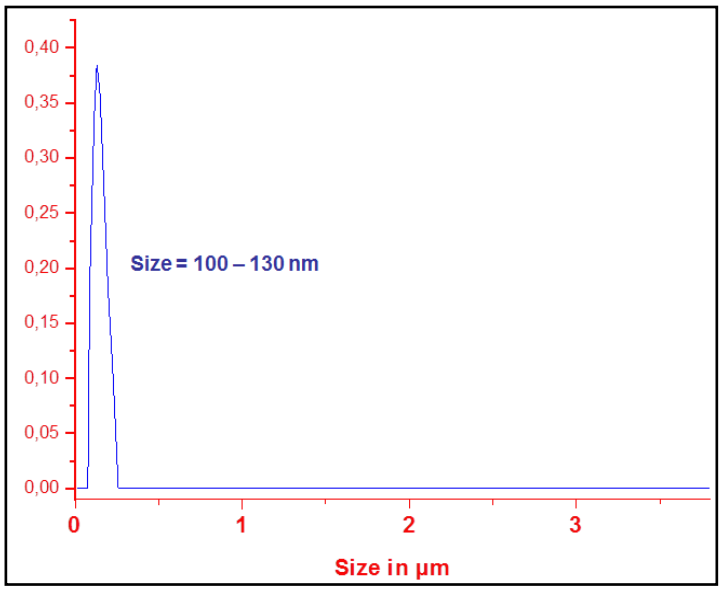

Figure 9: DLS data of particle size distribution of polymer D- 6 hours

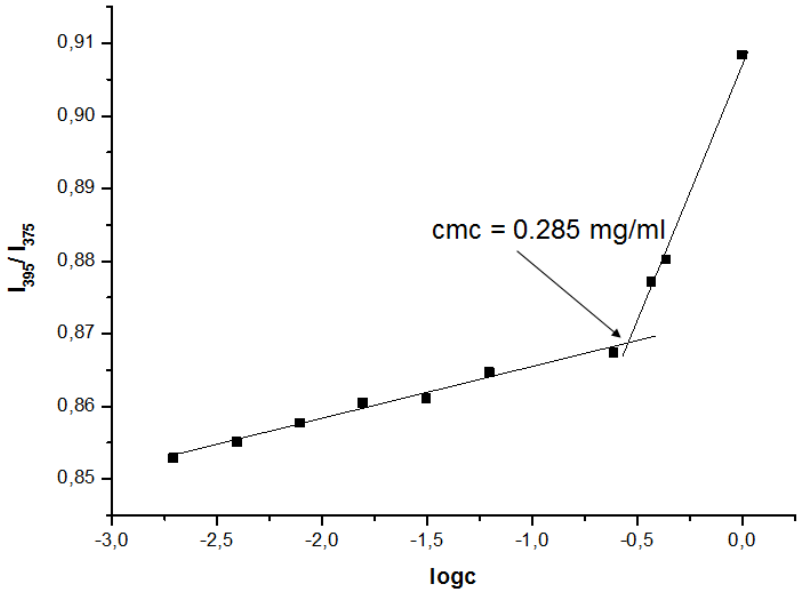

Figure 10: Plot of the intensity ratios from pyrene emission spectra as a function of concentration for copolymer C in aqueous medium

3.7 UV

First, UV spectroscopy is used in order to determine the drug loading capacity of the polymers. The standard calibration curve obtained by plotting the absorbance versus the concentrations of Ibuprofen is represented in Figure 11.

The slope for the Ibuprofen calibration curve is 2.1605. When Ibuprofen is mixed with the polymer solution, the measured absorbance is A = 3.875. By using (equation 5), the concentration of encapsulated Ibuprofen can be calculated.

$$C = \frac{A}{slope} \qquad \text{(Equation 5)}$$

Where

C is the encapsulated Ibuprofen concentration in the micelles,

A is the absorbance,

slope is the slope obtained from the calibration curve.

Thus, the concentration of Ibuprofen encapsulated in the polymer micelles is 1.7935 mg/mL. Knowing that the intrinsic solubility of Ibuprofen in water is determined from the calibration curve also (0.0635 mg/mL), we can deduce that the polymer solution is able to dissolve it 28 times using (equation 6) [9]:

$$ratio = \frac{S}{S_0} \qquad \text{(Equation 6)}$$

where

S is the solubility of the drug in the micelles,

S_0 is the intrinsic solubility of the drug in water only.

Second, UV is used in order to determine the value of the Encapsulation Efficiency of the polymer for Ibuprofen. The concentration of encapsulated Ibuprofen is determined using (equation 5) by using the slope corresponding to the calibration curve. Then, (equation 7) is used in order to calculate the Encapsulation Efficiency [9]:

$$\%\,EE = \frac{[drug]\,NPs}{[drug]intial} \qquad \text{(Equation 7)}$$

where

%EE is the Encapsulation Efficiency,

$[drug]_{NPs}$ is the Ibuprofen concentration entrapped in the nanoparticles,

$[drug]_{initial}$ is the initial concentration of drug added (2.5 mg/mL).

Thus, %EE of the synthesized copolymers for Ibuprofen is 71.74%.

The UV measurements verify that the synthesized copolymers are able to encapsulate the hydrophobic drug (Ibuprofen) and thus enhance their solubility in aqueous medium 28 times. On other hand, the UV technique validates the results of previous methods that state that PEG segment is larger than PLA segment. In fact, the %EE (71.74%) is relatively low, but can be the result of the disproportion between the hydrophobic and hydrophilic segments. Moreover, this relatively low value is attributed to the low amount of polymer in the mixture as discussed by Y. Dong et al. [13]. Thus, in further studies the effect of polymer concentration on the %EE can be investigated.

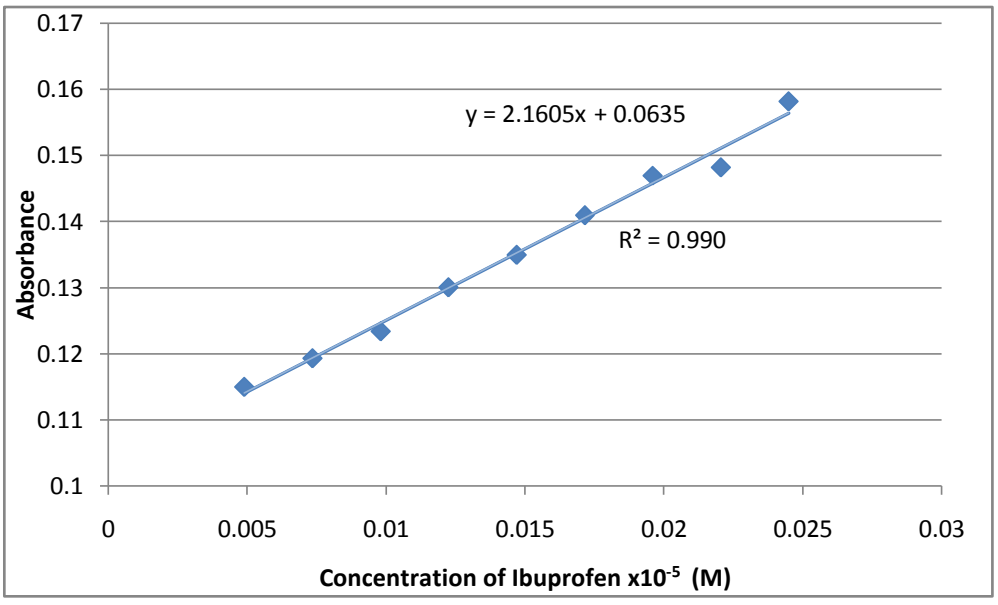

Figure 11: The standard calibration curve for Ibuprofen

4. Conclusion

As a conclusion, this study is a starting point for further research in order to enhance the properties of the synthesized block copolymer. First, the reaction conditions may be altered in order to have an extended hydrophobic segment. Thus, the CMC value would be lower and the polymer would have a better stability. On other hand, a

better hydrophobic character would increase the %EE of the copolymer. Consequently, the encapsulation capability of the copolymer for more hydrophobic drugs, as anticancer drugs, can be studied. Second, the amphiphilic character of the synthesized block copolymer may be an interesting property for further applications such as multiple-drug delivery and imaging agents. Third, the drug release characteristics can be studied in different media (human serum, different pH, different temperatures…) in order to have the optimal conditions for the drug delivery using this novel copolymer.

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