# Electronic Supplementary Information

## In situ Gelling Hydroxypropyl Cellulose Formulation Comprising Cannabidiol-Loaded Block Copolymer Micelles for Sustained Drug Delivery

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## EXPERIMENTAL

### Synthesis of diblock copolymers

Poly(ethylene oxide)-*block*-poly(*α*-cinnamyl-ε-caprolactone-*co*-ε-caprolactone) diblock copolymers was synthesized via two-step procedure involving ring-opening polymerization of ε-CL and *α*-propargyl-ε-caprolactone from methoxy poly(ethylene oxide) macroinitiator and subsequent grafting of cinnamyl groups via "click" reaction **[1]**.

#### *Synthesis of poly(ethylene oxide)-block-poly(α-propargyl-ε-caprolactone-co-ε-caprolactone)*

Polymerization was carried out in an oven dried 50 ml two-neck round bottom flask under an inert atmosphere. In a typical run, methoxy $PEO_{113}$-OH (1.5 g, 0.3 mmol, 1 eq.) dried by azeotropic distillation from anhydrous toluene, ε-CL (1.08 g, 9.45 mmol, 90 eq.), α-propargyl-ε-caprolactone (0.16 g, 1.05 mmol, 10 eq.), and toluene (15 mL) were placed in the flask. The solution was degassed by argon flow for 20 min and the catalyst $Sn(Oct)_2$ (21.5 mg, 0.053 mmol, 0.5 mol % of both monomers) was added, followed by further degassing for 20 min. The reaction mixture was stirred at 115 °C for 24 hours and poured into cold isopropanol. The precipitated copolymer was collected by filtration and dried thoroughly in vacuum. Yield 2.5 g. $^1$H NMR(600 MHz, $CDCl_3$) δ (ppm)= 4.21 (t, 2H, -C*H*$_2$O-), 4.05 (t, 54H, -C*H*$_2$O-), 3.50-3.82 (m, 450H, -C*H*$_2$O-), 3.37 (s, 3H, C*H*$_3$-O-), 2.53-2.58 (m, 1H, COC*H*CH$_2$), 2.43-2.49 (m, 1H, COCHC*H*$_2$), 2.35-2.42 (m, 1H, COCHC*H*$_2$), 2.30 (t, 54H, -COC*H*$_2$O-), 2.00 (2, 1H, -C≡CH-), 1.50-1.79 (m, 108H, CH$_2$-C*H*$_2$-C*H*$_2$-CH$_2$-O-), 1.30-1.48 (m, 54H, COCH$_2$C*H*$_2$).

***Synthesis of poly(ethylene oxide)-block-poly(α-cinnamyl-ε-caprolactone-co-ε-caprolactone)***

In an oven dried 50 ml two-neck round bottom flask the copolymer (4.3 % propargyl units; 1g, 0.124 mmol, 1 eq.), CuI (109.7 mg, 0.576 mmol, 4 eq.), and cinnamyl azide (45.8 mg, 0.288 mmol, 2 eq.) were added under an inert atmosphere, and degassed 3 times. After that, 5 ml of THF was added and the system was purged for approximately 20 min with inert gas, parallel to a vial of N,N-diisopropylethylamine. Finally, degassed DIPEA (74.4 mg, 0.576 mmol, 4 eq.) was added, the whole system was purged additionally with an inert gas for 20 min and the mixture was stirred at temperature 40°C for 24 h. Then, 50 ml of THF was added and the reaction mixture was passed through a neutral aluminium oxide ($Al_2O_3$) plug to remove the copper salts. The mixture was then dissolved in a minimal amount of THF and precipitated into cold isopropanol. Yield 0.98 g. $^1$H NMR(600MHz, $CD_2Cl_2$) ) δ (ppm)= 7.18-7.60 (m, 6H, Ar*H*), 4.21 (t, 2H, -C*H*$_2$O-), 4.05 (t, 54H, -C*H*$_2$O-), 3.45-3.95

(m, 450H, -C$H_2$O-), 3.40 (s, 3H, C$H_3$-O-), 2.26-2.38 (m, 54H, -COC$H_2$O-), 1.55-1.80 (m, 108H, $CH_2$-C$H_2$-C$H_2$-$CH_2$-O-), 1.33-1.46 (m, 54H, $COCH_2$C$H_2$).

***Synthesis of poly(ethylene oxide)-block-poly(ε-caprolactone)***

Polymerization was carried out in an oven dried 50 ml two-neck round bottom flask under an inert atmosphere. In a typical run, $PEG_{113}$-OH (1.5 g, 0.3 mmol,1 eq.) dried by azeotropic distillation from anhydrous toluene, ε-CL (1.2 g, 10.5 mmol, 35 eq.) and toluene (15 mL) were placed in the flask. The solution was degassed by argon flow for 20 min and catalyst $Sn(Oct)_2$ (21.5 mg, 0.053 mmol, 0.5 mol % of the monomer) was added, followed by further degassing for 20 min. The reaction mixture was stirred at 115 °C for 24 hours and poured into cold isopropanol. The precipitated copolymer was collected by filtration and dried thoroughly in vacuum. Yield 2.6 g. $^1$H NMR(600 MHz, $CDCl_3$) δ (ppm)= 4.22 (t, 2H, -C$H_2$O-), 4.05 (t, 57H, -C$H_2$O-), 3.50-3.85 (m, 450H, -C$H_2$O-), 3.37 (s, 3H, C$H_3$-O-), 2.31 (t, 57H, -COC$H_2$O-), 1.55-1.80 (m, 114H, $CH_2$-C$H_2$-C$H_2$-$CH_2$-O-), 1.33-1.43 (m, 57H, $COCH_2$C$H_2$).

***Table S1.*** *Composition and molecular characteristics of diblock copolymers.*

| Copolymer | $M_n^{(NMR)}$ (g/mol) | $M_n^{(SEC)}$ (g/mol) | $DI^{(SEC)}$ |
|---|---|---|---|
| $PEO_{113}$-b-P($CyCL_1$-co-$CL_{27}$)$_{28}$ | 8400 | 6200 | 1.04 |
| $PEO_{113}$-*b*-P($CyCL_1$-*co*-$CL_{12}$)$_{13}$ | 6680 | 5100 | 1.07 |
| $PEO_{113}$-*b*-$PCL_{29}$ | 8310 | 7950 | 1.12 |

[1] Atanasova, M-D, Grancharov, G, Petrov, PD. Poly(ethylene oxide)-*block*-poly(α-cinnamyl-ε-caprolactone-*co*-ε-caprolactone) diblock copolymer nanocarriers for enhanced solubilization of caffeic acid phenethyl ester. *J Polym Sci*. 2021; 59: 251–260.

## FIGURES

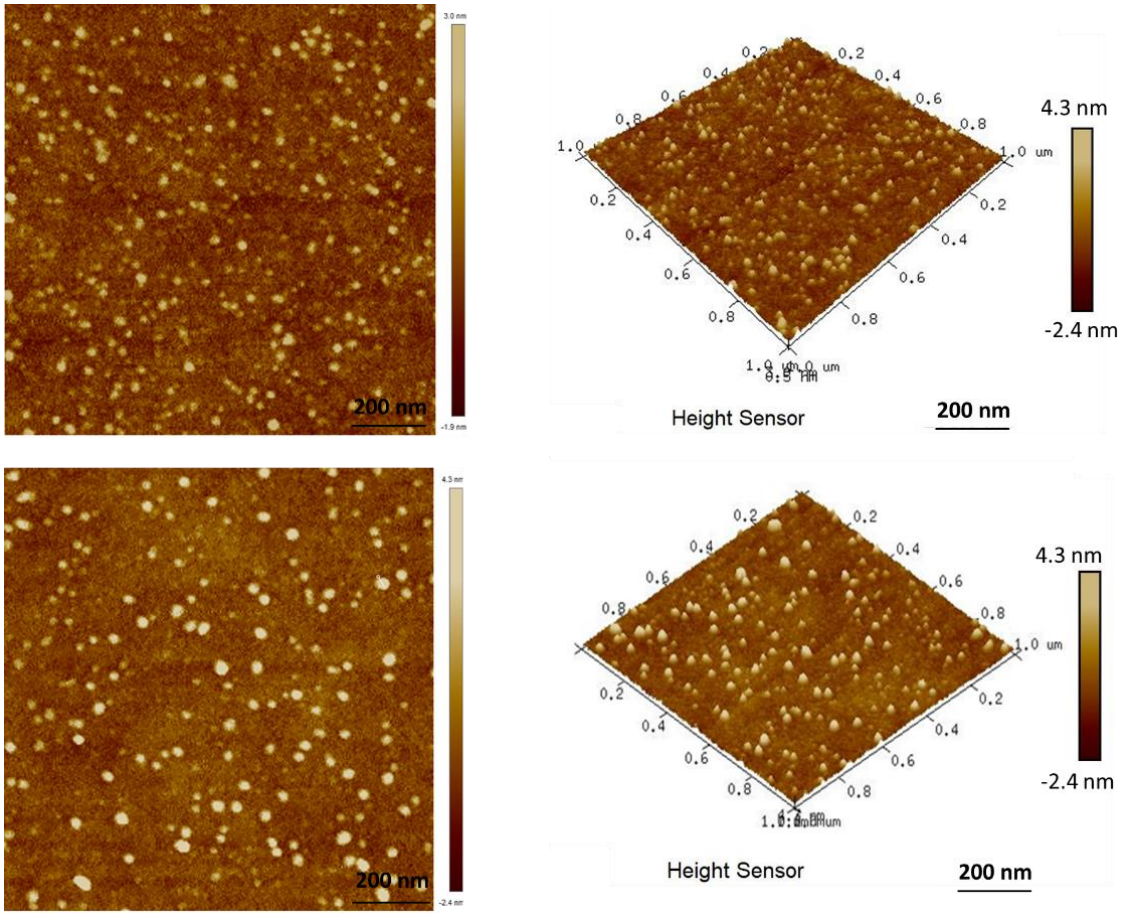
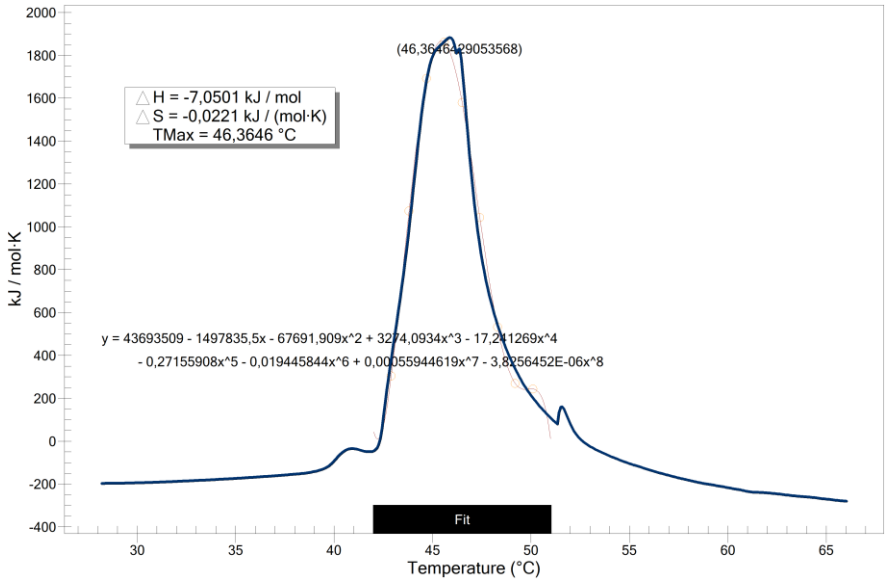



**Figure S1.** Representative 2D and 3D AFM images of blank (top) and CBD-loaded $PEO_{113}$-*b*-P($CyCL_1$-*co*-$CL_{27}$)$_{28}$ micelles (bottom).

Pure HPC



HPC + $K_2SO_4$

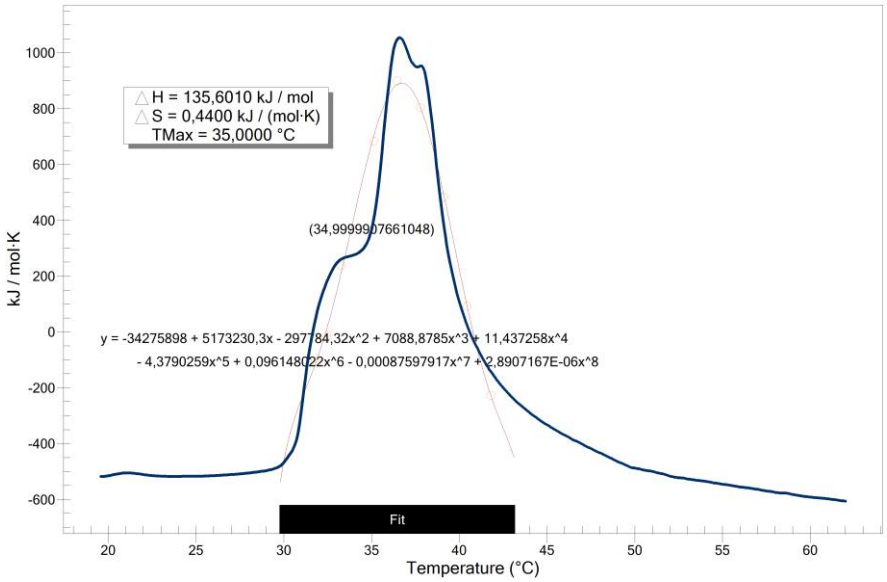



**Figure S2.** NanoDSC plots of aqueous HPC solutions (5 mass %), without (top) and with 0.15 $molL^{-1}$ $K_2SO_4$ (bottom).

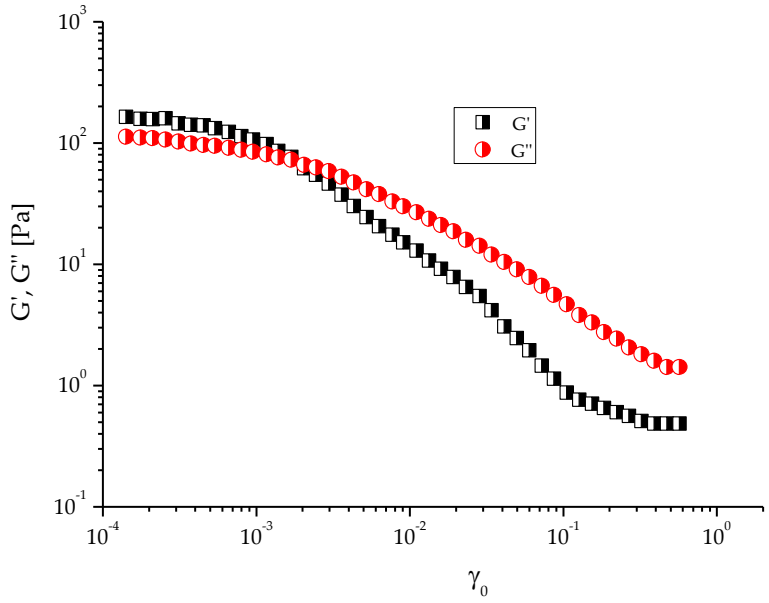



**Figure S3.** Variation in storage (G′) and loss (G′′) moduli as a function of the strain amplitude for HPC (10 mass %) hydrogel containing $K_2SO_4$ (0.15 $molL^{-1}$). The oscillation amplitude sweep tests were carried out at 37 °C at a frequency of 1 Hz in the $\gamma_0$ range from 0.0001 to 1.

**Figure S4**. Digital images of an aqueous HPC (10 mass %) solution, containing $K_2SO_4$ (0.15 $molL^{-1}$) and CBD-loaded micelles (1 $gL^{-1}$) at 25 $^oC$ (left), and the corresponding hydrogel formed at 37 $^oC$ (right).

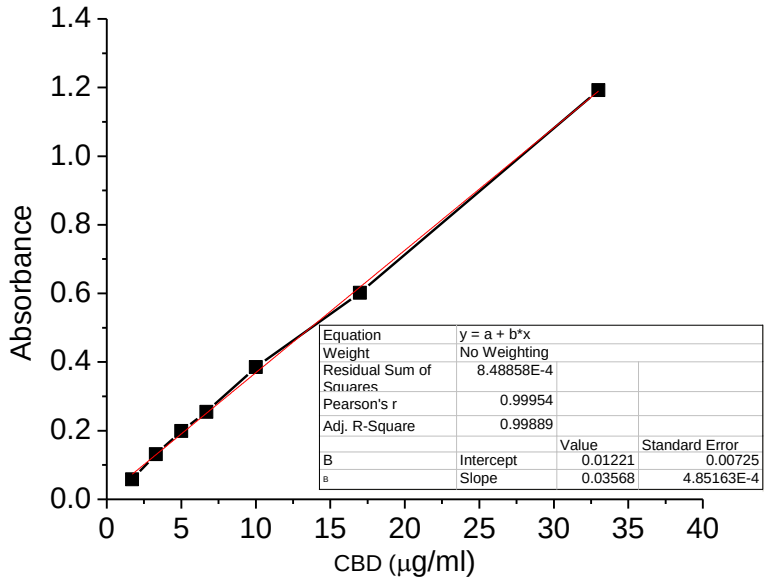



**Figure S5.** Standard curve of CBD in methanol at λ= 274 ($R^2$ = 0.99954).

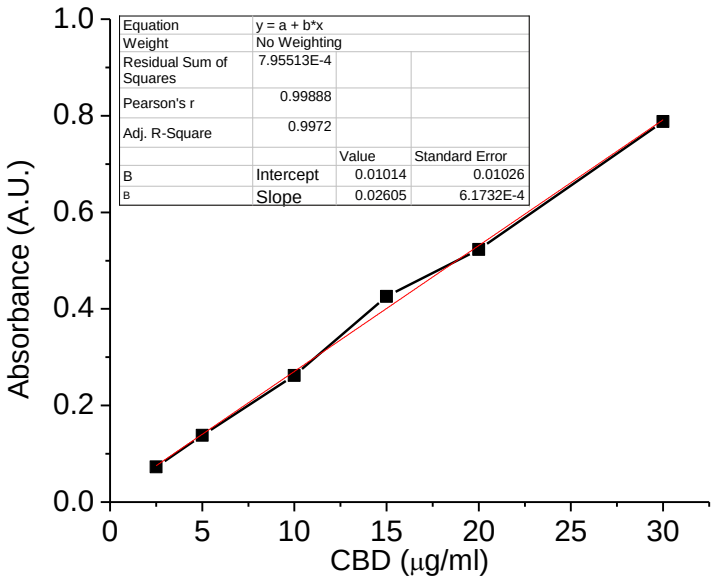



**Figure S6.** Standard curve of CBD in PBS + 5% ethanol at λ= 274 ($R^2$=0.9988).