

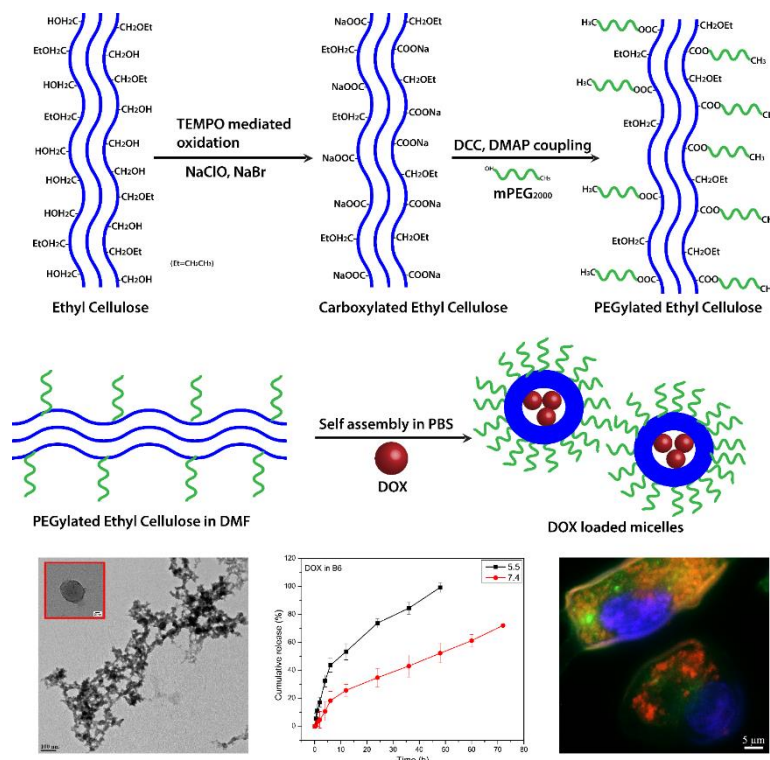
Supplementary Information

PEGylated Ethyl Cellulose Micelles as Nanocarrier for Drug Delivery

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Mechanism of oxidation: In the TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl) oxidation system, NaClO (sodium hypochlorite) and NaBr (sodium bromide) act as a primary and secondary oxidant respectively. The mechanism proceeds in two steps as shown in Figure S1. In the first step TEMPO selectively attacks the primary C6 hydroxyl group and converts it into an aldehyde group. In the second step, the aldehyde group converts to a carboxylic acid

group by NaClO. The reaction is performed in alkaline conditions since TEMPO decomposes in acidic media to hydrogenated derivative TEMPO-H, rather than its nitronium ion form. At higher pH > 10.5, the secondary oxidant used in the reaction starts consumption of OH⁻ ion to generate NaOH and $\dot{O}Cl$ radical, which retards the reaction. In some cases, the use of buffer solutions was reported to maintain the pH of reaction media (Isabel et al., 2006).

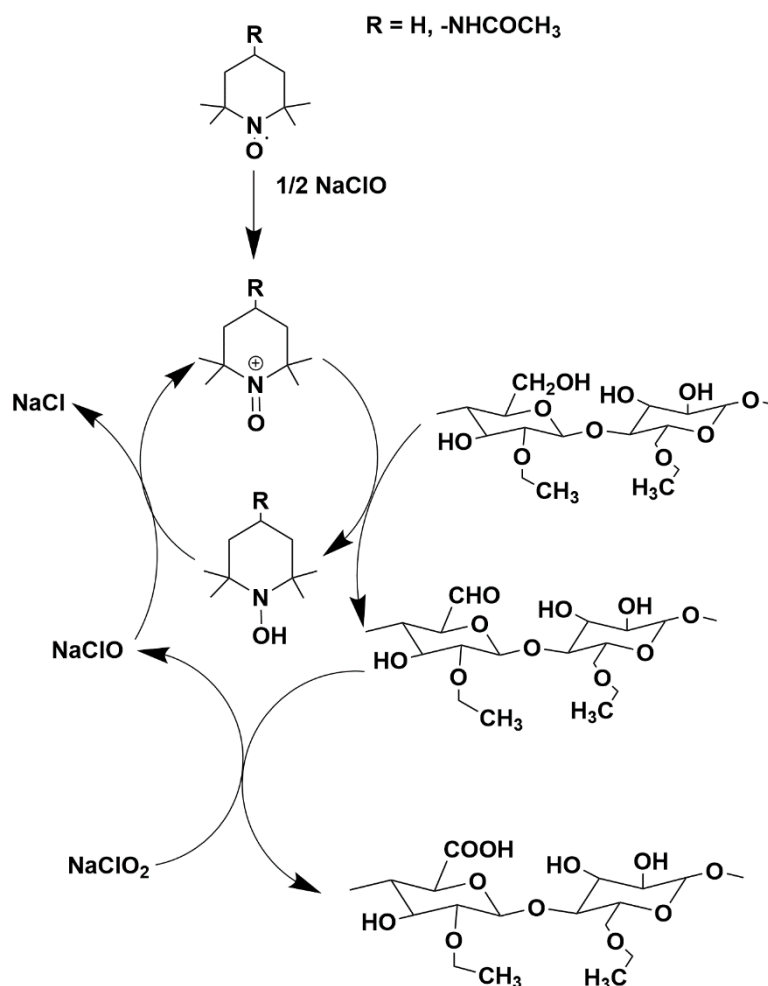


Figure S1: Scheme of TEMPO mediated oxidation of EC.

Conductometric titration and charge density estimation: The carboxylation of EC after TEMPO mediated oxidation was confirmed by conductometric titration. Briefly, carboxylated EC (CEC) was dispersed in 10 mL DI water at a concentration of 8 mg/mL by bath sonication and diluted to 80 mL DI water. The dispersion was properly stirred and a calibrated conductivity probe was dipped into the dispersion. 50 μ L of 12N HCl was added to this CEC dispersion which precipitated the CEC whiskers. To neutralize the acid groups, 20 μ L (0.5M) NaOH solution was added to this dispersion in a stepwise manner and the conductivity of the

solution was noted till the endpoint reached and the conductivity raised again. From the values of conductivity measured after the subsequent addition of NaOH in a stepwise fashion, a titration graph was plotted. From the titration graph, as represented in Fig S2, it is noted that there are two equivalence points (EP). The first EP is observed when the anions of the HCL are neutralized by the addition of NaOH. The next EP denotes the point where the carboxyl groups present on the oxidized EC were neutralized by the NaOH. The curve begins to rise again because of the conductivity of the excess OH⁻ ions of NaOH. The difference between the two EP's corresponds to the volume of NaOH needed to neutralize the accessible carboxylate groups on EC. This volume can be used to determine the charge density on EC as shown in the following equations.

From the graph we calculated the carboxylate charge density on EC

$$\text{Volume of NaOH } (\mu\text{L}) = \Delta x - x$$

$$\text{For } x: -1.564x + 2152 = 0.1185x + 534.24$$

$$\text{For } \Delta x: 0.1185x + 534.24 = 1.385x - 810.01$$

Solving the above equations, we got 100 μL

$$\begin{aligned} \text{Charge density (mmol/kg)} &= (\text{Vol. of NaOH (mL)} * 0.5) / (1000 * \text{mg of whiskers} * 10^{-6}) \dots \text{Eq S1} \\ &= (0.100 * 0.5) / (1000 * 80 * 10^{-6}) = \sim 625 \text{ mmol/kg.} \end{aligned}$$

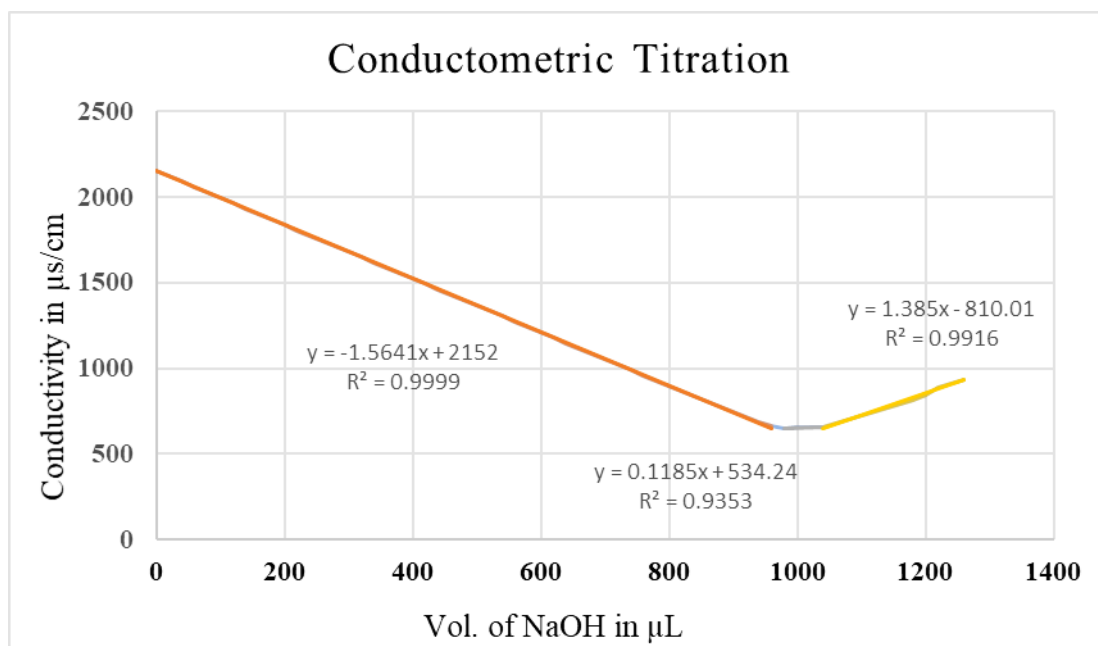


Figure S2: Graph of conductometric titration of CEC-HCl dispersion with NaOH.

^1H NMR:

^1H NMR (200 MHz) of mPEG: δ 3.92 ($-\text{OCH}_2\text{CH}_2\text{O}-$) (m, 4 H), δ 3.65 ($\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$) (m, 3 H).

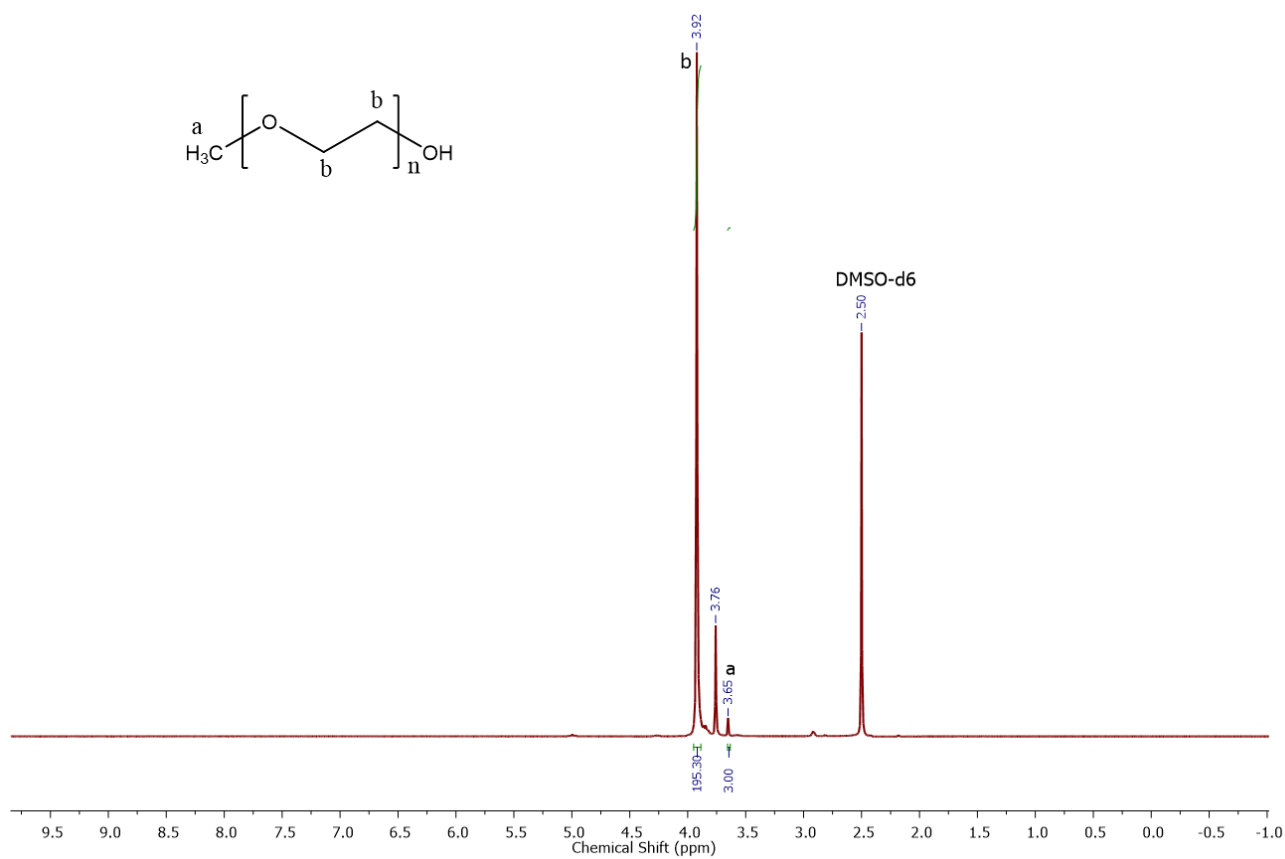


Figure S3. ^1H NMR spectrum of mPEG₂₀₀₀ in DMSO-d₆, recorded on Bruker AV-200 NMR.

¹³C NMR:

¹³C NMR of CEC: δ 15.75 ($\text{CH}_3\text{CH}_2\text{O}-$), δ 68.69 ($\text{CH}_3\text{CH}_2\text{O}-$), δ 103.84 ($-\text{OCHO}-$), δ 174.14 ($\text{OHCOCH}-$), δ 75.43 and 82.93 (C of the backbone of EC from C2 to C5).

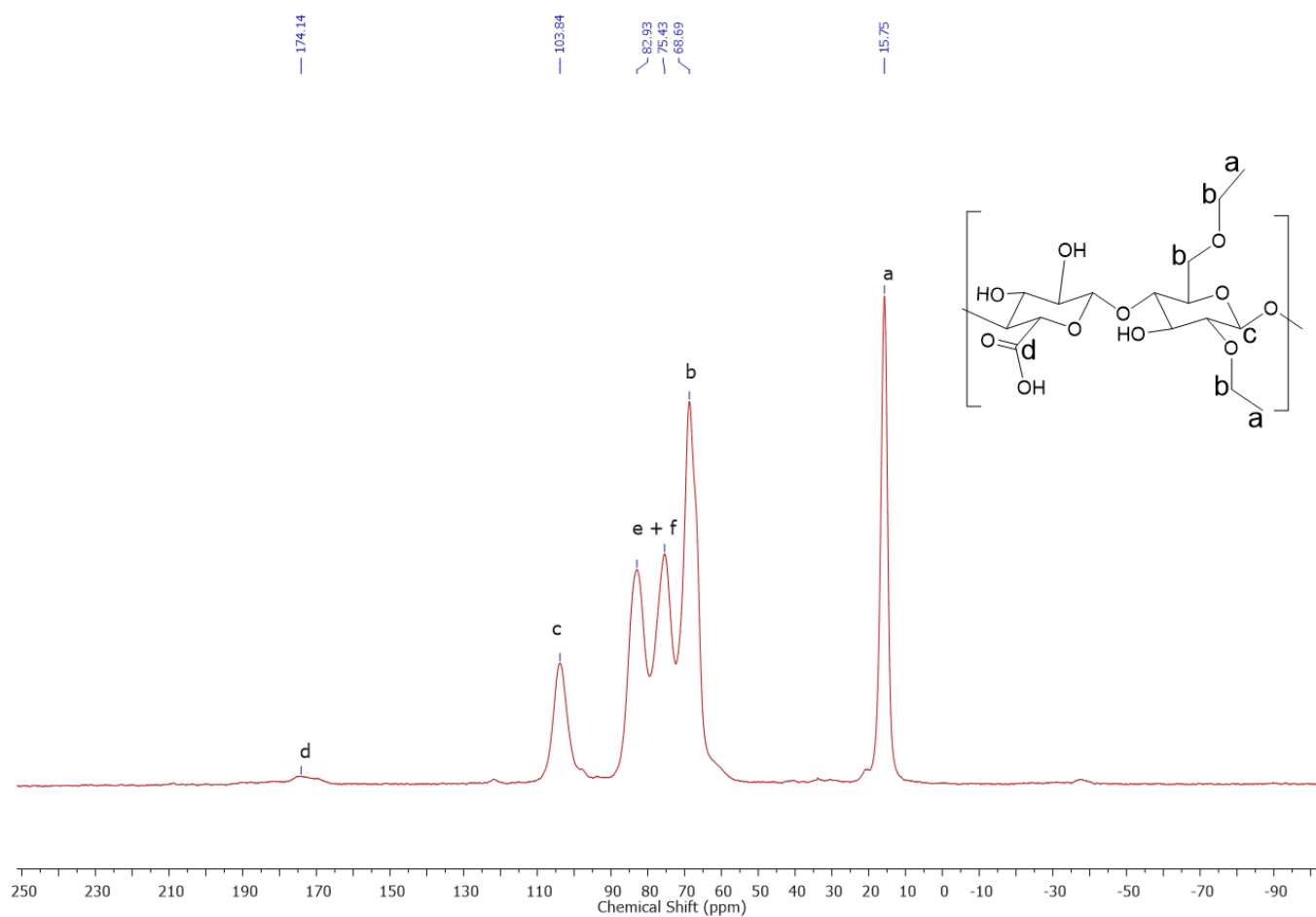


Figure S4. Solid state ¹³C NMR spectrum of CEC recorded on Bruker NMR spectrometer.

^{13}C NMR (125 MHz) of mPEG: δ 58.34 (CH_3OCH_2-), δ 60.49 ($-\text{OCH}_2\text{CH}_2\text{OH}$), δ 69.96 ($-\text{OCH}_2\text{CH}_2\text{OH}$), δ 70.16 ($-\text{OCH}_2\text{CH}_2\text{OCH}_2-$), δ 71.66 ($-\text{OCH}_2\text{CH}_2\text{OCH}_2-$), δ 72.67 ($\text{CH}_3\text{OCH}_2\text{CH}_2\text{O}-$).



Figure S5. ^{13}C NMR spectrum of mPEG₂₀₀₀ in DMSO-d₆, recorded on Bruker AV-500 NMR.

^{13}C NMR (125 MHz) of EC-PEG1: δ 15.75 ($\text{CH}_3\text{CH}_2\text{O}-$), δ 58.45 (CH_3OCH_2-), δ 69.98 ($\text{CH}_3\text{CH}_2\text{O}-$), from 60 ppm to 73 ppm all peaks observed in the spectrum of mPEG merged into the peaks of CEC backbone with an intense peak at δ 70.18 ($\text{CH}_3\text{OCH}_2\text{CH}_2\text{O}-$) due to the repeating unit of mPEG₂₀₀₀.

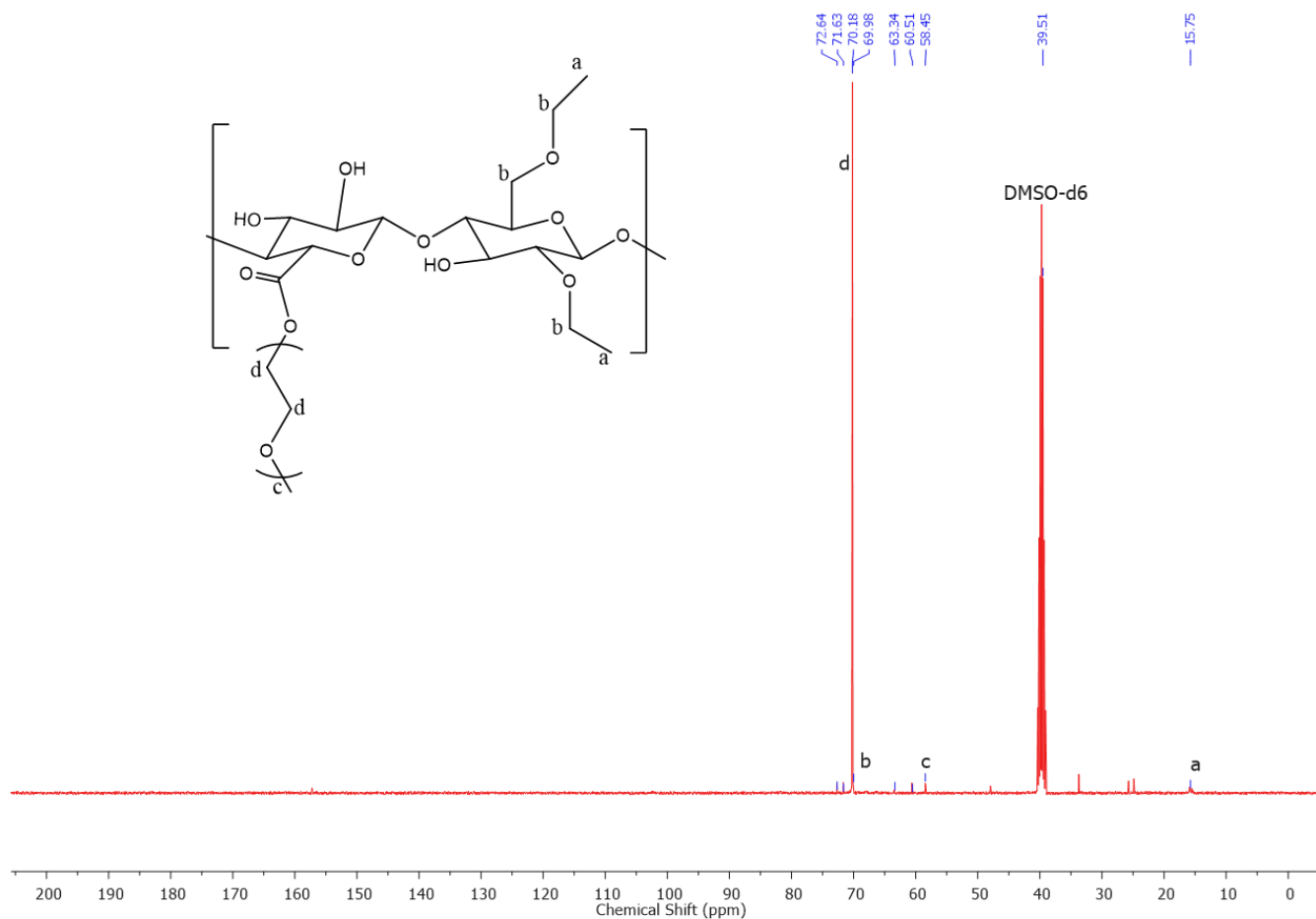


Figure S6. ^{13}C NMR spectrum of EC-PEG1 in DMSO-d₆, recorded on Bruker AV-500 NMR. [Note: The unassigned peaks are due to the traces of DCU (Dicyclohexylurea) formed during the DCC (N,N'-Dicyclohexylcarbodiimide) coupling].

FTIR:

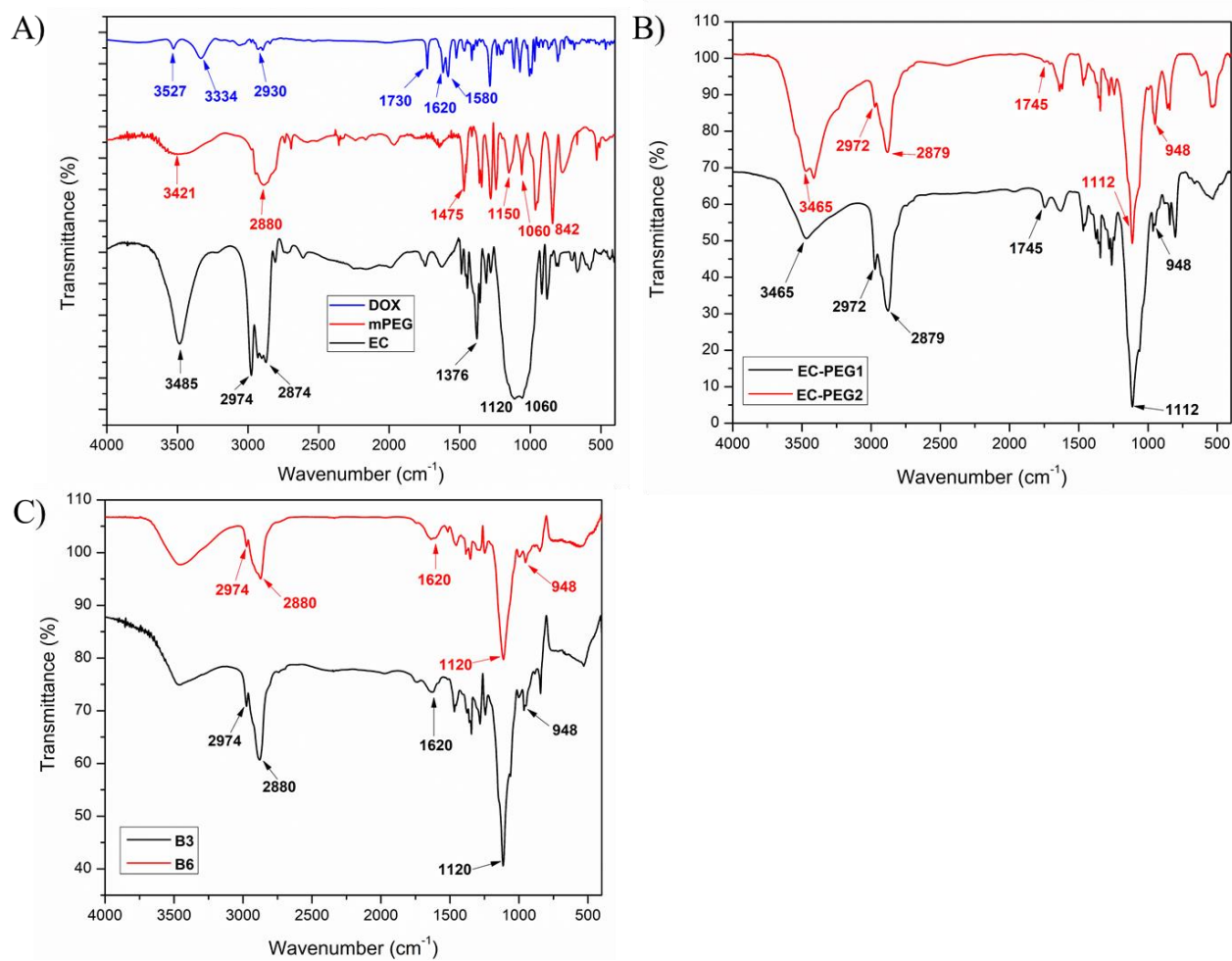
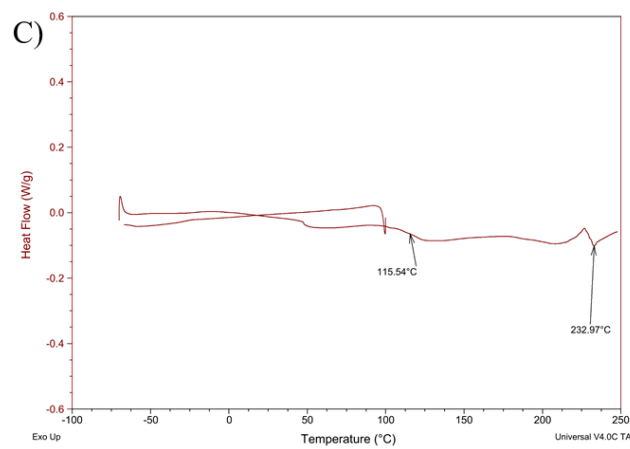
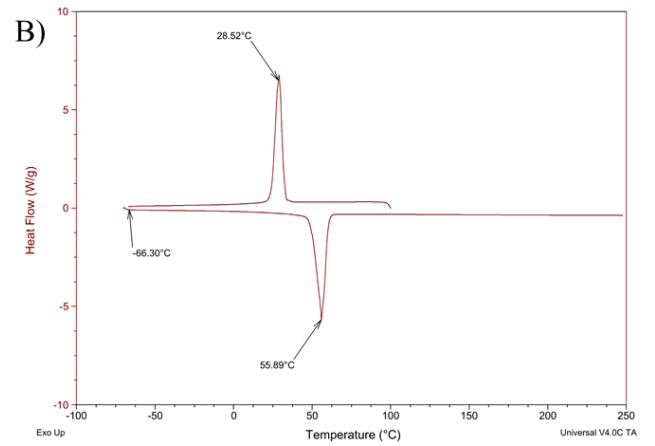
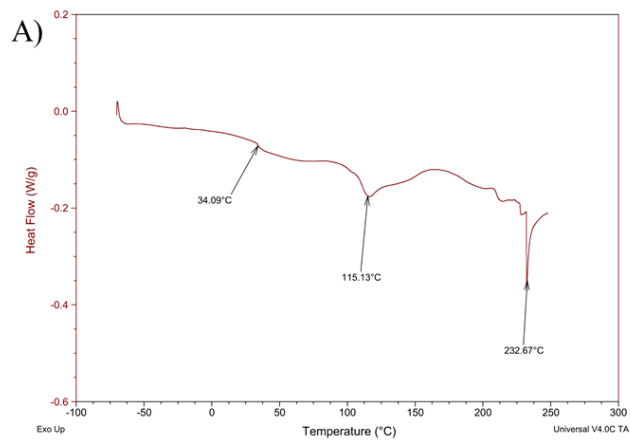


Figure S7. FTIR spectrum of A) EC, mPEG, DOX, B) EC-PEG1 and EC-PEG2, C) B3 and B6 micelles.

DSC:



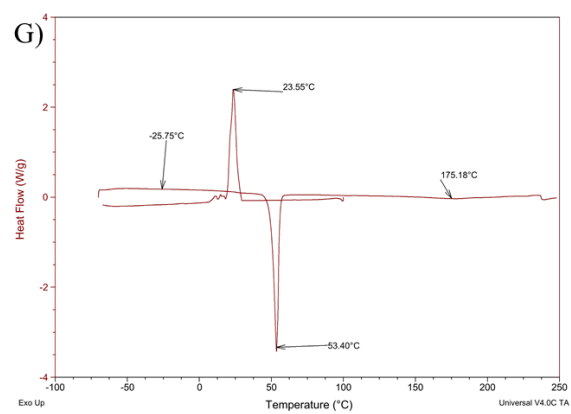
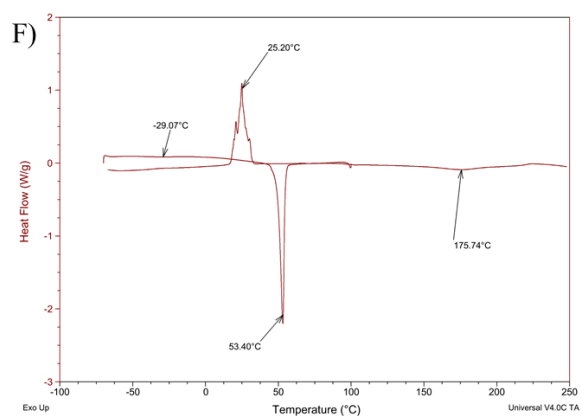
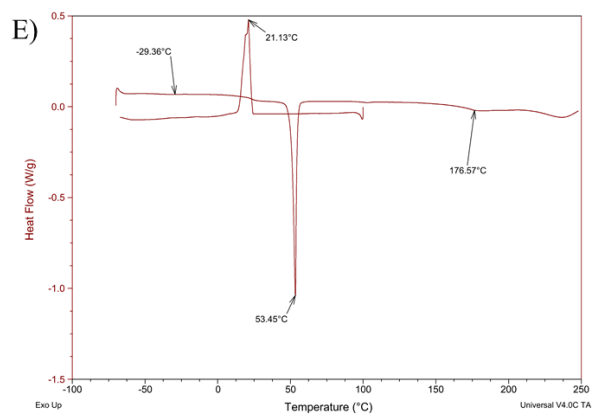
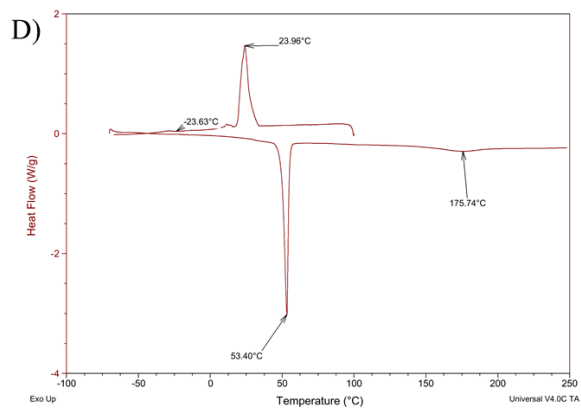


Figure S8: DSC thermograms of A) EC, B) mPEG, C) CEC, D) B1 micelles, E) B4 micelles, F) B3 micelles, G) B6 micelles.