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New Poly(Hydroxylauric-co-Lactic Acid) Liquid Polymer for Dissolving Lipophilic Drugs

Florentino C. Sumera[1]*, Shienna Marie A. Pontillas[2], Josanelle Angela V. Bilo[2] and John Marty Mateo[2,3]

[1] *Institute of Chemistry, University of the Philippines, Diliman, Quezon City 1101*
[2] *Natural Sciences Research Institute, University of the Philippines, Diliman, Quezon City 1101*
[3] *Institute of Plant Breeding, University of the Philippines, Los Baños, Laguna 4031*

ABSTRACT

A liquid, biocompatible polyester based polymer, which could facilitate injectable formulations by simple mixing with the active substance (drug) is much needed by the pharmaceutical companies. A favourite candidate is polylactic acid (PLA) which is biocompatible and biodegradable. However PLA is solid with high crystallinity. Thus, in this research, hydroxylauric acid (HOLA) was copolymerized with lactic acid (LA) in different ratios by polycondensation technique at 180 °C, without a metal catalyst and avoiding the formation of interfering lactides, to provide a liquid polyester. The copolymers molecular weights were determined by Gel Permeation Chromatography (GPC) and their physical states indicated as solid or liquid were noted. The structures as polyesters were confirmed by FT-IR and ^{1}H NMR spectroscopy. Poly(HOLA:LA) products from reactant ratios 0:100 is solid, while ratios of 20:80, 40:60 are mixed (paste) and 60:40, 80:20 and 100:0 are liquids. Thus, the liquid polyesters from the polycondensation of HOLA and LA without catalyst were picked as potential candidates for dissolving hydrophobic drugs that could be used as injectables in controlled drug delivery experiments.

Keywords: *poly(hydroxylauric acid-co-lactic acid); liquid polyester; lactic acid; hydroxy-lauric acid; polycondensation; injectables*

INTRODUCTION

Because of the interesting material properties of poly(lactic acid) PLA and its copolymers, such as biodegradability and as an example of sustainable materials being obtained from natural resources, extensive reports on it and its copolymers can be found in literature. PLA with its degradation product natural lactic acid is thus a first choice material for many applications in the medical field, e.g. in long lasting pharmaceutical implants (Wang SG *et al.*, 2005), degradable screws and sutures in reconstructive surgery (Middleton JC and Tipton AJ, 2000; Ikada Y and Tsuji H, 2000), and drug loaded microparticles (Ikada Y and Tsuji H, 2000) because of its good biocompatibility. A major problem, however, that limits the use of PLA is that it prevents the formulation of sensitive active substances into the polymer matrix due to its solid aggregate state and thus, heat or organic solvents are needed. PLA injectable modifications are not possible without formulating the materials as micro- or nanoparticles or adding further excipients (Trimaille *et al.*, 2005; Trimaille *et al.*, 2007). One solution to this is copolymerization. Copolymerization can actually be done by ring-opening polymerization (ROP). This method is actually used to produce biomedical grade PLA with controlled molecular weight and narrow polydispersities (Trimaille *et al.*, 2004). However, ROP needs dilactides to be synthesized first before

*Author to whom correspondence should be addressed; email: florentino.sumera@gmail.com

the final PLA polymerization. Furthermore, the degradation characteristics (Hyon *et al.*, 1998), release profile (Bitner *et al.*, 1998) or even decrease stability of the incorporated drug during formulation or storage (Rothen-Weinhold *et al.*, 2008) of the final polymer might be influenced by the residual dilactides present even after extensive purification. Also, in ROP, tin(II) 2-ethylhexanoate is generally used as catalyst but contaminates the final product up to 20–50 ppm (Stjerndal *et al.*, 2008). A reduction or entire avoidance of this compound is desired since tin catalyst were reported to show toxicological problems (Kricheldorf *et al.*, 2005). A better way of polymerization would be to avoid the synthesis of the intermediate lactide and the use of tin catalyst. A suggested acceptable catalyst in a one-step polycondensation is sulphuric acid (H_2SO_4). While an often mentioned disadvantage of polycondensation is its limitation to lower molecular weight products with higher polydispersities in comparison with ROP, this is not a disadvantage for the intended injectables. Nevertheless, PLA was synthesized in a one-step polycondensation with molecular weights up to 33,000 g/mol by Hiltunen *et al.* (1997). Also significantly higher molecular weight polyesters by efficient melt polycondensation and purification method were done by Asmus *et al.* (2011).

A liquid, biocompatible polyester-based polymer, which could be simply mixed with an active substance under mild conditions and thus facilitate injectable formulations is much needed by pharmaceutical companies. More than this, there are available lipophilic modern drugs (9 out of 10 new chemical entities are poorly water soluble) that can be dissolved into this new polymer and could be considered as still unmet need in the drug industry.

The objective therefore of this research is to 1) synthesize copolymers of hydroxylauric acid (HOLA) and lactic acid (LA) in different constitution ratios mainly to obtain liquid polyesters, poly (hydroxylauric-co-lactic acid) using no catalyst (to avoid metal contamination) in the (HOLA-LA) reactant ratios of 20:80, 40:60, 60:40, and 80:20 by polycondensation reaction 2) determine their products molecular weights by GPC, and physical states as liquid or solid after polymerization and 3) characterize their products by FT-IR and ^{1}H NMR.

Poly(hydroxylauric acid-co-lactic acid) is a novel polymer which combines hydrophobic long chain aliphatic methylene units and hydrophilic lactic acid units. Poly(HOLA:LA)'s longer aliphatic methylene chain can act as internal plasticizer, in comparison with homopolymer polylactic acid and hereby lead to a viscous liquid material. Moreover, the hydroxyl lauric acid comes from lauric acid, the major fatty acid of coconut oil, and is hydrophobic while lactic acid can be obtained from natural sources (Maharana *et al.*, 2009; Soderagard and Solt, 2002; Drumright *et al.*, 2000). Combination of the properties into a copolymer constitutes a potential biodegradability and biocompatibility property necessary for a lipophilic liquid polymer that can dissolve drugs for injectable formulations.

EXPERIMENTAL

Materials. Trifluoroacetic acid (TFA) was purchased from Merck. Hydrogen peroxide solution (≥30%) was obtained from Sigma-Aldrich, while Lactic acid with 85% purity was received from UNIVAR and was purified by distillation. Lauric acid came from TCI Chemicals and used as received without further purification. AR grade diethyl ether and n-hexane solvents were both purchased from RCl Labscan. All the other reagents used for this study were AR grade.

Methodology. *Synthesis of Hydroxylauric Acid (HOLA).* Hydroxylation of lauric acid was done using H_2O_2/TFA method as reported by Deno *et al.* (1977). To 75 mL of concentrated trifluoroacetic acid (TFA), 8.58 mL H_2O_2 (30% w/v by permanganate titration) was added and the solution stirred at room temperature for 5 minutes. Lauric acid (7.305 g) was added with stirring for another 5 minutes. The mixture was heated at 85–90 °C for two hours with stirring, poured on ice-water (equivalent volume as the reaction mixture) and extracted with diethyl ether (three extractions). The solvent ether was then evaporated *in vacuo*.

To completely hydrolyze the trifluoroacetate ester by-products, the dried product obtained from the previous reaction was reacted with five molar excess of 5M NaOH. The reaction mixture was refluxed for two hours at 85 °C. Afterwards, the product was acidified with 6 M HCl to pH 4 and extracted thrice with diethyl ether. The organic layer was then dried over sodium sulfate overnight and the solvent removed *in vacuo*. The product mixture containing HOLA was subjected to FT-IR, ^{1}H NMR, ^{13}C NMR and GC-MS.

The mixture, an oily yellowish liquid, consisted of ω-1 to ω-6 hydroxylauric acids (ω-1 16.5%, ω-2 19.2%, ω-3 19.3%, ω-4 20.3%, ω-5 and ω-6 with 24.7% (Casalme and Sumera, 2013). Yield = 80%. FT-IR (on KBr, cm^{-1}): 3400 (broad, OH stretch), 2700-2500 (broad, COO<u>H</u> stretch), 1713 (sharp and intense, C=O stretch). ^{1}H-NMR [$CDCl_3$, 400 MHz, δ (ppm)]: 6.16 (s, –COO<u>H</u> and –O<u>H</u>), 4.06 (ω-6-C<u>H</u>-OH), 3.81 (ω-5-C<u>H</u>OH), 3.63 (ω-4, ω-3, ω-2-C<u>H</u>OH), 3.54 (ω-1-C<u>H</u>OH), 2.32 (t, –C<u>H</u>$_2$-

COOH), 1.61 (m, –C$\underline{H}_2$-CH_2-COOH), 1.43 (m, –CH(-OH)-C$\underline{H}_2$–), 1.26-1.40 (m, –C$\underline{H}_2$-CH_2R), 1.22 (d, $\underline{H}_3$C-CH(-OH)–), 0.90 (m, –C$\underline{H}_3$). ^{13}C-NMR [$CDCl_3$, 100 MHz, δ (ppm)]: 179.38-179.62 (–COOH of mixture of hydroxy acids), 73.57 (ω-2 –$\underline{C}$HOH), 72.17 (ω-3 –$\underline{C}$HOH), 72.12 (ω-6-$\underline{C}$HOH), 71.94 (ω-5-$\underline{C}$HOH), 71.91 (ω-4-$\underline{C}$HOH), 68.41 (ω-1-$\underline{C}$HOH), 39.29 (–CH(OH)-$\underline{C}H_2$–), 34.1 (–$\underline{C}H_2$-COOH), 25.01-32.17 (–$\underline{C}H_2$-R), 22.65 ($H_3\underline{C}$-CH(OH)–), 9.88 ($H_3\underline{C}CH_2$CHOH–), 14.09 ($H_3\underline{C}$– of ω-3,4,5 and 6).

Vacuum Distillation of Lactic Acid. Lactic acid, commercially available as 85 to 90% aqueous solution was vacuum distilled to remove the water content. To do this, the pressure was reduced continuously, while the temperature was maintained below 80 °C to prevent formation of lactic acid oligomers.

Synthesis of Poly(hydroxylauric acid-co-lactic acid). The melt polycondensations were performed in batch sizes between 2.5g and 25.0g of the monomers HOLA and LA. The monomers without catalyst were added to a 25 mL polymerization tube. The reaction tube was continuously purged with nitrogen throughout the reaction with constant stirring. The temperature of the reaction was steadily increased to 180 °C for 3 h. The polymerization was then continued at a lower temperature 150 °C, under full vacuum for 24 h. Then the reaction mixture was cooled to room temperature to provide the product.

Molecular Weight Determination. The polymers (5-10 mg) dissolved in tetrahydrofuran were injected in a Shimadzu LC 10 attached to a UV-Vis detector and equipped with a mixed bed TSK-GEL G300HHR column. Samples were eluted using tetrahydrofuran at a flow rate of 1 mL/min. The molecular weights were determined using polystyrene standards.

Sterilization. Polymers synthesized from reactant ratios 60:40 and 80:20 of HOLA:LA were sterilized for 2h at 160 °C according to the standard dry heat method recommended by the European Pharmacopoeia. The molecular weight was measured before and after sterilization to investigate the effect of dry heat sterilization on the polymer properties.

RESULTS AND DISUSSION

Physical States and Molecular Weights of The Polymers. Shown below is Table 1 containing data, obtained from GPC, on the molecular weights range values of the polymer synthesized and their physical states (solid or liquid). As the reaction ratio was increased with the monomer HOLA, the greater the polymer's tendency to be in the liquid form. Hence, reactant ratios 60:40 and 80:20 (HOLA:LA) would be the best candidates for a polymer that can be used to absorb a hydrophobic drug as well as be compatible with a hydrophobic matrix because of the hydrophobic alkyl chain and the hydrophilic fragment of lactic acid. Choice of 100:0 would however mean that the drug would be fully covered by a purely hydrophobic polymer providing less opening for water to seep in or the drug to be released before or during the degradation phase after the introduction of the device into a more hydrophilic body of solution. Thus the choice of the ratios wherein there are more HOLA in the product polymer could dictate the kinetics of release of the hydrophobic drug.

Table 1. Molecular Weights and Physical States of Products of Homopolymers* and Copolymers from Different Formulations.

(HOLA:LA) Formulation	Molecular Weight (g/mol)	State
0:100*	356–621	solid
20:80	8,235–32,076	paste
40:60	5,627–22,098	paste
60:40	6,094–27,423	liquid
80:20	8,235–32,076	liquid
100:0*	11,940–50,331	liquid

The removal of tin octoate as catalyst in the polymerization did not seem to affect much the molecular weight ranges of the polymers as shown in Table 2, in comparison with the results from previous polymerization using tin octoate as catalyst recorded in our laboratory (Casalme and Sumera, 2012). Using tin octoate as catalyst with reactant ratio of 0:100 gave molecular weight ranges of 271–576 (solid), 15:85 gave 7430–24,771 (liquid) and ratio 100:0 gave 10,013–41,756. The small molecular weight reduction is however advantageous to the formation of the liquid polymer. As mentioned above the use of tin octoate imposes the presence of toxic heavy metal (even with purification) that is avoided in biocompatible devices for internal use.

Sterilization's Effect on Molecular Weights. Two (2) different ratios (80:20 and 60:40) of poly (hydroxylauric acid-co-lactic acid) in liquid state synthesized without catalyst were further examined for stability under sterilization conditions. These copolymers were sterilized for 2 hours at 160°C following the standard dry heat method recommended by the European Pharmacopedia. The molecular weights were measured before and after sterilization to investigate the effect of dry heat sterilization on the physical properties of the copolymer.

Table 2. Molecular Weights and Physical States of Homopolymers* and Copolymers of LA and HOLAs using Tin Octoate as Catalyst.

(HOLA:LA) Formulation	Molecular Weight (g/mol)	State
0:100*	271–576	solid
5:95	8327–27,557	paste
10:90	5,249–24,015	paste
15:85	7430–24,771	liquid
80:20	9,093–33,009	liquid
100:0*	10,013–41,756	liquid

As depicted in Table 3, the molecular weights of poly (hydroxylauric acid-co-lactic acid) in 2 different ratios (80:20 and 60:40) after dry heat sterilization decreased. However this was not so significant as to alter the physical states (liquid) of the copolymers. Thus, these copolymers were recommended for further use in the preparation of different drug formulations.

Table 3: Molecular Weights and Physical States of Two Different Formulations of Poly(HOLA:LA) before and after Sterilization.

(HOLA:LA) Formulation	Before Sterilization MW(g/mol)	After Sterilization MW (g/mol)	State
60:40	5,627–22,098	3,455–20,008	liquid
80:20	8,235–32,076	5,809–30,076	liquid

Spectroscopic Characterizations. The structure of the polymers produced were then confirmed using FT-IR and ^{1}H NMR. The FT-IR of a sample polyester (from the product of 80:20 ratio) shown in Figure 1 has distinct absorption at around 3350 cm^{-1} which indicates the formation of hydroxyl-carboxy telechelic polymers and a strong absorption at around 1750 cm^{-1} which corresponds to the stretching vibration of the C=O of saturated esters. The asymmetric vibration of the C-C(=O)-O shows strongly in the 1210–1163 cm^{-1} region, broad but as strong as the C=O absorption. Since the polymer contains esters of secondary alcohols, the O-C-C band appears at about 1100 cm^{-1}. The C-H stretching vibrations of the alkyl CH_2 and CH_3 groups appear between 2853 to 2961 cm^{-1} while the bending vibrations of the CH_2 groups are shown by the scissoring (1456 cm^{-1}) and twisting (1380 cm^{-1}) vibrations.

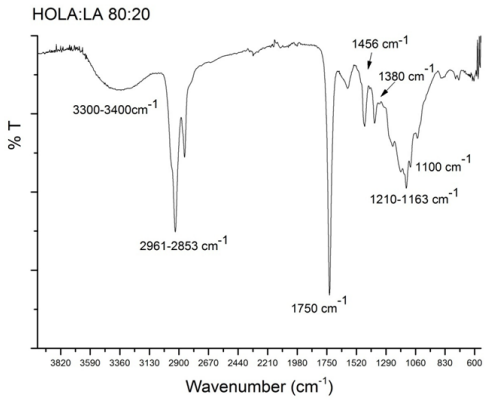

Figure 1. FT-IR Spectra of Poly(hydroxylauric acid-co-lactic acid) from 80:20 HOLA:LA Formulation.

Figure 2 gives the different types of protons of the polymer and Figure 3 shows a representative ^{1}H NMR of the polymer featuring the peaks due to the different types of protons. The assignments have been made possible by considering that the arrangement of the monomer fragments are in random positions as has been observed in other similar polycondensation reactions, that is by simply raising the temperature of the mixture to near melting as for example the reaction between ricinoleic acid, a hydroxy fatty acid and lactic acid (Sliviniak and Domb, 2005). The sample examined here is the liquid product from a 80:20 HOLA:LA formulation.

Shown in Figure 3 are the following a) the methyl groups of two laurate fragments (at 0.88 and 1.19 ppm). Seen are the methyls of ω-1 and ω-2 laurate fragments. b) the methyl groups of the lactate fragments overlapping with the methylene groups of the laurate fragments (at 1.41–1.67 ppm). c) the α hydrogens of the laurate fragment (at 2.04–2.28 ppm), d) the methylene group β to the alcoholate of the laurate fragments (at 2.375 ppm), e) the secondary hydrogens of the alcoholate of the laurate fragments (3.77–4.90 ppm) and f) the α hydrogens of the lactate fragments (at 5.03–5.17 ppm).

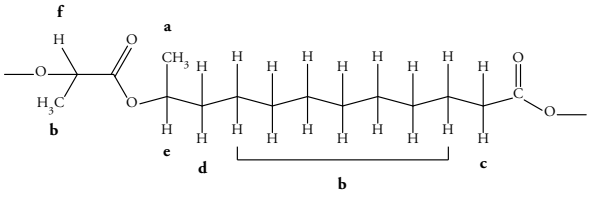

Figure 2. Proton Types of the Synthesized Polymers.

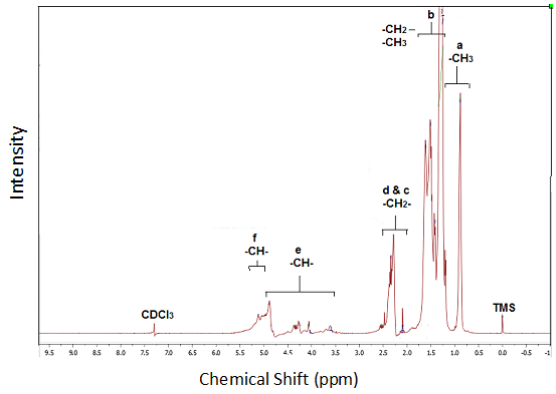

Figure 3. Poly(hydroxylauric-co-lactic acid) [1]H NMR from 80:20 HOLA:LA Formulation.

CONCLUSION

Lactic acid derived polyester in the liquid form was prepared by reacting lactic acid with methylene rich hydroxylauric acid in different ratios such as (0:100, 20:80, 40:60, 60:40, 80:20 and 100:0). No catalyst was added to avoid the presence of trace heavy metal that usually come from a metal salt catalyst (e.g. tin from tin octoate). Reactant ratios of HOLA:LA, 0:100 produce solids while 20:80 and 40:60 are pasty substances and 60:40, 80:20 and 100:0 are liquids. The molecular weights obtained from their polycondensation without catalyst do not differ much from that with tin octoate which is usually used as catalyst in polycondensation reactions. However, sterilization, a common hygienic procedure for substances used for medicinal application, decreases the molecular weights but still maintains their physical state as liquids. The polyesters structures are confirmed by FT-IR and ^{1}H NMR spectroscopy. The liquid products of HOLA:LA polycondensation (60:40 and 80:20) are thus recommended for use as matrix for injectable hydrophobic drugs in controlled drug delivery. Further characterization of the liquid with respect to the drugs' solubility is recommended.

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