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Chemical grafting of cholesterol on monomer and PDMMLA polymers, a step towards the development of new polymers for biomedical applications

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Racemic α,α,β-trisubstituted β-lactones are the monomer units of poly((*R*,*S*)-3,3-dimethylmalic acid) (PDMMLA) derivatives, new biopolyesters showing great potential for biomedical applications. Using different groups during the synthesis of these β-lactones allows a tailored synthesis of PDMMLA copolymers with adjustable hydrophilic/phobic ratio. The degradation kinetics of the employed material is one of the most important criteria in the development of bioresorbable implants. The degradation time of PDMMLA derivatives can be controlled using different β-lactones of different hydrophilicity levels during the polymerization stage. Furthermore, PDMMLA has chemically available groups on its side chain allowing to graft functional groups on the polymer *via* covalent bonds. In this work, following a Steglich esterification protocol, the chemical grafting of cholesterol was carried out on a PDMMLA monomer derived β-lactone as well as on homopolymer PDMMLA–H, and copolymer PDMMLAH$_{40}$-*co*-Hex$_{60}$ (PDMMLA 40/60). Nuclear magnetic resonance (NMR) analyses of the products confirm and quantify the grafting ratio. 100% of cholesterol grafting has been realized on the homopolymer PDMMLA–H giving PDMMLA–Chol, and 10% on the copolymer PDMMLA 40/60, giving PDMMLAH$_{30}$-*ter*-Chol$_{10}$-*ter*-Hex$_{60}$ (PDMMLA–Chol 30/10/60) as wished. Fourier-transform infrared (FT-IR) spectra, elemental analysis on the β-lactones and thermogravimetric analyses on the polymers also confirm the chemical modification of the products.

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Introduction

Racemic α,α,β-trisubstituted β-lactones are synthetic molecules (Scheme 1), serving as monomers in the synthesis of biodegradable polyesters: poly((*R*,*S*)-3,3-dimethylmalic acid) PDMMLA derivatives. These are new statistical biopolyesters, studied for their interesting properties to serve in medical treatments. The main aim in studying PDMMLA derivatives is to develop a polymer for cardiovascular metallic stent coating. Previous works proved the great potential of these polymers for this application in terms of mechanical properties,[1,2] degradation kinetics,[3] and cell response.[4]

PDMMLA derivatives are synthesized through an anionic ring opening polymerization (ROP) of the β-lactones[5] (Scheme 2). The use of different groups in the synthesis of the monomers, gives different hydrophilicity levels to the synthesized polymers. The increase in benzylic β-lactone **[1]** (the benzylic group is hydrolyzed into a carboxylic acid later) increases the hydrophilicity of the final polymer, which changes its degradation kinetics. The ability to control the degradation time of this biopolymer is an advantage compared to currently used biopolymers.[6]

Previous work has shown that the degradation products of PDMMLA are non-toxic and bio-assimilable.[3] In addition, the presence of available carboxylic acid groups on the side chain of PDMMLA makes the covalent grafting of active drugs possible, which is promising regarding the controlled release of the drug in order to limit an intra-stent restenosis after implantation.

In order to prove the possibility and efficacy of the chemical grafting, we first started with the grafting of cholesterol (Chol) on 4-carboxyl-3,3-dimethyl-2-oxetanone (acidic β-lactone) **[3]**, synthesized here for the first time with the catalytic hydrogenolysis of the benzylic β-lactone **[1]**. We realized the grafting reaction following the Steglich esterification protocol. Cholesterol is not an active drug, but a model molecule used in this work, only to prove the feasibility of the grafting. Its simple structure compared to that of real drugs allows easier analysis of the obtained data. Furthermore, cholesterol possesses only one

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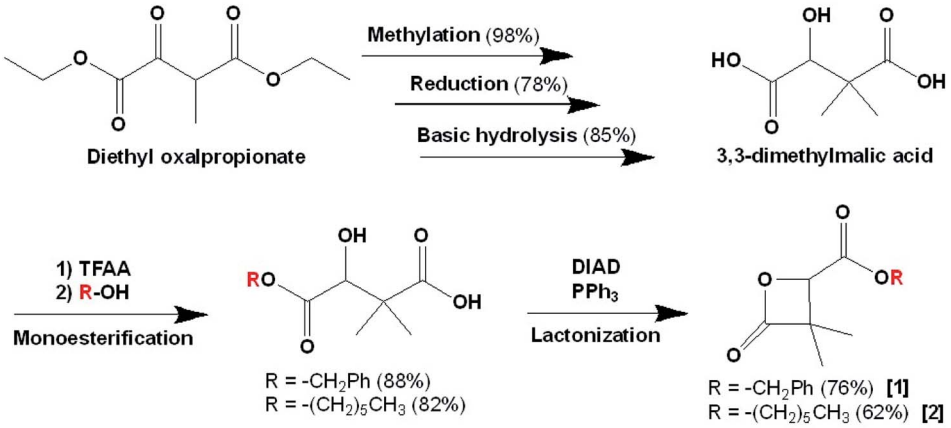


Scheme 1 Synthetic pathway of the α,α,β-lactones: 4-benzyloxycarbonyl-3,3-dimethyl-2-oxetanone (benzylic β-lactone) [1] 4-hexyloxycarbonyl-3,3-dimethyl-2-oxetanone (hexylic β-lactone) [2].

hydroxyl group, which makes evident that the reaction will take place involving this very group[7,8] to give 4-cholesteryloxycarbonyl-3,3-dimethyl-2-oxetanone (cholesterolic β-lactone) [4] (Scheme 3).

Steglich esterification is used to form an ester bond between a carboxylic acid and a hydroxyl (alcohol) group. *N*,*N*′-dicyclohexylcarbodiimide (DCC) activates the carboxyl group, forming an *O*-acylisourea intermediate.[9] The esterification of the carboxylic acid is improved by addition of a catalytic amount of 4-dimethylaminopyridine (DMAP), which leads to a more effective reaction.[10,11] In our case, the esterification takes place involving the carboxylic acid group of the monomer and/or the polymer and the available hydroxyl group of cholesterol.

Following the same protocol, we realized the grafting on PDMMLA polymers. In order to determine the maximal grafting percentage, the reaction has been carried out on the 100% hydrophilic homopolyester, PDMMLA–H (PDMMLA 100/0); then, on the 40% hydrophilic copolymer, PDMMLAH$_{40}$-*co*-Hex$_{60}$ (PDMMLA 40/60) in order to obtain the theoretical terpolymer PDMMLAH$_{30}$-*ter*-Chol$_{10}$-*ter*-Hex$_{60}$ (PDMMLA 10/30/60).

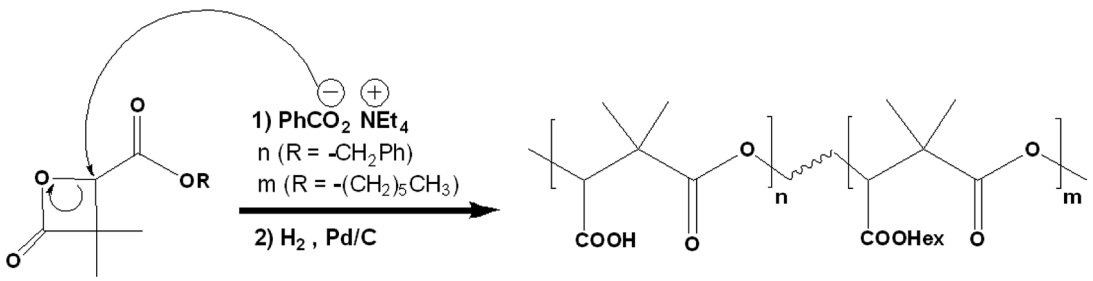
A study on the degradation kinetics of a series of PDMMLA derivatives showed that the copolymer with 30% of hydrophilic groups (PDMMLA 30/70) has the fastest degradation kinetics in a 6 months' time interval.[3] In order to accelerate this process, we synthesized a more hydrophilic copolymer, PDMMLA 40/60, which degrades even faster in order to prevent the post-implantation complications due to the presence of the polymer. On the other hand, our team has proved a good cell behavior on the PDMMLA 30/70.[4] By grafting 10% of an active agent, we aim to conserve 30% of hydrophilicity as in the case of PDMMLA 30/70, and accelerate the degradation of the remaining polymer after the complete release of the active agent.

^{1}H NMR technique was used to confirm the reaction and the grafting ratio. FT-IR spectra, elemental analysis on the β-lactones and thermogravimetric analyses on the polymers also confirm the chemical modification of the products.

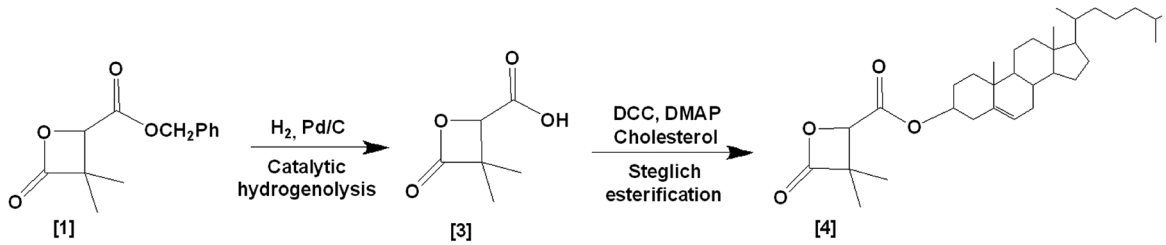
Results and discussion

Chemical grafting of cholesterol on the β-lactone and PDMMLAs was carried out *via* Steglich esterification. ^{1}H analysis of the products confirms the reaction *via* the modification of chemical shifts of the significant groups. Fig. 1 shows the ^{1}H NMR spectra of cholesterol, acidic β-lactone [3], and cholesterolic β-lactone [4].

Signals at 3.55 ppm (Fig. 1a) and 4.67 ppm (Fig. 1b) correspond to indicated protons on cholesterol and the β-lactone [3]. Changes in chemical shifts of these groups integrating for 1H



Scheme 2 Synthesis of PDMMLA polymers through a ROP of the β-lactones. The final copolymer contains carboxylic acid groups (–COOH) and hexylic ester groups (–COOHex).



Scheme 3 Synthesis of acidic β-lactone [3], and cholesterolic β-lactone [4].

each show that a chemical modification has taken place between these molecules with 100% conversion efficiency (Fig. 1c).

Regarding the polymers, chemical shift changes are different from the monomer despite similar electronic effects. This can be explained by the difference in mobility of the molecules. Indeed, the polymer chain is more flexible and mobile than the planar and rigid structure of the β-lactone. In the case of polymers, integral values of the peaks allow to calculate the grafting percentage.

For PDMMLA–Chol, one can observe 100% of cholesterol grafting since the integral values for the peaks at 3.40 ppm (H_3 on cholesterol) and 5.23 ppm (H_b on the polymer) are 1.04 and 1.05 respectively. Regarding the terpolymer, calculations using the integral values of the peaks at 3.45 ppm (H_3 integrating for 0.09H) and 5.28 ppm (H_b and H_6 integrating for 1.11H), give 10% of grafted cholesterol as wanted.

FT-IR analysis of the products before and after cholesterol grafting confirm also the esterification. With the β-lactone for example, the –OH stretching band of cholesterol at 3450 cm^{-1} disappears completely when grafted, indicating that the hydroxyl group was transformed to an ester. Furthermore, the absorption occurring at 1222 cm^{-1} corresponds to the C–O stretching of the new ester bond (Fig. 2). Similar results were observed with the polymers, confirming the esterification in all cases.

Elemental analysis of a molecule gives information about its chemical composition. Calculating the molar percentage of each present element in the molecule allows to confirm the expected composition of the sample. Indeed, experimental values obtained in the case of new cholesterolic β-lactone give coherent results with calculated theoretical values (C_{th} = 76.90%, C_{exp} = 76/32% and H_{th} = 10.21%, H_{exp} = 10.43%), showing that the expected composition is obtained and the esterification has taken place successfully.

TGA measurements of a polymer give information about the thermal stability of the polymer and its degradation temperature T_d.[12] From the determined values of T_d, we can thus define the maximum temperature lower than the T_d to carry out the DSC analysis of the copolymers without degrading them. DSC technique provides information about the thermal properties of a polymer, mainly the glass transition temperature T_g which shows structural changes in the backbone and melting temperature T_m.[13,14] Fig. 3 and 4 show the TGA and DSC thermograms of the grafted polymers respectively. Table 1 gathers the values obtained by TGA and DSC measurements.

Grafting cholesterol on the acidic β-lactone has increased its T_m from 48 to 160 °C. Regarding the polymers, they all show a T_d above 150 °C. High T_d value facilitates manipulation under heating conditions if necessary, without thermal degradation of the polymer. The increase of T_g in all cases indicates an addition of rigidity to the structure of the polymers. A significant increase is observed for the homopolymer (from 69.9 to 106.6 °C) since there is 100% of grafting. As for the terpolymer, the T_g increase is slight and less important (from 23.7 °C to 25.7 °C) since there is only 10% of grafted cholesterol.

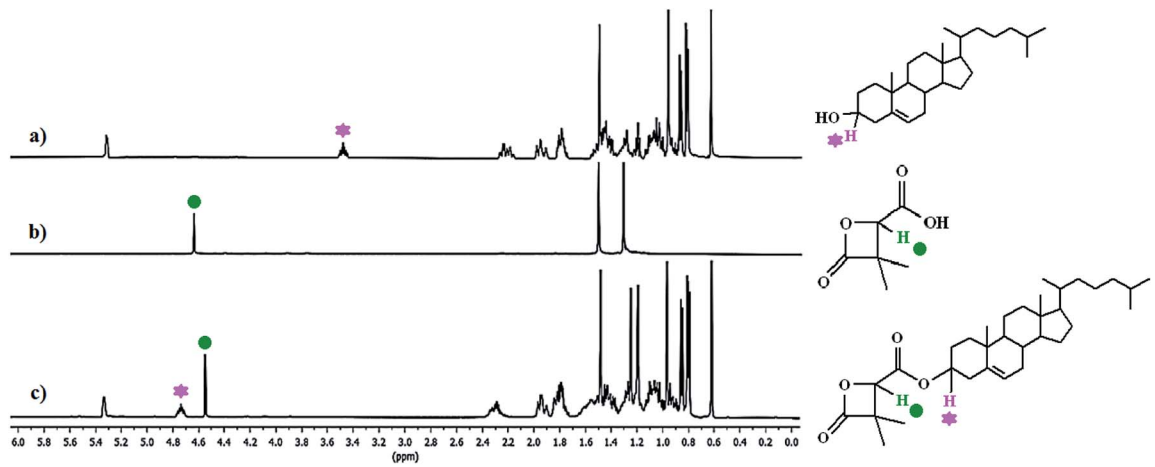


Fig. 1 ^1H NMR spectra of: (a) cholesterol, (b) acidic β-lactone [3], (c) cholesterolic β-lactone [4] in $CDCl_3$, 400 MHz.

Experimental

Materials and methods

Cholesterol was purchased from Sigma Aldrich Chemical Co. All other chemicals were purchased from Alfa Aesar chemical Co and employed as received.

Anhydrous tetrahydrofuran (THF) was distilled on sodium-benzophenone. In all other cases, the commercially available reagent-grade solvents were employed without purification. All reactions with anhydrous organic solvents were performed under nitrogen atmosphere. All glass apparatuses were kept one night in a drying-oven at 100 °C.

Thin Layer Chromatography (TLC) was performed using plates coated with Merck silica gel 60 Fi_{254} of 0.25 mm thickness. The TLC plates were first revealed under UV light (254 nm wavelength) then with *p*-anisaldehyde stain containing absolute ethanol (93 mL), *p*-anisaldehyde (2.5 mL), concentrated sulfuric acid (3.5 mL) and concentrated acetic acid (1 mL). Flash chromatography (FC) was carried out using silica gel (C–C 35–70 μm, 60 Å).

Nuclear magnetic resonance: ^{1}H and ^{13}C NMR spectra were recorded by a BRUKER AM-400 MHz spectrometer, using $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm.

Infrared: FT-IR spectra were recorded on AVATAR 370 FT-IR Thermo Nicolet OMNI-sampler ATR Smart Accessory (Ge, DTGS). Absorption bands are given in cm^{-1}.

Melting point of the solid compound was determined using a Stuart SMP11 melting point apparatus.

Thermogravimetric analysis (TGA) measurements of the polymers were registered using a TGA Q50 analyzer. Samples were heated from 10 °C to 500 °C with a heating rate of 10°C min^{-1} under N_2 atmosphere.

Glass transition temperature (T_g) of the samples was measures using differential scanning calorimetry (DSC) technique on a DSC Q2000 analyzer. Polymers were put in the furnace and heated from −25 °C to 160 °C (the maximal temperature was adjusted for each sample according to the T_d value obtained from the TGA experiment in the aim to avoid degrading the copolymer during the first run), cooled down to −25 °C, and reheated in order to realize the second heating cycle. The heating rate was set to 10°C min^{-1} and the T_g value was collected from the inclination point on the second heating curve.

Size exclusion chromatography (SEC) was realized at room temperature for the determination of absolute molecular weights of the polymers. A high performance size exclusion chromatography (HPSEC) was coupled to a multi-angle laser light scattering detector (MALLS), a viscosimeter and a differential refractive index (dRI) detector. THF was used as the carrier phase and was filtered through a 0.1 μm filter unit (Millipore, Billerica, USA), It was degassed (DGU-20 A3R Shimadzu, Kyoto Japan) and eluted at a 0.5 mL min^{-1} flow rate (LC10Ai Shimadzu, Kyoto Japan). 100 μL of a 0.2 μm-filtered sample solution (C = 10 mg mL^{-1}) were injected with an automatic injector (SIL-20A HT Shimadzu, Kyoto Japan). The column packing was a divinylbenzene gel. The MALLS photometer, a miniDawn TREOS from Wyatt Technology Inc. (Sanata Barbara, CA, USA) was provided with a fused silica cell and a Ga–As laser (λ = 665.8 nm). The whole collected data: light scattering (LS), dRI were analyzed using the Astra v6.0.6 software package. Molar masses were obtained with a Zimm order 1 method. The concentration of each eluted fraction was determined with dRI (RID10A Shimadzu, Kyoto Japan) according to the measured values of dn/dc (0.05 mL g^{-1}).[15]

β-lactone synthesis

As shown in the Scheme 1, α,α,β-trisubstituted β-lactones with benzylic ester and hexylic ester groups were prepared in five steps from the precursor diethyl oxalpropionate, following the protocols described in the literature.[16–18]

4-carboxyl-3,3-dimethyl-2-oxetanone [3] (Fig. 5a). This product is obtained by the catalytic hydrogenolysis of the benzylic β-lactone **[1]**. Benzylic β-lactone **[1]** (500 mg, 2.13 mmol) was dissolved in 20 mL of acetone. Pd/charcoal (50 mg, 10% of total mass) was then added. The air in the flask was vacuumed and replaced with H_2 gas. The reaction mixture was stirred for 24 h at room temperature and filtered through a 0.2 μm PTFE membrane. After evaporating the solvent, the final product (acidic β-lactone) **[3]** was obtained as a white powder, with a yield of 94%. Rf = 0.60. T_m = 48 °C. ^{1}H NMR, 400 MHz,

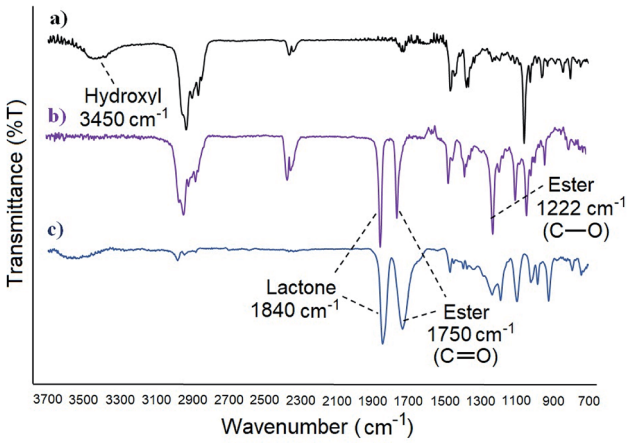


Fig. 2 FT-IR spectra of: (a) cholesterol, (b) cholesterolic β-lactone **[4]**, (c) acidic β-lactone **[3]**.

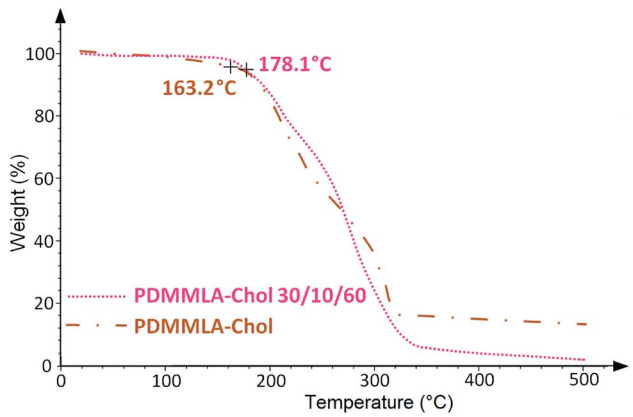


Fig. 3 TGA curves of PDMMLA–Chol, and PDMMLA–Chol 30/10/60.

Table 1 Melting point of the β-lactones and thermal analysis results of the polymers before and after cholesterol grafting

	T_d (°C)	T_g[a] (°C)	T_m (°C)
Acidic β-lactone	—	—	48
Cholesterolic β-lactone	—	—	160
PDMMLA–H	Undetermined	69.9	—
PDMMLA–Chol	163.2	106.6	—
PDMMLA 40/60	198.1	23.7	—
PDMMLA–Chol 30/10/60	178.1	25.7	—

[a] Determined by DSC at second heating.

($CDCl_3$) δ_H (ppm): 1.30 (s, 3H, H_e), 1.51 (s, 3H, H_f), 4.67 (s, 1H, H_d). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ_C (ppm): 17.52, 21.90 (C_e, C_f), 58.50 (C_c), 78.10 (C_d), 168.35, 17.97 (C_b, C_g). Elemental analysis for $C_6H_8O_4$ calculated theoretically: C: 50.00, H: 5.62; obtained experimentally, C: 49.86, H: 6.41.

Cholesterolic β-lactone [4] (Fig. 5b). Acidic β-lactone **[3]** (100 mg, 0.69 mmol, 1 eq.), cholesterol (267 mg, 0.69 mmol, 1 eq.), and DMAP (48 mg, 0.39 mmol 10% of the total mass) were placed in a round-bottom flask under nitrogen atmosphere and dissolved in 70 mL of freshly distilled THF at 0 °C. DCC (150 mg, 0.69 mmol, 1 eq.), was separately dissolved in anhydrous THF and added to the previous mixture. After 15 minutes, the reaction medium was brought to room temperature and stirred for 48 h. The final product was purified by flash chromatography using the eluent cyclohexane/ethyl-acetate (8/2). A white solid was obtained with a yield of 49%. $R_f = 0.85$. $T_m = 160$ °C. ^1H NMR, 400 MHz, ($CDCl_3$) δ_H (ppm): 0.63 (s, 1H, H_{18}), 0.88 (dd, 6H, H_{26}, H_{27}), 0.93 (d, 3H, H_{21}), 0.98 (m, 1H, H_9), 1–1.62 (aliphatics H_1, H_2, H_8, H_{11}–H_{17}, H_{20}, H_{22}–H_{25}), 1.03 (s, 3H, H_{19}), 1.24 (s, 1H, H_e), 1.51 (s, 1H, H_f), 1.85 (m, 2H, H_7), 2.01 (m, 2H, H_{12}), 2.28 (m, 2H, H_4), 4.52 (s, 1H, H_d), 4.74 (m, 1H, H_3), 5.37 (d, 1H, H_6). ^{13}C NMR, 100 MHz, ($CDCl_3$): δ_C (ppm): 11.81 (C_{18}), 17.54 (C_e), 18.45 (C_{21}), 19.42 (C_{19}), 21.09 (C_{11}), 22.07 (C_f), 22.58 (C_{27}), 22.84 (C_{26}), 23.84 (C_{15}), 24.31 (C_{23}), 28.03 (C_{16}), 28.25 (C_{25}), 31.66 (C_7), 31.90 (C_8), 35.80 (C_{10}), 36.20 (C_{20}), 36.51 (C_{22}), 37.26 (C_1), 39.53 (C_{12}), 39.78 (C_{24}), 42.30 (C_{13}), 42.32 (C_4), 50.13 (C_9), 56.11 (C_{14}), 57.72 (C_c), 56.65 (C_{17}), 71.81 (C_3), 76.06 (C_d), 121.74 (C_6), 140.76 (C_5), 166.74, 172.96 (C_b, C_g). Elemental analysis for $C_{33}H_{52}O_4$ calculated theoretically: C: 76.90, H, 10.20; obtained experimentally: C: 76.32, H: 10.43.

Polymer synthesis

The synthesis of the homopolymer[19] and the copolymer[5] was realized as described in the literature, using the β-lactones **[1]** and **[2]** as monomers, and tetraethyl-ammonium benzoate (Et_4N^+ $PhCOO^-$) as initiator. A monomer/initiator ratio (M/I) of 5×10^3 was applied for all polymers.

Copolymer PDMMLA 40/60 (Fig. 5c). Copolymer PDMMLA 40/60 (Fig. 5c) was prepared for the first time. Benzylic β-lactone **[1]** (1.1 g, 4.67 mmol, 0.4 eq.) and (hexylic β-lactone) **[2]** (1.6 g, 7.01 mmol, 0.6 eq.) were dissolved in 100 mL of freshly distilled THF. The lactone solution was then added to a round bottom flask containing the initiator Et_4N^+ $PhCOO^-$ (14.64 mg, 0.058 mmol, 5×10^{-3} eq.) under nitrogen atmosphere. After confirmation of the polymerization by FT-IR, 2 to 4 drops of acetic acid were added. The formed polymer was isolated by precipitation in ethanol. A catalytic hydrogenolysis using Pd/C (1.1 g) and H_2 gas was then carried out on the copolymer in order to remove the benzylic groups. PDMMLA 40/60 was thus obtained. Yield: 96%; $M_n = 29.630$ g mol^{-1}; $M_w = 29.640$ g mol^{-1}; $Đ = 1.000$. ^1H NMR, 400 MHz, ($CDCl_3$) δ_H (ppm): 0.81 (s, 3H, H_l), 1.22 (s, 12H, H_f, H_e, H_k, H_j, H_i), 1.54 (s, 2H, H_h), 4.06 (s, 2H, H_g), 5.26 (s, 1H, H_b). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ_C (ppm): 13.99 (C_l), 22.49 (C_f, C_e), 26.31 (C_k), 32.22 (C_i, C_j, Ck), 45.98 (C_c), 66.28 (C_g), 77.14 (C_b), 168.26 (C_a), 173.76 (C_d).

Cholesterolic homopolymer [PDMMLA–Chol] (Fig. 5d). Cholesterol was grafted to the homopolymer following the same protocol as for the product **[4]**, using the following quantities of reactants: PDMMLA–H (40 mg, 0.27 mmol, 1 eq.), cholesterol (104 mg, 0.27 mmol, 1 eq.), DMAP (20 mg, 0.16 mmol, 10% of the total mass) and DCC (56 mg, 0.27 mmol, 1 eq.) in 70 mL of anhydrous THF. The mixture was stirred under nitrogen atmosphere for 48 h at room temperature. After the reaction, THF was eliminated. The product was then dissolved in a little amount of chloroform and purified by precipitation in cyclohexane. PDMMLA–Chol is obtained as a white powder with a yield of 46%. ^1H NMR, 400 MHz, ($CDCl_3$) δ_H (ppm): 0.68 (s, 3H, H_{18}), 0,85 (d, 3H, H_{26}), 0.97 (d, 3.05H, H_{27}), 0.93 (d, 3.02H, H_{21}), 0.98 (m, 3H, H_{19}), 1–2.28 (35H, aliphatic H_1–H_4, H_7–H_9, H_{11}–H_{17}, H_{20}, H_{22}–H_{25}, H_f, H_e), 3.40 (m, 1.04H, H_3), 5.23 (s, 1.05H, H_b), 5.37 (d, 1.04H, H_6). ^{13}C NMR, 100 MHz, ($CDCl_3$): δ_C (ppm):

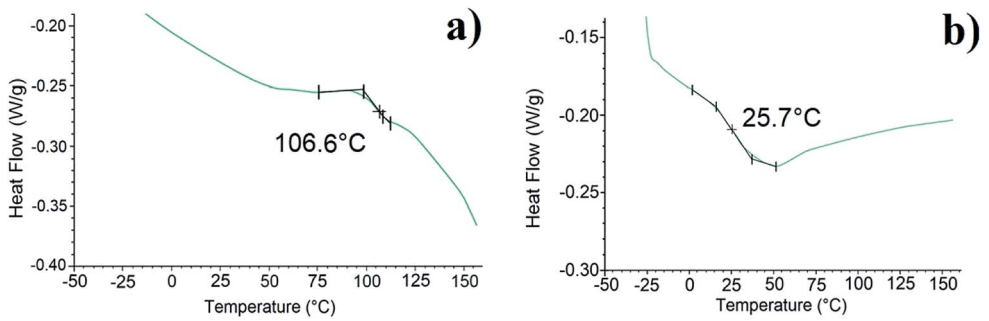


Fig. 4 DSC curves of (a) PDMMLA–Chol, (b) PDMMLA–Chol 30/10/60, zoomed in on the inclination point of the second heating curve.

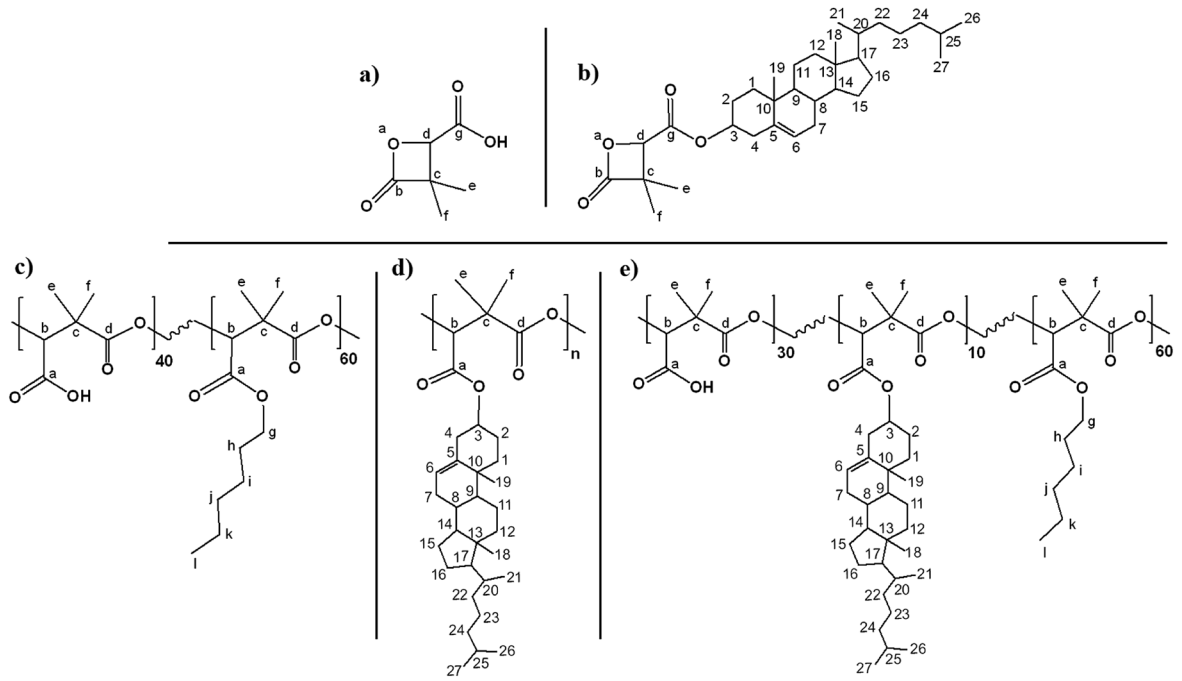


Fig. 5 Chemical structures of the synthesized molecules; (a) acidic β-lactone [3], (b) cholesterolic β-lactone [4], (c) PDMMLA 40/60, (d) PDMMLA–Chol, (e) PDMMLA–Chol 30/10/60.

11.94 (C_{18}), 18.86 (C_{21}), 19.47 (C_{19}), 18.90 (C_e), 21.11 (C_{11}), 22.53 (C_f), 22.61 (C_{27}), 22.90 (C_{26}), 23.86 (C_{15}), 24.32 (C_{23}), 28.07 (C_{16}), 28.30 (C_{25}), 31.57(C_7), 31.86 (C_8), 35.84 (C_{10}), 36.17 (C_{20}), 36.48 (C_{22}), 37.28 (C_1), 39.55 (C_{12}), δ_C 39.81 (C_{24}), 42.28 (C_{13}), 42.40 (C_4), 45.16 (C_c), 50.17 (C_9), 56.90 (C_{14}), 58.32 (C_{17}), 72.14 (C_3), 76.12 (C_b), 121.85 (C_6), 140.76 (C_5), 167.98 (C_a), 173.20 (C_d).

Cholesterolic terpolymer [PDMMLA–Chol 10/30/60] (Fig. 5e). Same protocol was employed using the following quantities of reactants: PDMMLA 40/60 (100 mg, 0.43 mmol, 1 eq.), cholesterol (16.69 mg, 0.043 mmol, 0.1 eq.), DMAP (12.61 mg, 0.10 mmol, 10% of the total mass), and DCC (8.90 mg, 0.043 mmol, 0.1 eq.). After precipitation in cyclohexane, PDMMLA 10/30/60 was obtained as a white powder with a yield of 38%. ^{1}H NMR, 400 MHz, ($CDCl_3$) δ_H (ppm): 0.66 (s, 0.27H, H_{18}), 0.83 (m, 6.19H, H_{26}, H_{27}, H_l), 0.94 (d, 0.26H, H_{21}), 1.05 (m, 0.25H, H_9), 1.1–1.50 (30.09H, aliphatic H_1, H_2, H8, H_{11}–H_{17}, H_{20}, H_{22}–H_{25}, H_e, H_f, H_k, H_i, H_j), 1.54 (s, 2.56H, H_h), 1.88 (m, 0.15H, H_7), 1.92 (m, 0.10H, H_{12}), 2.20 (m, 0.19H, H_4), 3.45 (m, 0.09H, H_3), 4.05 (m, 2.03H, H_g), 5.28 (d, 1.11H, H_6, H_b). ^{13}C NMR, 100 MHz, ($CDCl_3$): δ_C (ppm): 11.87 (C_{18}), 13.98 (C_l), 18.72 (C_f), 19.40 (C_{21}), 19.45 (C_{19}), 21.11 (C_{11}), 22.9 (C_e), 22.56 (C_{27}), 22.88 (C_{26}), 23.81 (C_{15}), 24.36 (C_{23}), 25.40 (C_j), 28.10 (C_{16}), 28.24 (C_{25}), 28.39 (C_k), 29.72 (C_i), 30.32 (C_h), 31.31 (C_7), 31.93 (C_8), 35.78 (C_{10}), 36.19 (C_{20}), 36.53 (C_{22}), 37.23 (C_1), 39.52 (C_{12}), 39.80 (C_{24}), 42.19 (C_{13}), 42.37 (C_4), 45.20 (C_c), 50.09 (C_9), 56.14 (C_{14}), 59.76 (C_{17}), 65.91 (C_g), 72.06 (C_3), 76.06 (C_b), 121.76 (C_6), 140.71 (C_5), 167.73 (C_a), 173.12 (C_d).

Conclusion

The purpose of this work was to study the possibility and efficiency of grafting functional groups on the chemically modifiable side chain of PDMMLA polymers. This grafting can be carried out on PDMMLAs with different functional groups and drugs having a hydroxyl, amine or sulfur function for various biomedical applications. For this reason, chemical grafting study on PDMMLAs was carried out with cholesterol having a simple chemical structure and only one functional group (–OH). A β-lactone derived from the monomer units of PDMMLA and polymers having 100% and 40% –COOH groups on their respective side chains (PDMMLA–H and PDMMLA 40/60, respectively) were used in this work. An ester bond was formed between the carboxylic acid group of the monomer/polymer and the hydroxyl group of the cholesterol following a Steglich esterification. NMR analysis allowed to confirm and quantify the grafting percentage, which prove the efficiency of the practiced grafting procedure (100% concordance with theoretical grafting percentage). ^{1}H NMR and FT-IR spectra show evident results confirming the grafting. TGA and DSC measurements show also the modification brought to the polymers due to the addition of the cholesterol to the basic structure of each polymer. Increases in glass transition temperature are a good indication to the addition of rigidity to the polymers' structure.

PDMMLA is a biocompatible and biodegradable polymer, developed in our team for biomedical applications. These experiments allowed to confirm the possibility of covalent grafting on PDMMLA derivatives (homopolymer or copolymer). Future works will be oriented to grafting a veritable active drugs on these polymers in order to improve healing conditions in medical intervention cases.

Conflicts of interest

There are no conflicts to declare.

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