Synthesis of (azelaic-co-dodecanedioic) polyanhydride by microwave technique

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Abstract. A polyanhydride was synthesized through microwave radiation using azelaic acid and dodecanedioic dicarboxylic acid at concentrations of 75:25, 50:50, and 25:75% w/w with acetic anhydride as crosslinking agent. Polymerization was carried out during 3 and 5 minutes. The copolymer with the highest molecular weight was selected using the intrinsic viscometry technique and by Huggin/Kraemer and Solomon/Ciuta methods. Based on these measurements, the 50:50 copolymer was selected with a polymerization time of 3 minutes in the microwave. This sample displayed the highest intrinsic viscosity (41.82 cm³/g), demonstrating the relevance of the microwave technique for the synthesis of biopolymers.

1. Introduction
Polyanhydrides are biodegradable polymers with suitable properties for biomedical applications. The products of decomposition are non-toxic diacid monomers that can be metabolized and eliminated by the body [1]. These biopolymers have been studied for the delivery of chemotherapeutic drugs including antibiotics and anesthetics [2,3]. Policondensation is the method of synthesis of this type of biopolymer. This process is carried out under rigorous conditions to obtain high molecular weight polymer with very long reaction times [4]. Microwave radiation offers significant benefits when compared to conventional heating since this technology allows a solvent-free and a fast polymerization by reaching high reaction temperatures [5,6].

The present work evaluates the synthesis of polyanhydrides from two dicarboxylic acids: azelaic acid and dodecanedioic acid, using the microwave technique and acetic anhydride as a crosslinking agent. The intrinsic viscosity method was used to determine the molecular mass of the synthesized copolymers as a function of the reaction time (3 and 5 minutes) and at different monomer concentrations (75:25, 50:50 and 25:75% w/w). Samples of the copolymers (0.1 g/mL) were prepared and suspended in a chloroform/ethanol solution (60/40% v/v). The Huggins and Kraemer equations were used to calculate intrinsic viscosity by lineal extrapolation, as well as the Solomon-Ciuta equation by single-point.

2. Materials and methods

2.1 Synthesis of the (azelaic-co-dodecanedioic) polyanhydride
All chemical reagents were used as received. Azelaic acid 90% and dodecanedioic acid 99% were used as reacting monomers. Microwave irradiation was performed using 1120W microwave. Pre-polymerization of both monomers was performed in covered boron-silicate vials of 10mL capacity by microwave irradiation (5 minutes) using a 1:3 relation of solid dicarboxylic acid to acetic anhydride. The copolymerization step was subsequently performed using concentrations of 75:25, 50:50 and
25:75% w/w of azelaic acid:dodecanedioic acid, respectively. This stage was performed by heating the pre-polymers mixture in the microwave and varying reaction time between 3 and 5 minutes.

2.2 Determination of the intrinsic viscosity of the synthesized copolymers

A chloroform/ethanol (60/40% v/v) solution was used as solvent for these measurements. At a first stage, 1g of the copolymer was dissolved into 10mL of solvent. Dilutions were then prepared from this solution to obtain samples with concentrations of 0.005, 0.0075 and 0.01g/mL. Intrinsic viscosity measurements were carried out using a capillary viscometer, which was vertically submerged in a thermal bath at 25°C [7]. A sample volume of 7mL was taken, and a standby time of 10 minutes was applied as factor for achieving thermic equilibrium. In a typical procedure, the sample was suctioned through the capillary until that the polymer solution reached the upper mark. Then, a measurement of the time was registered when the fluid reached the bottom mark of the capillary. Afterwards, the viscometer was washed with ketone and dried. This procedure was repeated for each copolymer solution, as well as for the chloroform/ethanol solution. All measurements were conducted in triplicate.

3. Results

Intrinsic viscosity of the copolymers was determined as a function of their relative viscosity, according to Huggins and Kraemer equations (Equation 1) [8],

$$
\frac{\eta_{sp}}{c} = [\eta] + k_H [\eta]^2 c
$$

$$
\ln \frac{\eta_r}{c} = [\eta] - k_K [\eta]^2 c
$$

(1)

where $\eta_{sp}$ is the specific viscosity, $\eta_r$ is the relative viscosity and $c$ is the concentration in g/mL, $k_H$ and $k_K$ are dimensionless constants, called as Huggins constant and Kramer constant, respectively.

Table 1 shows the results that were obtained with the capillary viscometer. It can be observed that the sample of the 50:50 copolymer with 3 minutes of microwave irradiation presented the highest values of relative viscosity, which were between 1.2 and 1.25 for the studied range of concentrations [9].

| Relative viscosity | Intrinsic viscosity |
|--------------------|---------------------|
| 0.005g/mL | 0.0075g/mL | 0.010g/mL | Solomon-Ciuta | Huggins-Kraemer | Standard deviation |
| 75:25 | 0.99 | 1.12 | 1.16 | 10.65 | - | - |
| 50:50 | 1.20 | 1.21 | 1.25 | 29.44 | 41.82 | 7.30 |
| 25:75 | 1.05 | 1.08 | 1.11 | 11.39 | 12.48 | 0.41 |

Table 1. Relative and intrinsic viscosities of the copolymer samples (azelaic-co-dodecanedioic) prepared in the microwave.

Polymerization time of 5 min in the microwave

| Relative viscosity | Intrinsic viscosity |
|--------------------|---------------------|
| 0.005g/mL | 0.0075g/mL | 0.010g/mL | Solomon-Ciuta | Huggins-Kraemer | Standard deviation |
| 75:25 | 1.01 | 1.049 | 1.08 | 6.04 | 4.07 | 2.80 |
| 50:50 | 1.02 | 1.034 | 1.04 | 4.69 | 4.98 | 0.54 |
| 25:75 | 1.02 | 1.028 | 1.05 | 4.48 | 2.83 | 0.90 |

Determination of intrinsic viscosity was achieved by plotting the values of $\eta_{sp}/c$ and $\ln \eta_r/c$ versus concentration, according to Huggins and Kraemer equations. Figure 1 shows these plots. This analysis did not display an adequate lineal adjustment for the 75:25% w/w relation of azelaic acid:dodecanedioic acid that was prepared under 3 minutes of microwave irradiation presented the highest values of relative viscosity, which were between 1.2 and 1.25 for the studied range of concentrations [9].
used when describing this behaviour; the closer the values of SP for both solvent and solute, the solution is more suitable [10]. This implies that for relative viscosities lower than 1.0, there is no lineal correlation; it is only for values higher than 1.2 that a suitable accuracy and linearity are achieved with use the Huggins and Kramer equations through extrapolation of data for deducting intrinsic viscosity [11]. The copolymer synthesized with a ratio of 50:50% w/w azelaic acid:dodecanedioic acid at 3 minutes in the microwave (Figure 1(b)) presented higher intrinsic viscosity, since the intercepts of the Huggins and Kraemer straight lines exhibited a higher value when it is compared to the ones achieved in the remaining samples. This leads to the deduction that such values of monomer concentrations and polymerization time allowed the formation of a polyanhydride with a higher molecular mass.

The Solomon-Ciuta (SC) equation (Equation 2) was used to validate the data of intrinsic viscosities that were graphically obtained from the Huggins and Kramer equations [12]. Table 1 shows a summary of the results in this comparison.

\[
[\eta] = \left[ \frac{2(\eta_{sp} - \ln \eta_p)}{c} \right]^{\frac{1}{2}}
\]  

(2)

![Figure 1](image-url)  

Figure 1. Determination of intrinsic viscosity by Huggins (♦) and Kraemer (■) methodology for the (azelaic-co-dodecanedioic) copolymers synthesized by microwave irradiation. Polymerization time of 3 minutes for the (a) 75:25, (b) 50:50, and (c) 25:75 proportions. Polymerization time of 5 minutes for the (d) 75:25, (e) 50:50, and (f) 25:75 proportions.

A JEOL JSM-6490LV scanning electron microscope (SEM) coupled to an energy dispersive spectroscopy (EDS) was used to get images of the synthesized (azelaic-co-dodecanedioic)
polyanhydride that was prepared with a concentration of 50:50% w/w after 3 minutes of microwave irradiation. Figure 3 shows this photograph. There, the formation of a non-regular, porous morphology with microchannels can be observed. Additionally, EDS allowed the determination of an elemental composition of about 72% weight of carbon and 28% weight of oxygen for this copolymer.

Figure 3. SEM image of the (azelaic-co-dodecanedioic) polyanhydride that was prepared with a concentration of 50:50% w/w after 3 minutes of microwave radiation.

4. Conclusions
Microwave radiation proved to be a suitable method for the synthesis of biomaterials. It allows a simple, fast and economic procedure for the production of polyanhydrides from dicarboxylic acids. Capillary viscometry represents a low cost as useful technique for the determination of intrinsic viscosities and the deduction of molecular masses for polymeric materials. The highest intrinsic viscosity (41.82 cm³/g) was achieved with a copolymer that presented a 50:50 proportion of monomers and a polymerization time of 3 minutes. This reflects the polymer-solvent affinity and evidences that the resulting concentration of the copolymer depends on the relative reactivity of each monomer, as well as on their proportions in the reaction mixture. Thus, materials with combined properties can be produced by copolymerization, instead of using separate homopolymers.

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