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Synthesis and Characterizations of Poly (Lactic Acid) by Ring-Opening Polymerization for Biomedical Applications

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The development of biomaterials for application in medicine is one of the great challenges of research in material science. The poly (a-hydroxy acids) are the principal biodegradable and bioresorbable polymers used in tissue engineering. Among the biomaterials (biopolymers) used in the medical field, the poly (lactic acid) (PLA) has received significant attention. It is produced from lactic acid, a naturally occurring organic acid that can be produced by fermentation. The attractive price and commercial availability of lactic acid are important reasons for PLA development. PLA and its copolymers are being used in biomedical area in the form of implants or devices due to its excellent biocompatibility and biodegradability. In this study, lactide was synthesized and Poly lactic acid produced. The objective of this study was to investigate the PLA production in laboratory scale. Characterization by FTIR of the lactide and PLA production was made to confirm the polymerization and a possible use as biomaterial.

1. Introduction

Tissue engineering is one of the most important areas of material science, in which multidisciplinary scientists are contributing to human health care, combining knowledge in medicine, biology and engineering integrated technology of cells, engineering materials, and suitable biochemical factors to create artificial organs and tissues, or to regenerate damaged tissues. The advent of tissue engineering has been motivated by the challenge of producing tissue substitutes that can restore the structural features and physiological functions of natural tissues in vivo (Vanolen et al., 2010; Freed et al., 2009).
The interest in using the bioabsorbable polymer is mainly because they are degraded by hydrolysis; thereby preventing the patient undergoes a second surgery to remove the device, reducing cost and trauma. Synthetic polymers can stimulate isolated cells to regenerate tissues. Currently they are being extensively studied as scaffolds for cell transplantation in vitro and in vivo (Hu et al., 2012).
Biopolymers are used as replacements for damaged tissue and / or stimulate its regeneration. Among the various bioreabsorbable polymers are the poly (α-hydroxy acids). These polymers are considered bioreabsorbable due to its good biocompatibility and its decomposition products are eliminated from the body via metabolic pathways.
Poly (lactic acid) (PLA) is highly versatile, biodegradable, aliphatic polyester derived from 100% renewable resources (Drumright et al., 2000). It has extensive applications in biomedical fields, including suture, bone fixation material, drug delivery microsphere, and tissue engineering (Nampoothiri et al., 2010). Because of these properties the PLA has been widely studied for use in medical applications. PLA is the prime example of a ‘‘biomaterial’’ with emerging multidimensional applications, points to a promising future for their applications in medical science and particularly in tissue engineering and other human health care fields (Savioli lopes et a., 2012).
In this study the lactide was synthesized and PLA produced. It has been shown that the ring-opening polymerization is a viable process for the PLA production in these studied conditions.

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1.1 Poly-lactic acid

Polylactic acid (PLA) is a highly versatile, biodegradable, aliphatic polyester derived from 100% renewable resources (Drumright et al., 2000). It has extensive applications in biomedical fields, including suture, bone fixation material, drug delivery microsphere, and tissue engineering (Nampoothiri et al., 2010). Because of these properties the PLA has been widely studied for use in medical applications.

The chemistry of PLA involves the processing and polymerization of lactic acid monomer. Since, lactic acid is a chiral molecule, PLA has stereoisomers, such as poly(L-lactide) (PLLA), poly(D-lactide) (PDLA), and poly(DL-lactide) (PDLLA). Isotactic and optically active PLLA and PDLA are crystalline, whereas relatively atactic and optically inactive PDLLA is amorphous (Bouapao et a, 2009; Griffith, 2010). The L-isomer is a biological metabolite and constitutes the main fraction of PLA derived from renewable sources since the majority of lactic acid from biological sources exists in this form (α, β, and γ) (Lim et a., 2008). PLLA has gained great attention because of its excellent biocompatibility and mechanical properties. However, its long degradation times coupled with the high crystallinity of its fragments can cause inflammatory reactions in the body. In order to overcome this, PLLA can be used as a material combination of L-lactic and D, L-lactic acid monomers, being the latter rapidly degraded without formation of crystalline fragments during this process (Fukushima and Kimura, 2008).

1.2 Poly-lactic acid production

PLA can be obtained using different routes (Figure 1). In general, there are three methods which can be used to produce high molecular mass PLA of about 100 000 Daltons: (a) direct condensation polymerization; (b) azeotropic dehydrative condensation and (c) polymerization through lactide formation, the ring-opening polymerization (Aura et al., 2004). Currently, direct condensation and ring-opening polymerization are the most used production techniques.

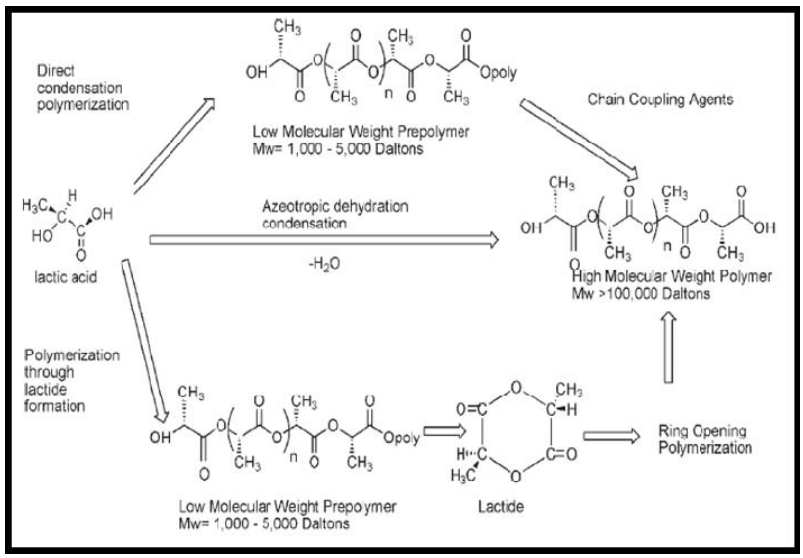

Figure 1: PLA synthesis methods (Aura et al., 2004).

Ring-opening polymerization (ROP) of the lactide needs catalyst but results in PLA with controlled molecular weight (Gupta et al., 2007). Depending on monomer used and controlling reactions conditions, it is possible to control the ratio and sequence of D- and L-lactic acid units in the final polymer.

In this study, the ring-opening polymerization was select. The lactide was synthesized and PLA produced.

1.3 Poly-lactic acid application

Poly lactic acid (PLA) is biodegradable, and it has extensive applications in biomedical fields, including suture, bone fixation material, drug delivery microsphere, and tissue engineering (Nampoothiri et al., 2010). PLA has been utilized as ecological material as well as surgical implant material and drug delivery systems, and also as porous scaffolds for the growth of neo-tissue (Nampoothiri et al., 2010; Yamane and Sasai 2003). PLA has been approved by the Federal Drug Administration (FDA, USA) for use as a suture material because of features that offer crucial advantages (Benicewicz et a., 1991; Davis et al., 1996). The

medical applications of this polymer arise from its biocompatibility: the degradation product, lactic acid, is metabolically innocuous. The fibers may be fabricated into various forms and may be used for implants and other surgical applications such as sutures. Tissue engineering is the most recent domain where poly (lactic acid) is being used and is found to be one of the most favorable matrix materials (Nampoothiri et al., 2010).

The use of poly-lactic acid in these applications is not based solely on its biodegradability nor because it is made from renewable resources. PLA is being used because it works very well and provides excellent properties at a low price4. It is difficult to obtain a material with all the properties required for an application, but the diversification of PLA applications is such that a single polymer may prove useful in many applications by simple modifications of its physical-chemical structure, resultant of chirality of lactic acid molecule with two asymmetric centers existing in four different forms (Cheng et al., 2009).

2. Materials and methods

The polymerization process of lactic acid is initiated by dehydration of the monomer, which generates a prepolymer chains consisting of oligomers and low molecular weight PLA. This process, starting from lactic acid involves three distinct stages: polycondensation, obtaining lactide and ring-opening polymerization.

Lactic acid (LA reagent grade) with 85 wt% of purity was used in the polymerization process, and Stannous octoate ($Sn(Oct)^2$) was used as catalyst.

In the first step, lactic acid was dehydrated to produce oligomers at temperatures of PLA 160 °C for 2 hours using the reaction system shown in Figure 2. The removal of product water from the condensation reaction was carried out at atmospheric pressure and also employing the use of inert atmosphere of N2.

In the second step, the system was heated to a temperature of 220 °C and a reduced pressure of 200 mmHg, so that the lactide produced (second step) could be recovered by distillation and collected in a condensate flask. The condenser was maintained at approximately 90 °C in order to prevent solidification of the product, for 4 hours of reaction. The lactide was then obtained by distillation, and the solid phase recovered in condensing flask. The crude product was washed with cold water, separated by filtration and then dried overnight at a temperature of 40 °C.

In the third and final step of the reaction, the lactide produced was mixed with the catalyst (1wt%) at a temperature of 140 °C for 2 hours and the PLA produced.

The functional groups of PLA and LA were analyzed by Fourier Transform Infrared Spectroscopy (FTIR).

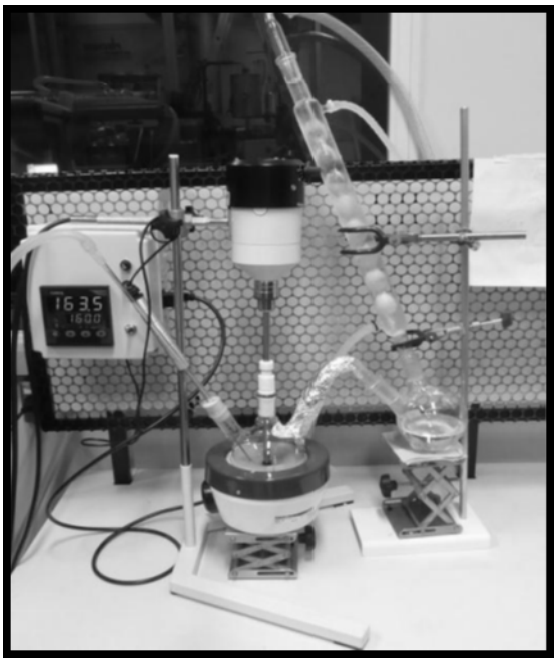

Figure 2: Polymerization experimental system.

3. Results and discussion

PLA polymerization by Ring-opening polymerization (ROP) from lactic acid was carried out in three steps. There is no standard method to synthesize PLA. Therefore, several experiments were made with various conditions in order to determine the appropriate reaction temperature for each step.

In the first part of the synthesis occurs the pre-polymer formation, in which lactic acid is heated and, vacuum is used to remove water generated by the union of the monomer molecules. To avoid the reaction of the acid at this stage, was made a rigorous temperature control with gradual increase until it reached 160 °C. A large amount of fumes were collected by distillation, the condensate flask.

Formation of PLA oligomers was performed initially at 200 °C and atmospheric pressure according the procedure described in the literature (Yoo and Kim, 2006). However, the results in step synthesis of lactide were not expected, therefore, modified the conditions. It was necessary to reduce the vacuum in the reaction, since it was realized that few vapors were being produced.

The experimental system initially assembled and used in the previous step was also used in obtaining lactide, however, it was necessary to change the condenser. In the previous step was utilized condenser bubbles, which showed effectiveness in the reaction. Already at this stage, the heat transfer between the walls in this type of capacitor is not sufficient and due to the vacuum used, the product gas just being dragged, promoting the crystallization of the parts vacuum line. If the process was done with less vacuum removal of lactide from the reaction mixture was not effective.

Realizing the difficulty at this time of the reaction, it was decided to change the reaction system. The bubble condenser was replaced by a condenser coil, it was possible to recover the distilled product in the flask.

In the third and last step, the lactide produced was mixed with stannous octoate catalyst (1%wt) in the reaction flask at a temperature of 140 °C for 2 hours. Figure 3 shows the polymer obtained at the end of the reaction.

Figure 3: PLA produced.

During tests we observed that when the reaction was carried out without nitrogen, the water removal was slower, i.e, the nitrogen flow helped in removing the water vapor formed in reactor.

FTIR analyses were made to determine the functional groups of the products obtained in order to understand more deeply what happens in the polymerization of Poly (lactic acid). A qualitative analysis of absorption bands with reaction time shows a decrease in the intensity of some bands and, the formation of new ones, indicating the end groups which decrease and those formed due to the polymerization reaction progress.

Analysis of FTIR spectrum of the sample from step obtaining lactide allows us to confirm that there was formation of the product, verifying the characteristic bands of the material. Figure 4 shows the spectrum obtained compared to lactide of lactic acid. It can be seen the band around 3500 cm-1, which decreases the ring lactic acid, as well as the characteristic bands of the ring indicating that there was formation of lactide, a dime of structure cyclic.

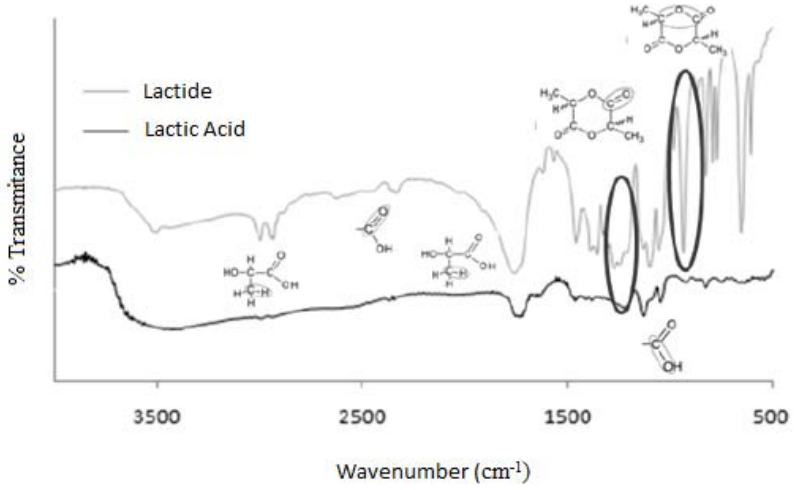

Figure 4: FTIR of lactide and lactic acid.

Figure 5 shows the FTIR spectrums of the monomer and the poly (lactic acid) which was obtained from 2 of reaction. The PLA spectrum shows the bands at 2,754.94 and 2,766.51 cm-1 from symmetric and asymmetric valence vibrations of C-H from CH3, respectively. It is possible to observe a band shift related to the C=O stretch in the monomer in 1,727.06 to 1,757.92 cm-1 in the polymer. These bands that show shifts of monomer to polymer also show a difference in the peak intensity which suggests the arrangement of molecules in the polymer chain. Bands corresponding to bending vibrations of CH3 (asymmetric and symmetric) were found in 1,433.94 and 1,511,08 cm-1 in the polymer spectrum as greater intensity peaks compared with those from monomer found in 1,408.87 and 1,476.37 cm-1. C-O-C asymmetrical and symmetrical valence vibrations were found at 1,250.73 and 1,200.59 cm-1 respectively; at 1,333.68 cm-1 is detected the C-O-C stretching vibration. The band around 3200 cm-1 is related to the stretching of OH group and this decreases from the monomer to the polymer due to reaction polyesterification that consumes the OH groups when they react with the acid groups to form the ester bond. These statements are similar those described in the literature (Nikolic et a., 2010).

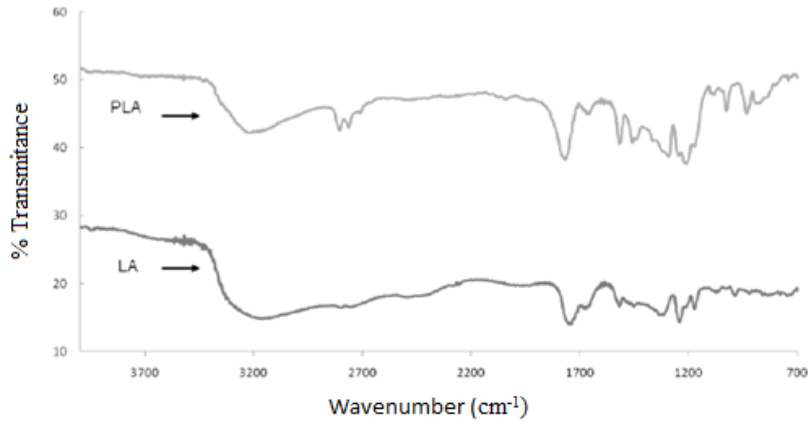

Figure 5: FTIR of PLA and lactic acid.

4. Conclusions

The experimental system set up to carry out the synthesis had to be suited to the needs of the reaction. In step for obtaining lactide, condenser bubbles had to be replaced with a spiral, ensuring better heat exchange between the walls. The use of nitrogen provided an inert atmosphere favorable to the occurrence of the polymerization reaction.

The analysis of FTIR spectrum of the sample of lactide and PLA were confirmed checking the characteristic bands of the material. The spectrum compared lactic acid and this material indicated that was formation of lactide, a cyclic dimer structure.

This study has proved that the ring-opening polymerization is a viable process for the production of PLA from lactic acid in these studied conditions. This material has been widely used in the medical area. The study and understanding of this synthesis makes possible its use as a biomaterial.

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