Supplementary Information for

Self-assembled nanomaterials enable extended lithium release

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Contents

1. Materials and Methods

A. Chemicals

All chemicals and reagents used in these studies were purchased from Sigma Aldrich as reagent grade and used without further purification unless otherwise stated. 18 MΩ ultrapure water was obtained from a Sartorius Arium Mini unit.

B. Alginate beads

Alginate beads were prepared using a multi-step procedure. First, 20 mL of 1% solution of alginic acid, sodium salt (Thermo Fisher Scientific) was added to 40 mL of hexane in a plastic beaker. This mixture was immersion blended for 30 seconds using the medium speed setting on the blender. Next, 3 mL of 20 wt% Tween 80 (TCI America) was added, and this solution was again immersion blended for another 30 seconds at the same speed. After 30 seconds, 8 mL of calcium chloride was added dropwise to the solution while immersion blending. Isopropyl alcohol (40 mL, Fisher Chemical) was added, and the mixture was again immersion blended for 30 seconds at the same speed. The mixture was collected in two 50 mL conical tubes and centrifuged at 4500 rpm for 5 mins. The supernatant was removed, and the resultant pellet was resuspended in 25 mL isopropyl alcohol. The pellet was resuspended and washed in isopropyl alcohol three times total. Following washing, the pellet was lyophilized for 24 h, after which the alginate beads were stored at -20 ^{o}C.

C. MPN formation:

Stock solutions of 0.94 mM tannic acid (TA), 1.5 mM iron (III) chloride,12 M lithium chloride and 1 mg/mL alginate beads were freshly prepared prior to experimentation. For characterization experiments, MPNs were prepared in 96-well plates. First, 100 µL of 1 mg/mL alginate beads was added to each well, and the plate was centrifuged at 4,000 rpm for 4 mins. The supernatant was then discarded, leaving pellets of alginate particles in each well.

For the iron-only MPNs, 50 µL of ultrapure water was initially added to a well, followed by 50 µL of 0.94 mM TA in ultrapure water. 50 µL of 1.5 mM $FeCl_3$ in ultrapure water was then added. Finally, 150 µL of 20 mM MOPS, pH 7.5 was added to the well, and the solution was mixed thoroughly.

For the lithium-containing MPNs, 50 µL of 0.94 mM TA in ultrapure water was added. Next, 50 µL of 1.5 mM $FeCl_3$ and 50 µL of 12 M LiCl (both generated in ultrapure water) were premixed and added simultaneously to the TA-alginate bead solution. Finally, 150 µL of 20 mM MOPS, pH 7.5 was added, and the solution was thoroughly mixed by pipetting. The well plate was then centrifuged at 4,000 rpm for 4 mins. The supernatant was removed, and the resulting pellets were resuspended in ultrapure water.

D. Formation of coated particles for drug release studies

i. Coating, no hydrogel:

For drug release studies, MPNs were generated at 100x concentration in 50 mL conical tubes. 10 mL of 1 mg/mL alginate beads were added to the conical tubes and centrifuged at 4000 rpm for 4 minutes. The supernatant was removed, after which 5 mL of 0.94 mM TA was added. Next, 5 mL of 1.5 mM $FeCl_3$ and 5mL 12 M LiCl were premixed and added simultaneously. Finally, 15 mL of 20 mM MOPS, pH 7.5 was added to the solution, and

the complete solution was vortexed. The solution was pelleted at 4000 rpm for 4 mins and the supernatant removed. The pellet was washed once with 30 mL of ultrapure water and spun down again at 4000 rpm for 4 mins. The supernatant was discarded. The pellet was resuspended in 400 µL of simulated serum.

ii. Coating, with hydrogel

100 µL of MPN-coated alginate beads were mixed with 100 µL of 1% sodium alginate, after which 20 µL of 700 mM $CaCl_2$ was added and mixed to form a hydrogel.

E. MPN Characterization

i. UV-Visible Spectroscopy

UV-Vis was measured on 1 µL samples using a NanoDrop One (Thermo).

ii. SEM and EDX

SEM and EDX images were taken using a Zeiss Merlin high-resolution scanning electron microscope (Jena, German). Lyophilized particles were drop-cast on double-sided carbon tape that was mounted on a standard, aluminum pin stub mount.

iii. FTIR Spectroscopy

FTIR was performed with the following parameters: resolution: 4 cm^{-1}, scan time: 32, background scan time: 32, range: 4000 cm^{-1} to 400 cm^{-1}.

F. Drug Release Studies

i. Simulated Serum

100 µL of the MPN-alginate beads in simulated serum was placed inside of a 7,000 MWCO dialyzer tube (Thermo Scientific, Rockford, IL). The dialysis tube was inserted into a 2 mL microcentrifuge tube filled with artificial serum and placed in a shaking, 37 ^oC incubator. Time points were taken at t=0 h, 4 h, 8 h, 24 h, 48 h, 74 h, and 98 h. At each time point, the dialysis tube was transferred to a fresh 2 mL microcentrifuge tube filled with fresh simulated serum and placed back in the incubator at 37^oC. Aliquots were stored to later perform ICP-MS.

ii. Upper intestinal fluid

The entire hydrogel encasing the MPN-alginate beads was placed inside of a 7,000 MWCO dialyzer tube (Thermo Scientific, Rockford, IL). The dialysis tube was inserted into a 2 mL microcentrifuge tube filled with simulated upper intestinal fluid (U.I.F) (106 mM NaCl, 28.7 mM NaH_2PO_4, pH 6.5) and placed in a shaking 37^oC incubator. Time points were taken at t=0 h, 4 h, 8 h, 24 h, 48 h, 74 h, and 98 h. At each time point, the dialysis tube was transferred to a fresh 2 mL microcentrifuge tube filled with fresh simulated U.I.F. and placed back in the incubator at 37^oC. Aliquots were stored to later perform ICP-MS.

G. ICP-MS

Samples were digested at a 1:10 ratio with 70% HNO_3 overnight. Samples were then diluted such that the final concentration of nitric acid was 2%. Germanium was added as an internal standard and samples were run with an Agilent ICP-MS in no-gas mode to measure lithium and in gas-mode to measure iron and calcium.

2. Supplementary Figures

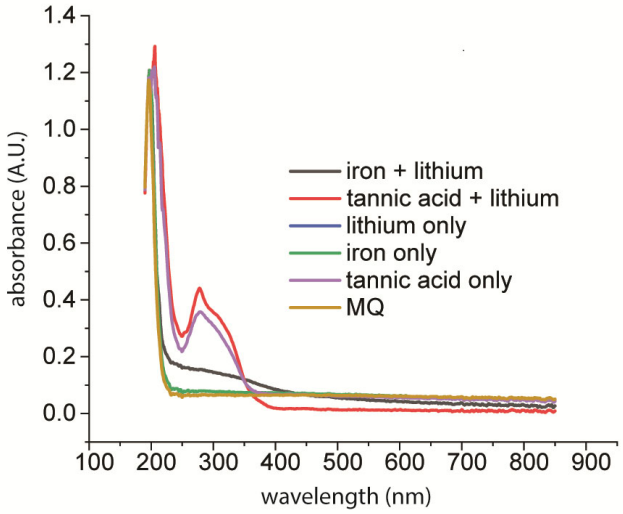

Figure S1. UV-Vis characterization of control conditions. Control conditions include solutions of individual components of the MPN formulation: MQ water, tannic acid only, iron only and lithium only. Additional controls include iron and lithium only as well as tannic acid and lithium only. A phenolic peak at around 300 nm is present only for conditions where tannic acid is present. No LMCT band is present for any of the control conditions.

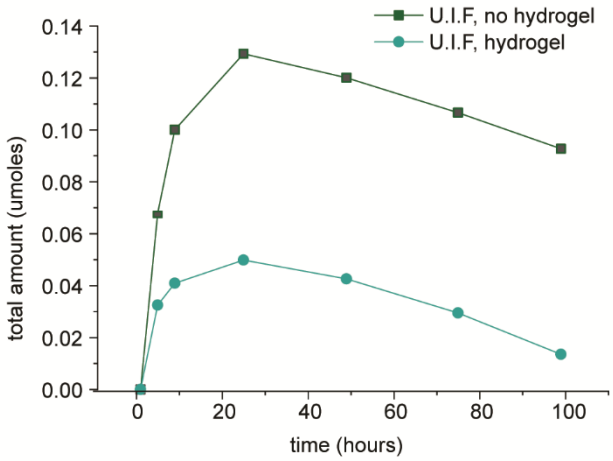

Figure S2. Drug release profile of lithium in simulated upper intestinal fluid (U.I.F). The amount of lithium released appears to decrease over time because amounts of lithium released are low enough to be at the lower detection limit of the ICP-MS.

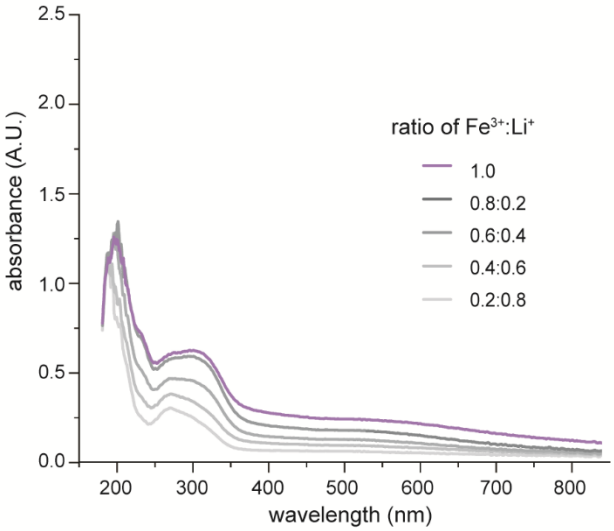

Figure S3. Optimization of Li^+-MPN formulation. While optimizing the formulation, the ratio of lithium to iron was increased while keeping the total molar amount of metal ions constant. UV-Vis spectroscopy shows decreasing phenol absorbance and LMCT bands as the ratio of iron: lithium is increased.