Supplementary Information

Development of poly(1,8-octanediol-co-citrate-co-ascorbate) elastomer with enhanced ascorbate performance for use as a graft coating to prevent neointimal hyperplasia

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**Chemical synthesis**

2,3-**di-MEM-L-ascorbic acid**: ascorbic acid (1 g, 5.7 mmole) and N,N-Diisopropylethylamine (DIPEA) (2.4 mL, 13.6 mmole) was added to 30 mL dichloromethane (DCM). The mixture was stirred for 10 minutes at room temperature. 2-Methoxyethoxymethyl chloride (MEM-Cl) (1.3 mL, 11.4 mmole) was added to the mixture. The mixture was stirred for 1 hour at room temperature. The final product was further purified by flash column. Yield was 62.5%. 2,3-**di-MEM-L-ascorbic acid**: 

1H NMR (400 MHz, CDCl₃, ppm) δ 5.74-5.72 (d, J=5.8 Hz, 1H), 5.42-5.41 (d, J=5.8 Hz, 1H), 5.28-5.22 (d, J=25.1 Hz, 2H), 4.74 (d, J=1.9 Hz, 1H), 4.02-4.01 (d, J=6.2 Hz, 1H), 3.91-3.82 (d, J=36.2 Hz, 5H), 3.59-3.55 (d, J=16.5 Hz, 4H), 3.38 (s, 6H); 13C NMR (400 MHz, CDCl₃, ppm) δ 169.36, 155.95, 120.68, 95.8, 95.42, 75.97, 71.72, 71.50, 69.64, 69.38, 69.19, 63.25, 59.1, 53.55; FTIR (KBr, cm⁻¹): 1761.5 (C=O), 1679.2 (C=C); ESI-MS [M+H]⁺: calculated: 353.3360, found: 353.1439.

**Compound (1)** (5,6-**O-isopropylidene-L-ascorbic acid)****: Acetyl chloride (1.6 mL, 22.7 mmole) was added to a stirred suspension of L-ascorbic acid (40 g, 227.1 mmole) in 300 mL anhydrous acetone. The reaction was stirred for another 16 hours at room temperature. The mixture was centrifuged at 5000 rpm for 30 minutes and the supernatant acetone was removed by pouring off. The final product was washed by ethyl acetate once and dried under vacuum to collect a white solid without further purification. Yield was 90.3%. Compound (1): 1H NMR (400 MHz, DMSO, ppm) δ 11.27 (s, 1H), 8.46 (s, 1H), 4.71-4.70 (d, J=2.9 Hz, 1H), 4.28-4.24 (d, J=16.3 Hz, 1H), 4.11-3.86 (dd, J=15.4 Hz, 2H), 1.25 (s, 6H); 13C NMR (400 MHz, DMSO, ppm) δ 170.33, 152.48, 118.28, 109.11, 74.35, 73.55, 64.96, 25.92, 25.52; FTIR (KBr, cm⁻¹): 1754.3 (C=O), 1663.1 (C=C); ESI-MS [M+H]⁺: calculated: 217.1890, found: 217.0706.
**Compound (2)** (5,6-\(O\)-isopropylidene-2,3-\(di\)-benzyl-\(L\)-ascorbic acid): Compound (1) (30 g, 138.7 mmole) and \(K_2CO_3\) (42.2 g, 305.3 mmole) was added into 500 mL dried acetone and heated at 30°C for 10 minutes. Benzyl bromide (44.1 mL, 367.4 mmole) was added to the mixture and heated at 50°C overnight. Acetone was removed completely by vacuum and the final product was washed by water/diethyl ether several times to collect a white solid without further purification. Yield was 50.5%. Compound (2): \(^1\)H NMR (400 MHz, \(CDCl_3\), ppm) \(\delta 7.41-7.19\) (dd, \(J=64.8Hz\), 10H), \(5.21-5.07\) (d, \(J=57.4Hz\), 4H), \(4.54-4.53\) (d, \(J=3.2Hz\), 1H), \(4.27-4.23\) (d, \(J=16.7Hz\), 1H), \(4.13-4.09\) (d, \(J=44.1Hz\), 2H), \(1.41-1.37\) (d, \(J=16.9Hz\), 6H); \(^{13}\)C NMR (400 MHz, DMSO, ppm) \(\delta 168.89, 157.4, 135.99, 135.55, 128.47, 128.45, 127.68, 120.58, 109.25, 74.26, 73.41, 73.17, 72.81, 64.85, 25.72, 25.28\); FTIR (KBr, cm\(^{-1}\)): 1752.8 (C=O), 1676.5 (C=C). ESI-MS [M+H]\(^+\): calculated: 396.4390, found: 397.0872.

**Compound (3)** (2,3-\(di\)-benzyl-\(L\)-ascorbic acid): 50 g of the protected \(L\)-ascorbic acid compound (2) was dissolved in 400 mL acetonitrile and hydrochloric acid solution (2 M, 250 mL) was added to remove the isopropylidene protecting group. The mixture was stirred for 3 hours at 30°C. Crude product was dissolved in ethyl acetate and then washed by DI water and brine. The ethyl acetate layer was dried over anhydrous magnesium sulfate, and then filtered and concentrated under vacuum. The final product was recrystallized at -20°C from a light yellow oil to collect compound (3), with pure compound (3) used to seed the crystallization. Yield was 92.5%. Compound (3): \(^1\)H NMR (400 MHz, DMSO, ppm) \(\delta 7.43-7.3\) (d, \(J=52.3Hz\), 10H), \(5.25-5.19\) (d, \(J=31.6Hz\), 2H), \(5.14-5.13\) (d, \(J=6.3Hz\), 1H), \(4.99-4.93\) (d, \(J=25.6Hz\), 2H), \(4.9\) (d, \(J=1.3Hz\), 1H), \(4.88-4.85\) (d, \(J=11.3Hz\), 1H), \(3.73-3.68\) (d, \(J=21.2Hz\), 1H), \(3.49-3.38\) (d, \(J=42.3Hz\), 2H); \(^{13}\)C NMR (400 MHz, DMSO, ppm) \(\delta 169.47, 158.17, 136.32, 135.81, 135.75, 128.71, 128.51, 128.5, 120.75, 74.74, 73.66, 72.72, 68.86, 61.76\); FTIR (KBr, cm\(^{-1}\)): 1736.5 (C=O), 1662.2 (C=C). ESI-MS [M+H]\(^+\): calculated: 357.3740, found: 357.1329.
Compound (4) (1,8-octanediol-co-citrate-co-2, 3-di-benzyl-L-ascorbic acid) prepolymer was prepared using the APDS-based method as follows: citric acid, 1,8-octanediol, and 2, 3-dibenzyl-L-ascorbic acid (compound (3)) were mixed at a mole feed ratio of 5:5:1. The mixture was melted at 200°C under nitrogen flush for 10 minutes. The mixture was then transferred to 140°C for curing under nitrogen flush until the speed of the stir bar reduced to 100 rpm. The reaction was stopped by incubation of the flask in an ice bath for 20 minutes. The prepolymer was dissolved in ethanol to make a 60 wt% solution and then aliquotted into 50 mL plastic centrifuge tubes (4 g per tube) for water precipitation. The resulting precipitated prepolymer was lyophilized for 3 days for further use. Compound (4): 1H NMR (400 MHz, DMSO, ppm) δ 7.43-7.31 (-C6H52-, from AA), 5.27-5.19 (-C2H5O-, from AA), 4.99-4.93 (-C2H5O-, from AA), 4.90-4.89 (-OCH(CH)C-CH-, from AA), 4.04-3.95 (-OCH2CH2(CH2)4-, from OD), 3.73-3.68 (-OCH(CH)CH2-, from AA), 3.47-3.41 (-OCH2CH-, from AA), 3.47-3.33 (-CH2CH2CH2O-, from OD), 2.87-2.63 (-OCOC\text{H}2\text{C(OH)}\text{CH}2-\text{OCO}-, from CA), 1.53-1.26 (-OCH2 \text{(CH}2\text{)}\text{6} \text{CH}2\text{O-}, from OD).

Compound (5) (1,8-octanediol-co-citrate-co-L-ascorbic acid) prepolymer was prepared by dissolving compound (4) in excess methanol and placing into an autoclaved vessel with 10% palladium on carbon as a catalyst for hydrogenolysis. The mixture was incubated under 56 psi hydrogen gas at room temperature for 4 hours. Palladium on carbon catalyst was removed by filtration, followed by centrifugation to completely remove any remaining catalyst from solution. The final product was collected by evaporation in vacuum oven for 3 days to completely remove a small amount of residual toluene. Compound (5): 1H NMR (400 MHz, DMSO, ppm) δ 4.71 (-OCH(C)CH-, from AA), 4.04-3.95 (-OCH2CH2(CH2)4-, from OD), 3.73-3.71 (-OCH(CH)CH2-, from AA), 3.44-3.4 (-OCH2CH-, from AA), 3.32 (-CH2CH2CH2O-, from OD), 2.86-2.63 (-OCOC\text{H}2\text{C(OH)}\text{CH}2-\text{OCO}-, from CA), 1.53-1.26 (-OCH2 \text{(CH}2\text{)}\text{6} \text{CH}2\text{O-}, from OD).
**Compound (6)** poly(1,8-octanediol-co-citrate) was prepared as follows: citric acid and 1,8-octanediol were mixed together at a mole feed ratio of 1:1. Citric acid and 1,8-octanediol were melted at 165°C under nitrogen gas flush for 10 minutes. The mixture was then transferred to 140°C for curing under nitrogen gas flush for 1 hour. The reaction was stopped by incubation of the flask in an ice bath for 20 minutes. The crude prepolymer was dissolved in ethanol to make a 60 wt% solution and then aliquotted into 50 mL plastic centrifuge tubes (4 g per tube) for water precipitation. The resulting prepolymer was lyophilized for 3 days for further use. **Compound (6)**: $^1$H NMR (400 MHz, DMSO, ppm) 4.04-3.95 (-OC\textsubscript{H}2\textsubscript{CH}(CH)\textsubscript{2}-, from OD), 3.47-3.33 (-CH\textsubscript{2}\textsubscript{4}CH\textsubscript{2}OH-, from OD), 2.87-2.63 (-CO-C\textsubscript{H}2C(OH)CH\textsubscript{2}-OCO-, from CA), 1.53-1.26 (-OCH\textsubscript{2}(CH\textsubscript{2})\textsubscript{6}CH\textsubscript{2}O-, from OD).

**Compound (7)** poly(1,8-octanediol-co-citrate-co-L-ascorbate) was prepared as follows: citric acid, 1,8-octanediol, and L-ascorbic acid were mixed at a mole feed ratio of 5:5:1. The mixture was melted at 165°C under nitrogen gas flush for 10 minutes. The mixture was then transferred to 140°C for curing under nitrogen gas flush for 1 hour. The reaction was stopped by incubation of the flask in an ice bath for 20 minutes. The prepolymer was dissolved in ethanol to make a 60 wt% solution and then aliquotted into 50 mL plastic centrifuge tubes (4 g per tube) for water precipitation. The resulting precipitated prepolymer was lyophilized for 3 days for further use. **Compound (7)**: $^1$H NMR (400 MHz, DMSO, ppm) δ 4.71 (-OCH(C)CH-, from AA), 4.04-3.96 (-OCH\textsubscript{2}CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{4}CH-, from OD), 3.73-3.71 (-OCH(CH)CH\textsubscript{2}-, from AA), 3.46-3.4 (-OCH\textsubscript{2}CH-, from AA), 3.32 (-CH\textsubscript{2}\textsubscript{4}CH\textsubscript{2}OH-, from OD), 2.87-2.63 (-CO-C\textsubscript{H}2C(OH)CH\textsubscript{2}-OCO-, from CA), 1.53-1.26 (-OCH\textsubscript{2}(CH\textsubscript{2})\textsubscript{6}CH\textsubscript{2}O-, from OD).
Figure S1. GPC analysis of POC, Un.POCA, and APDS POCA prepolymer. POC and Un.POCA prepolymer were synthesized with heating at 165°C for 10 minutes and at 140°C for 60 minutes. APDS POCA prepolymer was prepared with heating at 200°C for 10 minutes and at 140°C until the stir bar speed reduced to 100 rpm.
Figure S2. Mass spectra of (A) POC, (B) Un.POCA, and (C) APDS POCA prepolymers.
Figure S3. ATR-FTIR comparisons of (A) Un.POCA elastomer and prepolymer, and (B) APDS POCA elastomer and prepolymer.

Figure S4. AFM (top) and SEM (bottom) images of (A, D) POC elastomer, (B, E) Un.POCA elastomer, and (C, F) APDS POCA elastomer surface morphology.
Figure S5. (A) POC, Un.POCA, and ADPS POCA elastomer mass remaining after incubation in 1×PBS at 37°C for 12 weeks. (B) Ascorbate release, determined by AA kit, from Un.POCA, and ADPS POCA elastomer after incubation in 1×PBS at 37°C for 6 weeks.

Figure S6. TGA analysis of POC, Un.POCA, and APDS POCA elastomers under nitrogen atmosphere.
Figure S7. (A) GSNO and (B) SNAP standard curves determined by Hg²⁺-based Griess reaction.

Figure S8. Adhesion rate of (A) HASMCs and (B) HAECs after 2 hours and 6 hours in culture on polymer films. The percentage represents the number of adhered vascular cells compared to the initial number of seeded vascular cells.
NMR Spectra

2,3-di-MEM-L-ascorbic acid

Compound (1)
Compound (6)

Compound (7)