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Real-time monitoring of the release of multiple payloads from nanomaterials

Jindaporn Janprasit, Albert Schulte,* Daniel Crespy*

Department of Material Science and Engineering, School of Molecular Science and Engineering, Vidyasirimedhi Institute of Science and Technology (VISTEC), Payupnai, WangChan, Rayong 21210, Thailand.

E-mail: albert.s@vistec.ac.th, daniel.crespy@vistec.ac.th

Experimental section

Materials

4-Hydroxybenzaldehyde (99%, Acros Organics), 8-hydroxyquinoline (8HQ, > 99%, TCI), sulfathiazole (STZ, ≥ 98%, Fluka), poly(vinyl formal) (PVF, Sigma-Aldrich), chloroform ($CHCl_3$, ≥ 99%, QRëC), dimethylformamide (DMF, 99.8%, RCI Labscan), potassium dihydrogen phosphate (KH_2PO_4, ≥ 99.5%, Merck), sodium hydroxide (NaOH, ≥ 97%, Carlo Erba) and hydrochloric acid (HCl, 37%, Carlo Erba) were used as received. All buffer solutions were prepared with ultrapure deionized water and filtered before use.

Preparation of PVF nanofibers loaded with 9.1wt% 8HQ and 9.1wt% STZ

Known amount of PVF and 8HQ or/and STZ were dissolved in a 50 vol% solution of DMF in CHCl3. For the fibers containing one inhibitor, the PVF:8HQ or STZ weight ratio was 10:1 while it was 9:1:1 for the fibers containing both inhibitors at the same time (PVF:8HQ:STZ). The concentration of PVF was 8wt% compared to all compounds forming the mixture. The mixture was loaded into a 2.5 mL plastic syringe with a 22G blunt-ended stainless needle with a diameter of 0.4 mm. The nanofibers were spun at a relative humidity of 65-70% and 25 °C from a tubeless spinneret holder of an electrospinning apparatus (TL-Pro-BM, Tong Li Tech) with an applied voltage of -10/+18 kV, a flow rate of 2.0 mL/h controlled by a syringe pump (TL-F6, Tong Li Tech) and a distance between needle and collector of 15 cm.

Preparation of PVF nanofibers loaded with 4.55wt% 8HQ and 4.55wt% STZ or 13.0wt% 8HQ and 9.1wt% STZ

PVF, 8HQ and STZ (weight ratios of 20:1:1, for the fibers loaded with 4.55wt% 8HQ and 4.55wt% STZ or 9:1:1.5, for the fibers loaded with 13.0wt% 8HQ and 9.1wt% STZ) were dissolved in a 50 vol% solution of DMF in $CHCl_3$. The mixture of solvent contained 8wt% PVF in all experiments. The mixture was loaded into a 2.5 mL plastic syringe with a 22G blunt-ended stainless needle with a diameter of 0.4 mm. The nanofibers were spun at a relative humidity of 55% and 25 °C from a tubeless spinneret holder of an electrospinning apparatus (TL-Pro-BM, Tong Li Tech) with an applied voltage of -10/+18 kV, a flow rate of 2.0 mL/h controlled by a syringe pump (TL-F6, Tong Li Tech) and a distance between needle and collector of 15 cm.

Release of payloads from PVF nanofibers

A weighed amount of the non-woven of the electrospun nanofibers (5 mg) was immersed in 40 mL of a 0.1 M phosphate buffer solution at pH 7.0. The contact of the loaded fibers with the release medium was ensured by application of a mild shaking (250 rpm) of the solution. All release trials were carried out at 37 °C.

Electrochemical experiments

The release of payloads was monitored either as individual release from PVF nanofibers loaded with a single payload or as simultaneous release of both payloads from nanofibers loaded with the two inhibitors. Measurements were performed in a three-electrode electrochemical cell with a Pt wire as counter electrode (CE) and an Ag/AgCl/3 M KCl as reference (RE) electrode. A boron-doped diamond (BDD) disk (3-mm diameter, sealed in polyether ether ketone (PEEK), BioLogic Sciences Instruments) was employed as the working electrode (WE). The payloads release screening with electrochemical detection was conducted at ~ 30 °C in 40 mL of a 0.1 M phosphate buffer solution (pH 7.0) with a PalmSens4 potentiostat (GA Houten, The Netherlands) which was controlled with the PSTrace5.8 software. Prior to the voltammogram acquisition for a given time point, the BBD WE was cleaned through careful polishing on a soft polishing pad that was soaked with a suspension of fine alumina powder in water. The typically used potential scan range, potential step height, potential step amplitude and potential step frequency for the square wave voltammetry were +0.0 to +1.2 V, 0.01 V, 0.05 V and 5 Hz, respectively. Available through the software of the PalmSens4 potentiostat were square wave voltammogram (SWV) plots of the forward (I_f), reverse (I_r) and net ($I_{net} = I_f - I_r$) WE current versus the WE potential (Fig S1 in ESI). For 8HQ, the calibration curve was constructed using the reverse current at E = 0.60 V while the net current at E = 0.84 V was used for the construction of the calibration curve of STZ. To calculate the amount of 8HQ and STZ in solutions containing both compounds, the reverse and forward currents of phosphate buffer alone were subtracted from the reverse current at E = 0.60 V and net current at E = 0.84 V of the mixture solution, respectively. Limit of detection (LOD) and limit of quantification (LOQ) were calculated as LOD = $3.3\cdot(\sigma_b/a)$ and LOQ = $10\cdot(\sigma_b/a)$, σ_b being the standard deviation of y-intercept and a is the slope of calibration curves plotted with the current as y-axis and the concentration of 8HQ or STZ as x-axis.

Complementary analytical tools

The pH of buffer solutions was measured with a Hanna model HI5221 pH meter. For the control experiments, UV-Vis spectroscopy (Cary100, Agilent, USA) was also performed to monitor the individual releases of 8HQ or STZ at 239 and 280 nm, respectively. Aliquots (1 mL) were taken at different time intervals from the release media and placed back after measurement. The morphologies of the nanofibers were observed with a scanning electron microscope (SEM, JSM-7610F, JEOL) and a transmission electron microscope (TEM, JEOL, JEM-ARM200F) with an accelerating voltage of 200 kV. Samples for TEM were prepared by electrospinning the nanofibers on copper grids. The average diameter of nanofibers was calculated by counting 100 fibers with the ImageJ 1.53e software. Static water contact angle on nanofibers was measured with a contact angle goniometer (Ossila, England) by dropping a drop of DI water (5 µL) on electrospun nanofibers placed on glass substrates. For the determination of the encapsulation efficiency, 30-60 mg of fibers were dissolved in DMSO-d6 and 4-hydroxybenzaldehyde (4HBA) was added as internal standard. The encapsulated efficacy was calculated by comparing the integrals of signals related 8HQ and STZ with integrals of signals of 4HBA. ^{1}H-NMR spectra the solutions were measured with a 600 MHz nuclear magnetic resonance spectrometer (AVANCE III HD, Bruker).

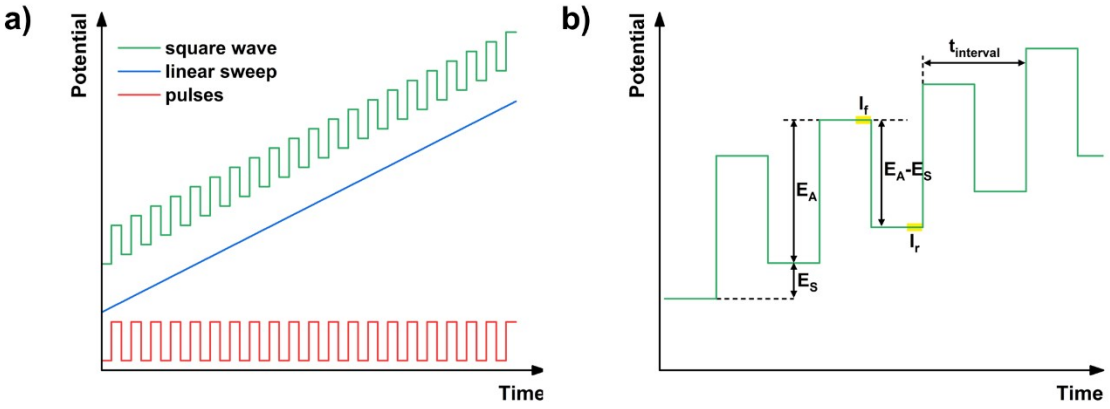

Fig. S1. (a) Graphical illustration of the linear sweep (blue) and pulse (red) potentials that are combined by the potentiostat software to obtain the potential profile used at the working electrode in the electrochemical cell for square wave voltammetry data acquisition (green). (b) Scheme of the parameters defining current acquisition in square wave voltammetry. E_A is the amplitude, E_s the step potential, I_f the forward current, I_r the reverse current. The yellow markings are parts of the signals in which forward and reverse currents are measured. Forward, reverse and net currents, that can be plotted as function of the electrode potential, the latter being considered as square wave voltammogram. The graphics have been adapted based on information available for users of Palmsens potentiostats on the Palmsens company website www. Palmsens.com.

Table S1.

Static contact water contact angle on nanofibers loaded with 8HQ and STZ.

Fibers	**Water contact angle [°]**
PVF	124 ± 4
PVF with 9.1wt% 8HQ	125 ± 3
PVF with 9.1wt% STZ	122 ± 3
PVF with 9.1wt% 8HQ and 9.1wt% STZ	125 ± 3

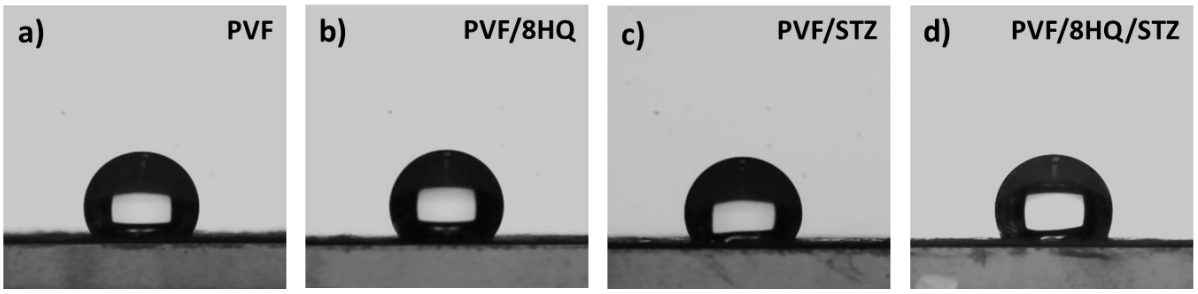

Fig. S2. Photographs of water contact angle on nanofibers of (a) PVF, (b) PVF containing 9.1wt% 8HQ, (c) PVF containing 9.1wt% STZ and (d) PVF containing 9.1wt% 8HQ and 9.1wt% STZ.

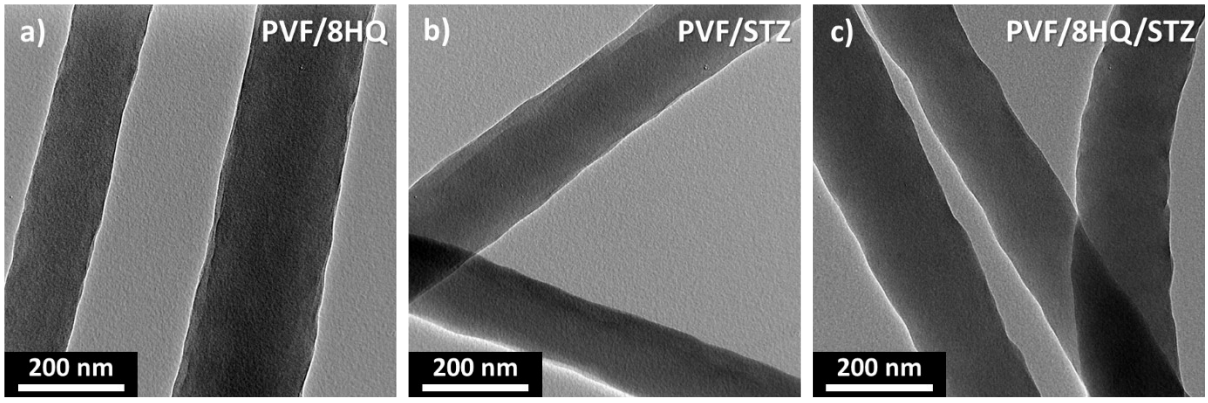

Fig. S3. TEM micrographs of PVF nanofibers loaded with (a) 9.1wt% 8HQ, (b) 9.1wt% STZ and (c) a mixture of 8HQ (9.1wt%) and STZ (9.1wt%).

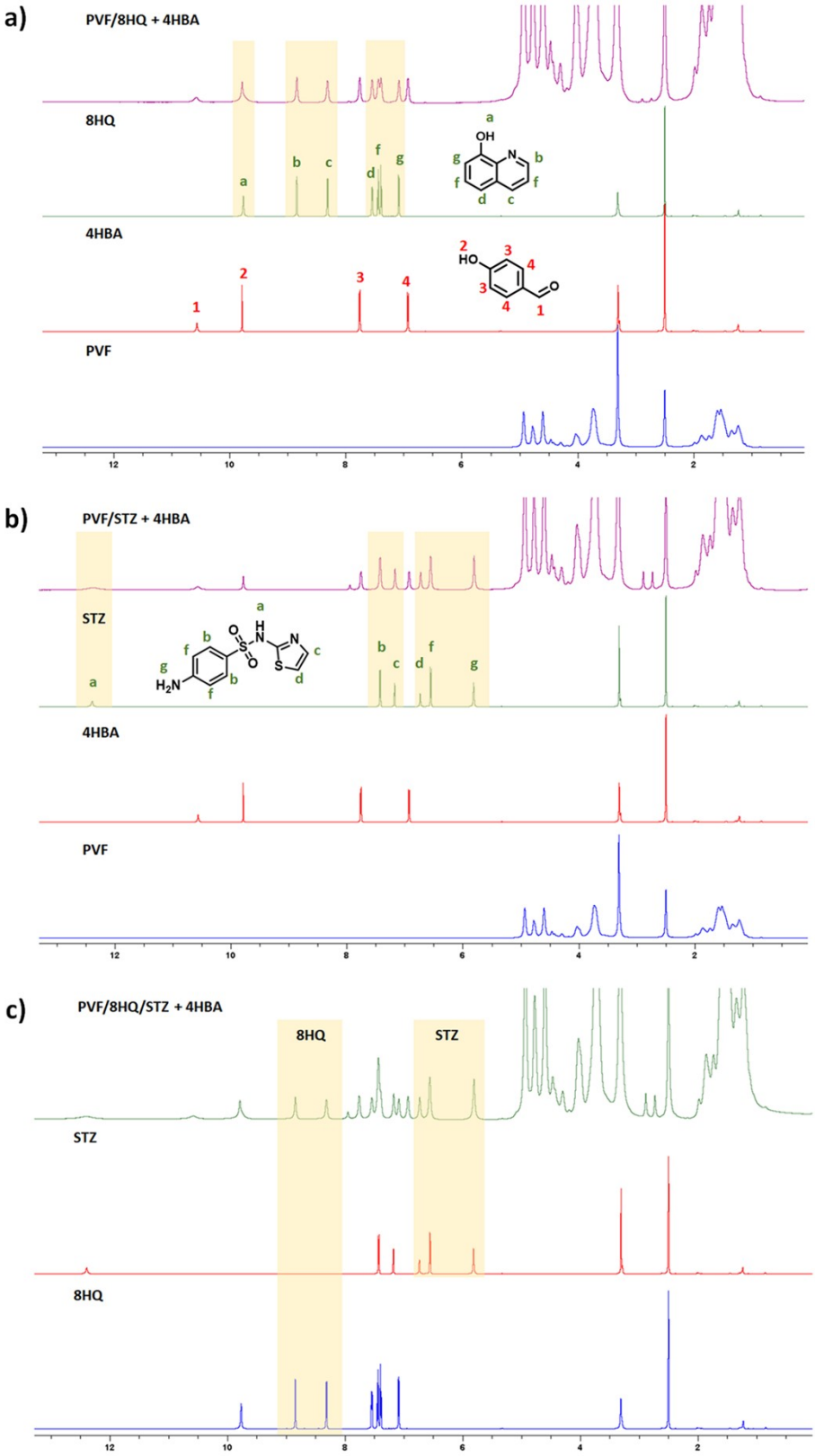

Fig. S4. ^{1}H-NMR spectra of (a) PVF/8HQ, (b) PVF/STZ and (c) PVF/8HQ/STZ nanofibers in DMSO-d6 in the presence of 4-hydroxyl benzaldehyde as standard.

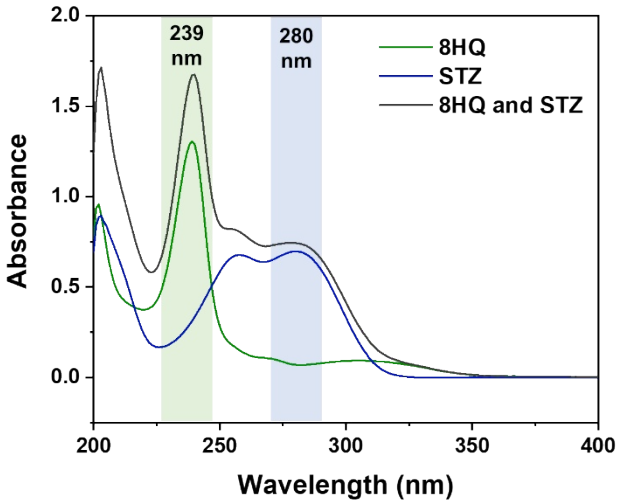

Fig. S5. UV-Vis spectra of 8-hydroxyquinoline (8HQ, green line), sulfathiazole (STZ, blue line) and a mixture of 8HQ and STZ (40 μM for both compounds, grey line) at pH 7.0. In presence of 8HQ and STZ, the absorption spectrum of 8HQ was overlapping with the absorption spectrum STZ.

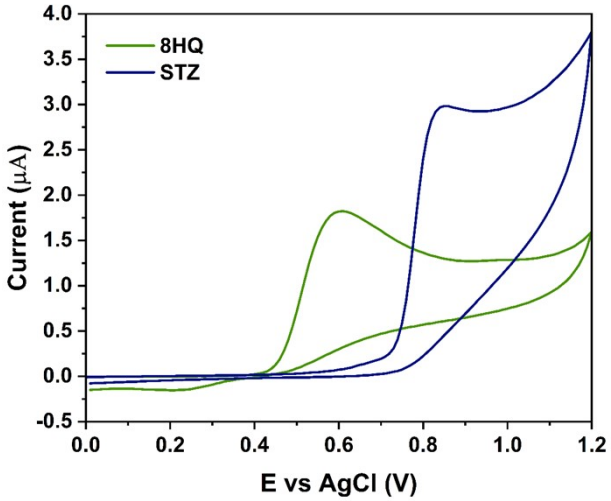

Fig. S6. Cyclic voltammograms of 8-hydroxyquinoline (8HQ, green line) and sulfathiazole (STZ, blue line) at pH 7.0. Scan speed was 50 mV/s and the 8HQ and STZ concentrations were 100 μM.

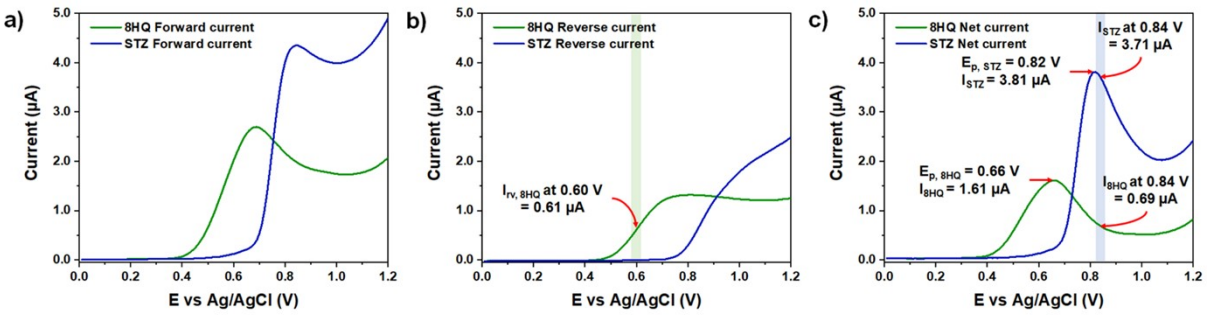

Fig. S7. Forward (a), reverse (b), and net current (s) plots of the square wave voltammograms of 100 µM solutions of 8-hydroxyquinoline (8HQ, green) and 100 µM sulfathiazole (STZ, blue) at pH 7.0. Square wave voltammetry parameters: potential step height, 0.01 V; potential step amplitude, 0.05 V and potential step frequency 5 Hz. Explanations of the meaning of forward, reverse, and net current components are included the Experimental section.

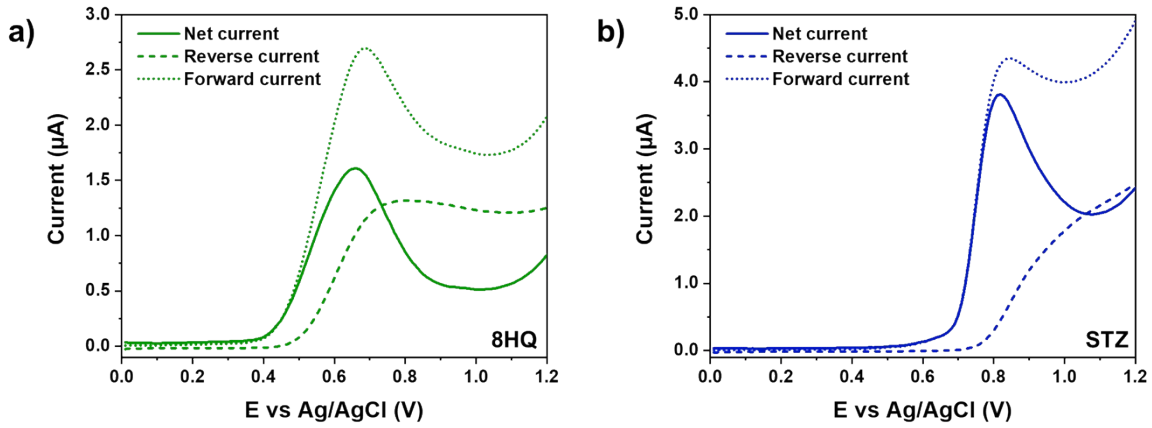

Fig. S8. Forward, reverse and net current plots obtained by square wave voltammetry measurements at pH 7.0 with (a) 100 µM 8-hydroxyquinoline (8HQ) and (b) 100 µM sulfathiazole (STZ). Square wave voltammetry parameters: potential step height = 0.01 V; potential step amplitude = 0.05 V and potential step frequency = 5 Hz.

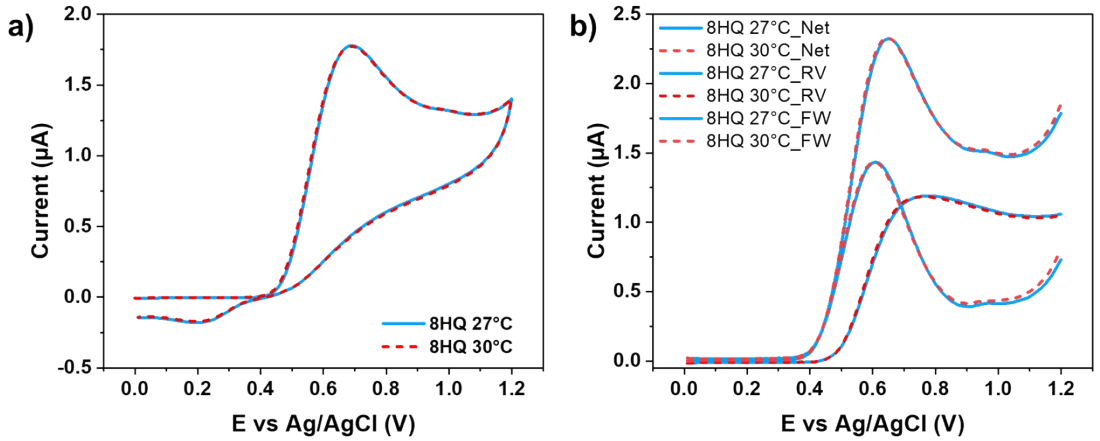

Fig. S9. Cyclic voltammograms (a) and square wave voltammogram of 100 µM 8HQ at pH 7.0 at 27°C (solid line) and 30°C (dashed line).

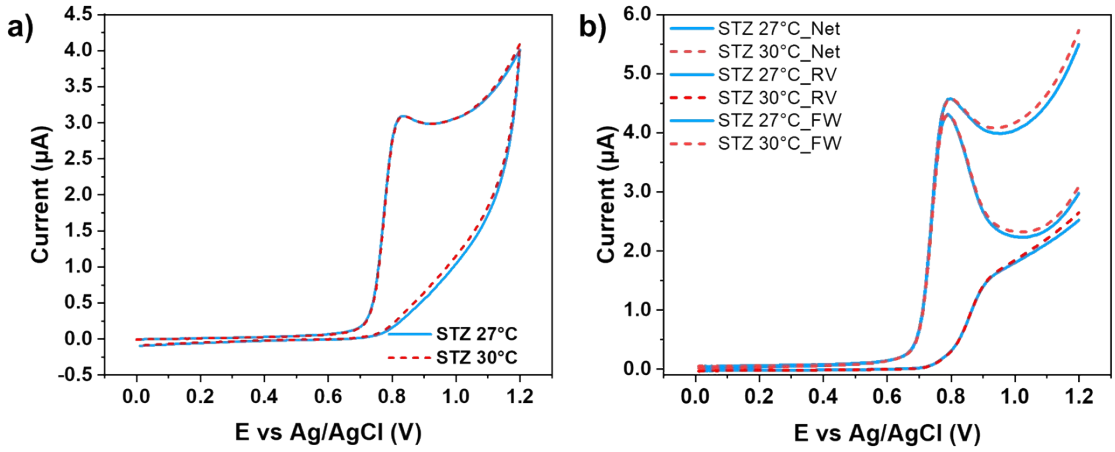

Fig. S10. Cyclic voltammograms (a) and square wave voltammogram of 100 µM STZ at pH 7.0 at 27°C (solid line) and 30°C (dashed line).

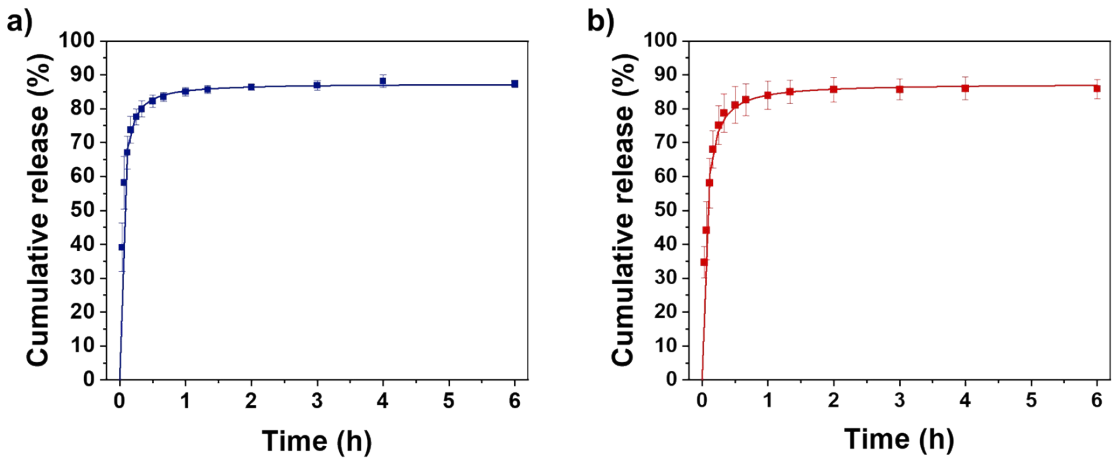

Fig. S11. Effect of nanofiber diameter on temporal evolution of the concentration of released 8HQ from the nanofibers with an average diameter of 331 ± 64 nm (a) and 230 ± 42 nm (b) at pH 7.0 measured by UV-Vis spectroscopy.

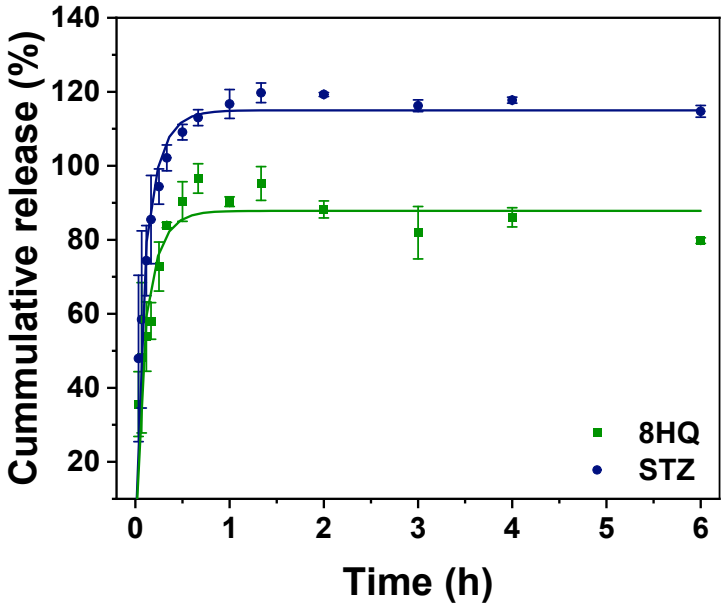

Fig. S12. Temporal evolution of the simultaneous release of 8HQ (green squares) and STZ (blue circles) from nanofibers loaded with 4.55wt% 8HQ and 4.55wt% STZ at pH 7.0, as measured by square wave voltammetry.

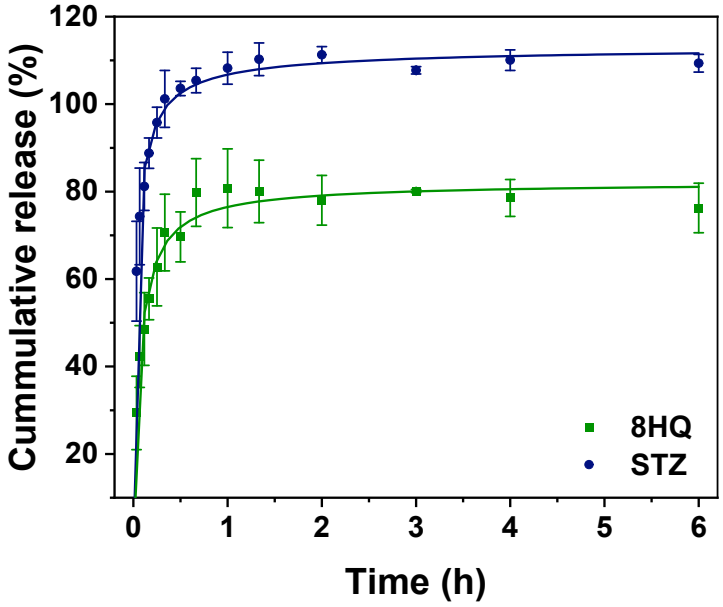

Fig. S13. Temporal evolution of the release of 8HQ (green squares) and STZ (blue circles) from nanofibers co-loaded with 9.0wt% 8HQ (corresponding to 13.0wt% 8HQ initially fed and an encapsulation efficiency of 70%) and 9.1wt% STZ at pH 7.0, as measured by square wave voltammetry.