Electronic Supplementary Material (ESI) for Chemical Communications

Electronic Supporting Information (ESI) of the paper entitled

Synthesis of novel lidocaine-releasing poly(diol-co-citrate) elastomers by using deep eutectic solvents

By M. Concepción Serrano et al.

Experimental Part

Chemicals

All chemicals were purchased from Sigma-Aldrich and used as received.

Polymer synthesis

Prepolymer DES-assisted synthesis was initiated upon addition of citric acid to DESs composed of lidocaine and 1,8- octanediol in a 1:3 molar ratio (*e.g.* DESLO13). The DES of choice was DESLO13 because the excess of 1,8-octanediol not participating in the formation of the DES was more readily available for polycondensation with citric acid. Besides, citric acid was fully dissolved in DESLO13 within the first 6-8 hours even when the temperature was maintained at 90 °C during prepolymer synthesis. The resulting prepolymer solution was aged at 80 °C over different times to obtain the crosslinked polymer. Synthesis temperature was controlled by using a temperature probe with an accuracy of ±5 °C.

The addition of citric acid to DESLO11 failed in the formation of an elastomer because, in this case, 1,8-octanediol was strongly interacting with lidocaine (see DSC) and hence, not available for polycondensation. Moreover, the solubility of citric acid in DESLO11 was not as good as in DESLO13 and part of citric acid remained in suspension 12 hours after its addition.

Conventional POC synthesis (in absence of lidocaine) was performed as previously described (*e.g.* several minutes at 160-165 °C followed by 60 min at 140 °C for prepolymer synthesis and subsequent aging at 80 °C over different times) [references 4 and 5 in the main text].

We also attempted to incorporate lidocaine in a conventional POC synthesis. However, the addition of lidocaine to a solution composed of 1,8-octanediol and citric acid at 160 °C raised in fumes that were not observed when conventional POC synthesis was carried out in absence of lidocaine.

When the conventional POC synthesis (*i.e.* in absence of lidocaine) was carried out at 90 °C (rather than at 160 °C), part of citric acid remained as a precipitate even 12 hours after its addition to 1,8-octanediol. It is worth noting that the stoichiometric excess of carboxylic groups in citric acid versus hydroxyl groups in 1,8-octanediol seemed to compensate this situation, and the elastomer resulting from this prepolymer (aged at 80 °C) exhibited M_c values in range to those obtained for conventional POC elastomers.

Samples characterization

^{1}H NMR spectra (500 MHz) were recorded using a Bruker spectrometer DRX-500. DESs samples were placed in capillary tubes and analyzed in DMSO-d_6 as external reference (δ: 2.5ppm) at 80 °C, well about the melting points of components. ^{1}H NMR spectra of DESLO11, DESLO12 and DESLO13 are included in the *supporting information* as **Fig. 1-SI**. Prepolymer samples were analyzed in DMSO-d_6 as a solvent, while released products were placed in capillary tubes using deuterium water and analyzed in chloroform as external reference (δ: 1.60, 4.80 and 7.30 ppm). ^{1}H NMR spectra of prepolymers obtained from DESLO13 (POCDESLO133) and in conventional conditions are included in the *supporting information* as Fig. 3-SI and Fig. 4-SI, respectively.

DSC studies were performed using a Calorimeter DSC Q-100. Briefly, samples were exposed to an initial cooling segment from room temperature to -90 °C at 5 °C min^{-1}, followed by an isothermal segment at -90 °C held for 10min, then ramped from -90 °C to 100 °C at 5 °C min^{-1}, and finally cooled from 100 °C to -90 °C at 5 °C min^{-1}. This cycle was repeated twice and the behaviour on the second cycle was used to determine the thermal transitions of the samples.

The degree of post-polymerization was evaluated by calculating the molecular weight between cross-links (M_c) by swelling studies in DMSO [reference 30 in the main text].

Mechanical characterization

The complex Young's modulus (viscoelastic behaviour) of samples soaked in distilled water at 37 °C overnight was measured by Dynamic Mechanic analyser at 1 Hz in triple point bending configuration using a DMA 7e from Perkin Elmer. The force used in the experiment has been chosen not to produce strains larger than 0.3% in order to maintain the mechanical response within the linear range. The dimensions of the samples were parallelepipeds of 12 x 2.5 x 3 mm^3. Data was collected by triplicate. The error in the measurement was estimated around 20% (intrinsic to the measurement technique), which allows comparison between the outgoing data.

Controlled release studies

Polymer samples (0.5 cm^3 in volume, *ca.* 200 mg in mass) were incubated at 37 °C in phosphate buffer saline (PBS, 0.1M) and distilled water (10 ml) for different times. For each collection, polymer samples were transferred to clean tubes and fresh solution added to continue the release. Supernatants were freeze-dried to recover released products (^{1}H NMR spectrum is included in the *supporting information* as Fig. 4-SI) and dissolved in either PBS or ethanol. LD release was monitored in the supernatants by absorbance measurements at 260nm by using a Cary-4000 UV-Vis spectrophotometer (Varian). Lidocaine standard curve used to convert absorbance values to concentration is included in the *supporting information* (Fig. 5-SI). Release studies in distilled water are included as Figure 6-SI for comparison.

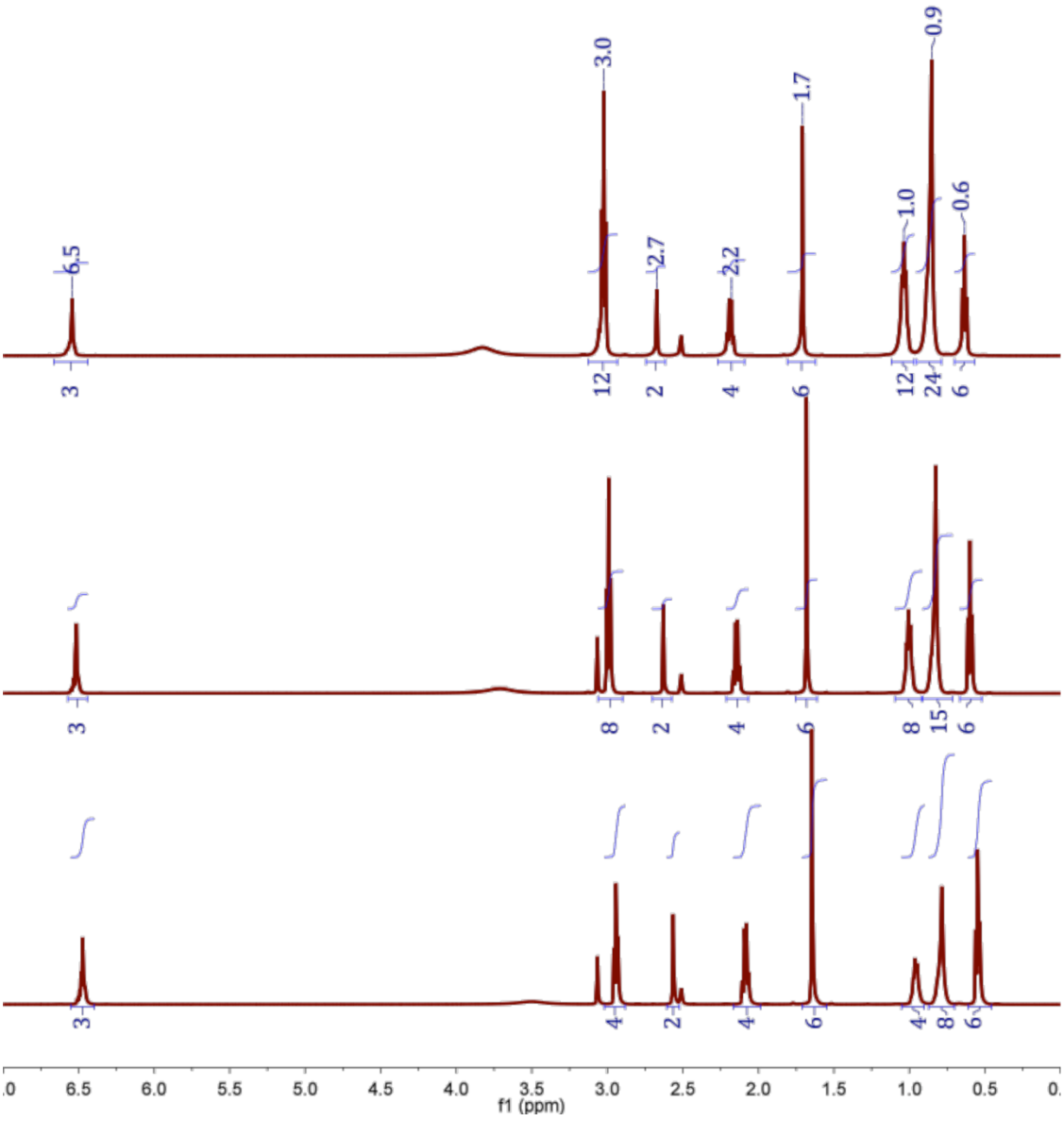

Figure 1-SI. ^{1}H-NMR spectra of DESLO11 (bottom), DESLO12 (middle) and DESLO13 (top).

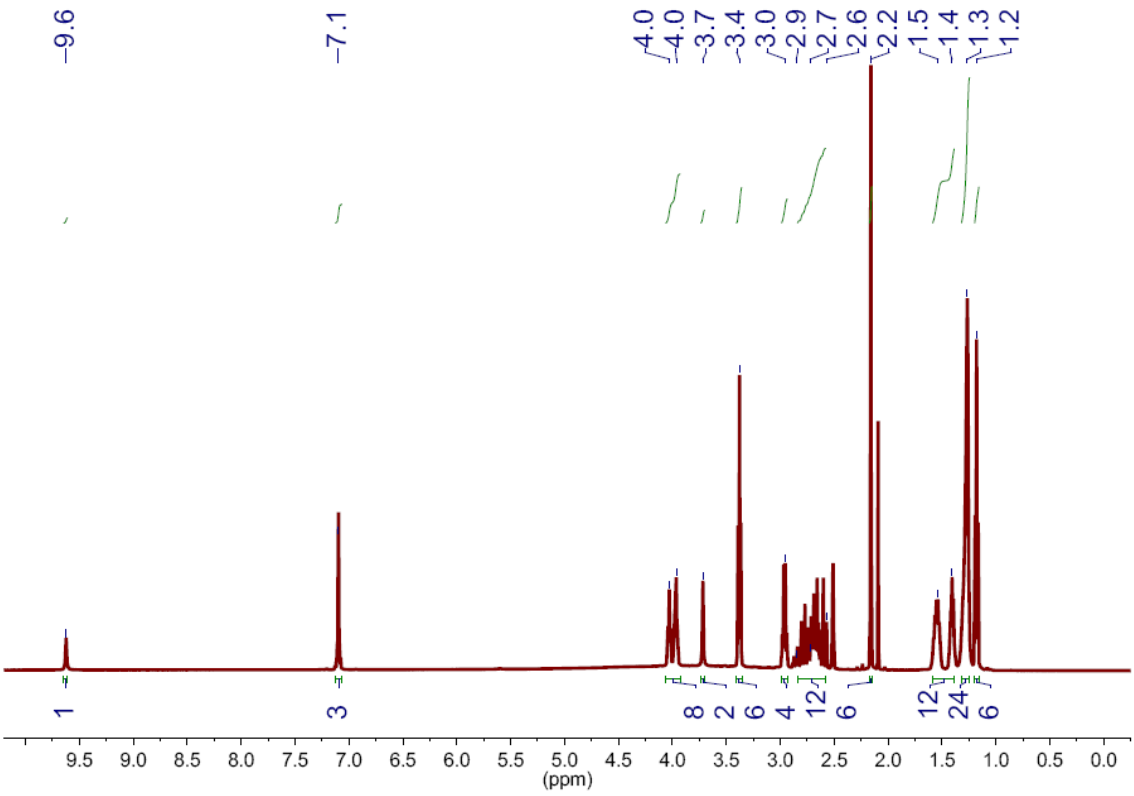

Figure 2-SI. ^{1}H-NMR spectrum of the prepolymer obtained from POCDESLO133.

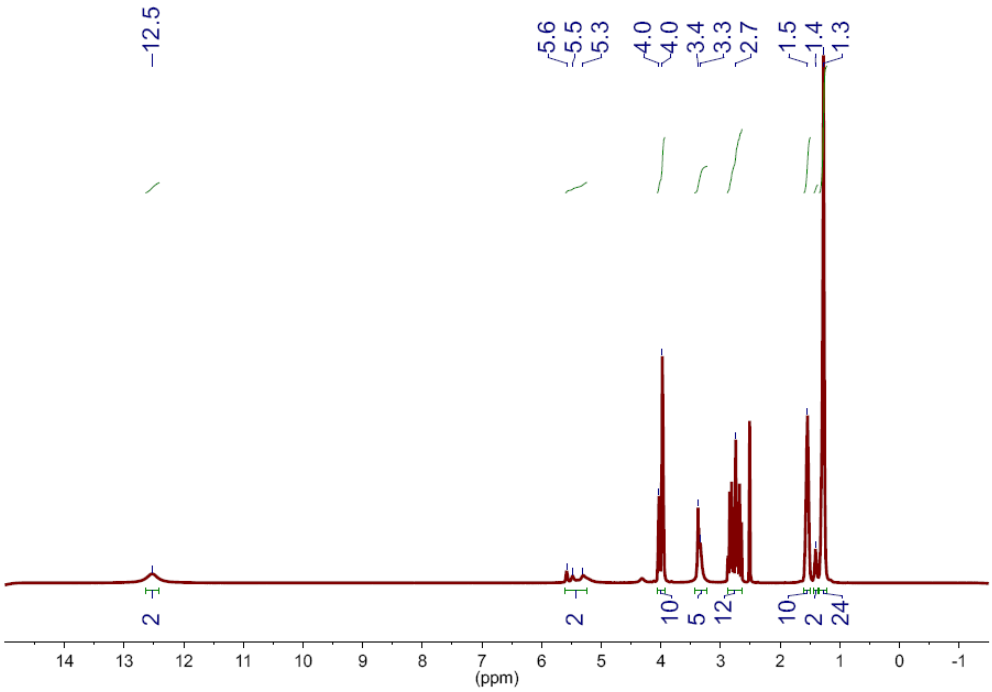

Figure 3-SI. ^{1}H-NMR spectrum of POC prepolymer synthesized in standard conditions.

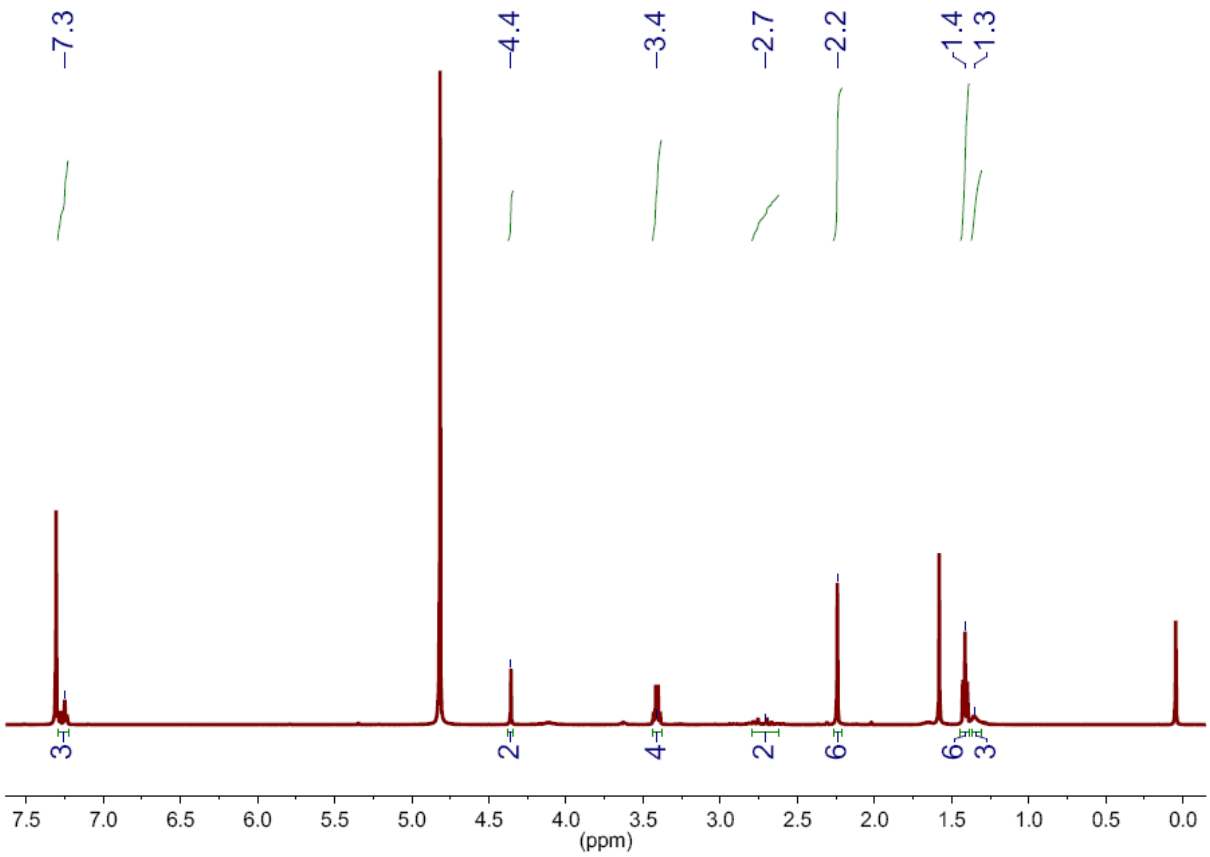

Figure 4-SI. ^{1}H-NMR spectrum of the products released from POCDESLO133 in distilled water. The chemical shifts at 1.41, 2.24, 3.30, 4.36, and 7.25 ppm correspond to lidocaine. As mentioned in the main text, there was a certain release of POC oligomers as a consequence of the intrinsic biodegradable character of these elastomers. The integrals of the peaks assigned to the released oligomers revealed a 2:1 molar ratio of citric acid:1,8-octanediol in the released products. Please notice that this 2:1 molar ratio does not refer to the molar ratio of citric acid and 1,8-octanediol used in the synthetic process. The most plausible molecular structure fitting with this molar ratio corresponds to one 1,8-octanediol molecule condensed at both ends with citric acid (two molecules, one at every end). Interestingly, an oligomer holding this molecular structure is the most hydrophilic one among all the different possibilities. The preferred release of this particular oligomer is not surprising considering that the solution used for the release experiments was water.

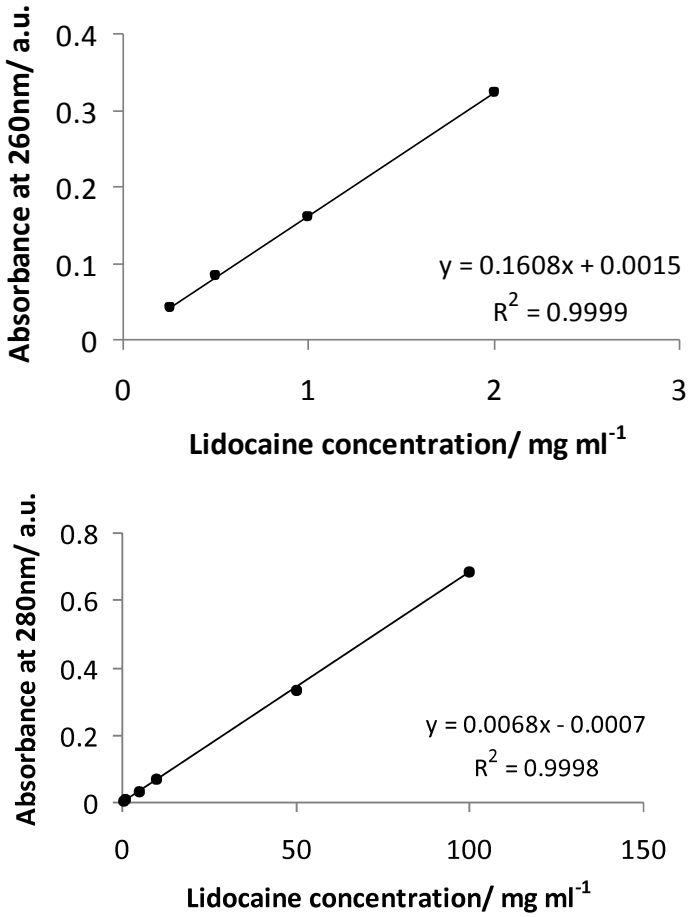

Figure 5-SI. Linear correlation of lidocaine concentration *vs* absorbance at 260nm in PBS (top) or ethanol (bottom) (standard curves).

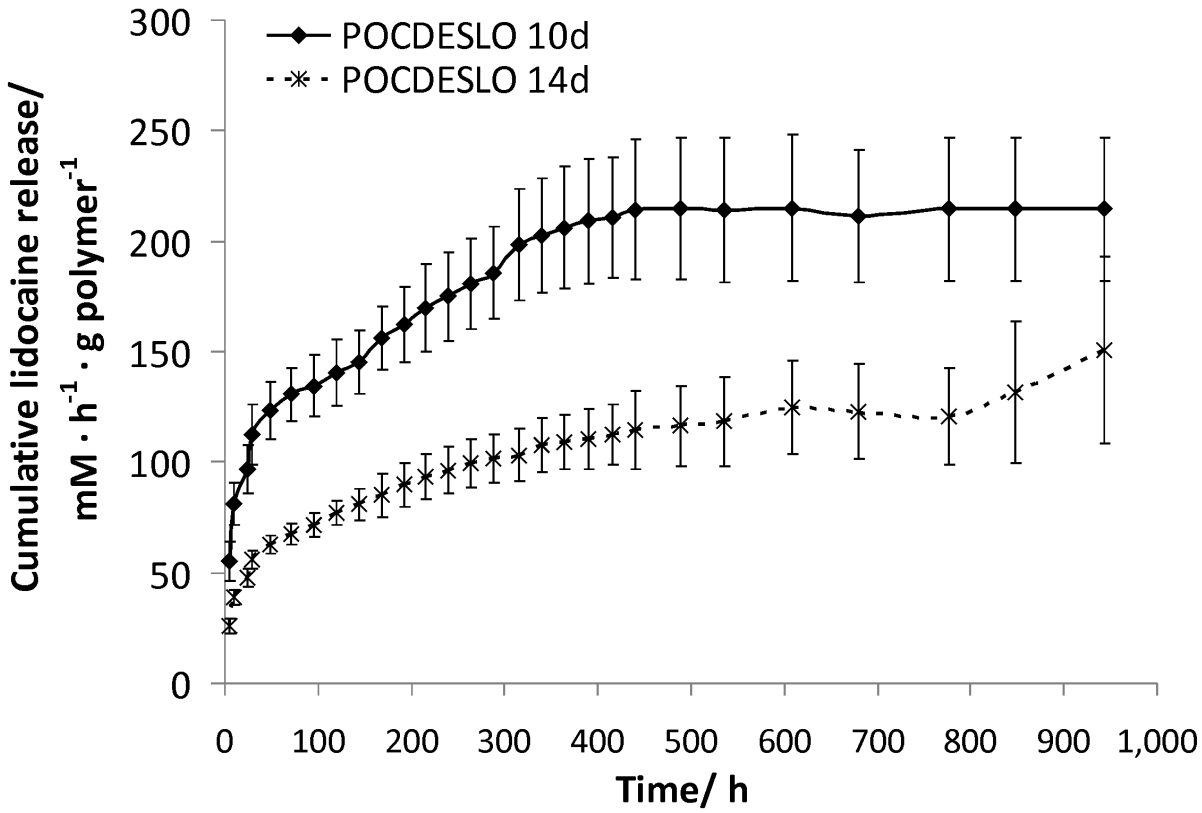

Figure 6-SI. Cumulative lidocaine release in distilled water (measured by absorbance at 280 nm) from POCDESLO133 elastomers with different crosslinking degrees.