Electronic Supplementary Material (ESI) for Nanoscale.

Supplementary Information

Double loaded self-decomposable SiO_2 nanoparticles for sustained drug release†

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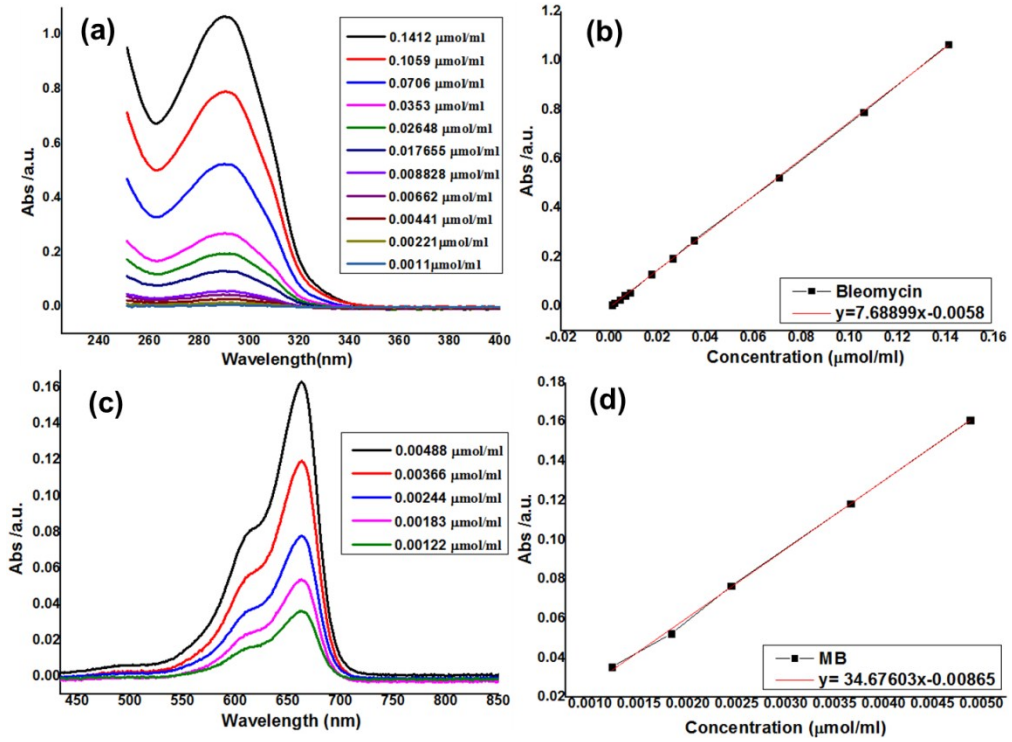

Figure S1. The absorbance spectra of (a) BLM and (c) MB in aqueous solution at different concentrations; and their calibrated standard equation of (b) drug BLM (absorption peak at 290 nm) (d) drug MB (absorption peak at 660 nm) obtained by linear fitting.

The calibration of the drug amount was carried out based on their respective absorbance spectra. Specifically, a series of BLM or MB absorbance spectra of different concentrations were measured (Fig. S1).The concentration of BLM was proportional to its absorbance peak intensity at 290 nm (Fig. S1a) with the standard equation y=7.68899x-0.0058 (Fig. S1b, x is the molar concentration of BLM, y is the peak intensity of BLM at 290 nm). As for MB, the drug concentration was proportional to its absorption peak intensity at 660 nm (at low concentrations) (Fig. S1c). The standard equation of drug MB is y=34.67603x-0.00865 (Fig. S1d, x is the molar concentration of MB, y is the peak intensity of MB at 660 nm).

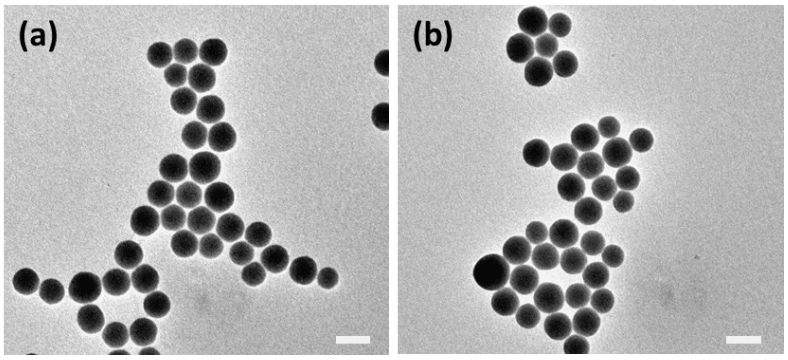

Figure S2. TEM images of pure SiO_2 NPs (a) before and (b) after being immersed in deionized water at 37 °C for 16 days. No change in the NP morphology was observed. The scale bar is 100 nm for both images.

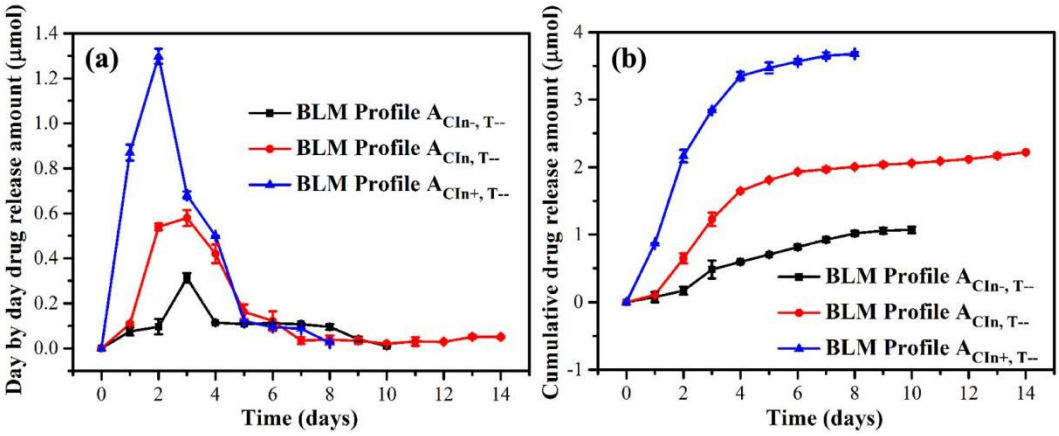

Figure S3. (a, b) Day-by-day and cumulative profiles of BLM release from the SiO_2-BLM NPs with different BLM load amount (CIn-=~ 1 μmol, CIn=~ 2.2 μmol, and CIn+=~ 3.7 μmol) monitored in deionized water at 37 °C. The corresponding NP samples $A_{CIn-,\ T--}$, $A_{CIn,\ T--}$, $A_{CIn+,\ T--}$ were synthesized at the same TEOS amount T--=0.15 mL.

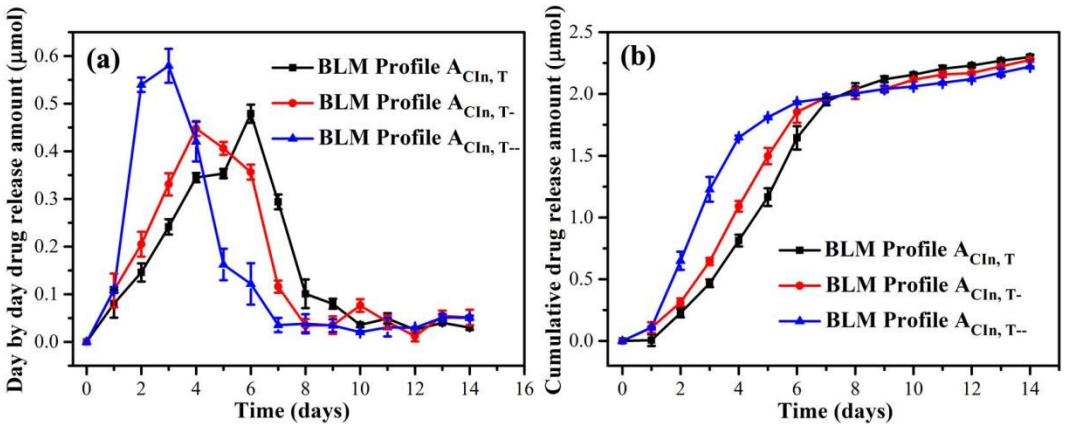

Figure S4. (a, b) Day-by-day and cumulative profiles of BLM release from the SiO_2-BLM NPs with different TEOS amount (T--= 0.15 mL, T-= 0.2 mL, and T= 0.23 mL) monitored in deionized water at 37 ^{o}C. The corresponding NP samples $A_{CIn,\ T--}$, $A_{CIn,\ T-}$, and $A_{CIn,\ T}$ were synthesized with the same BLM load amount CIn=~2.2 µmol.

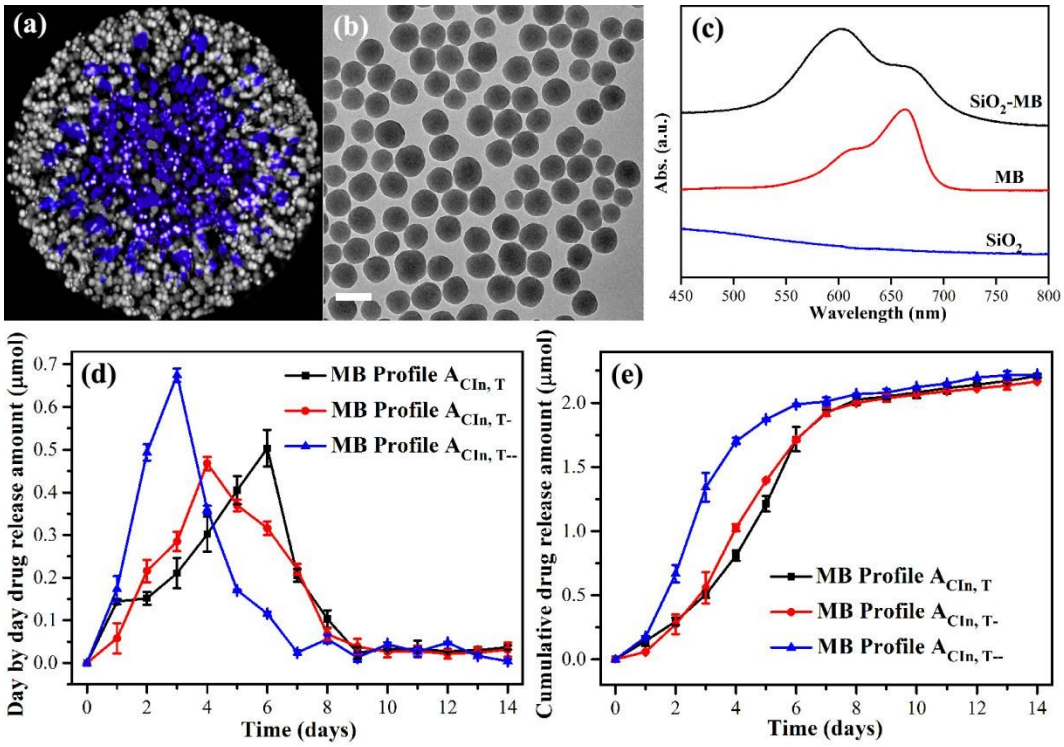

Figure S5. (a) Illustration of the SiO_2-MB self-decomposable NP (A model); (b) Low magnification TEM image of the as-synthesized SiO_2-MB NPs. The scale bar is 100 nm; (c) Optical absorption spectra taken from pure SiO_2, pure MB, and SiO_2-MB NPs; (d) Day-by-day and (e) cumulative release profiles of MB from SiO_2-MB NPs synthesized with different TEOS amount (T--= 0.15 mL, T-= 0.2 mL, and T= 0.23 mL) monitored in deionized water at 37 ^{o}C. The corresponding NP samples $A_{CIn,\ T--}$, $A_{CIn,\ T-}$, and $A_{CIn,\ T}$ were synthesized at the same MB load amount CIn=~2.2 μmol.

The *in vivo* drug release profiles of A model (e.g. SiO_2-BLM NPs, T= 0.23 mL, CIn= ~ 2.2 µmol) and B model (BLM-SiO_2-MB NPs, T= 0.23 mL, CIn= ~ 2.2 µmol, and CAb= ~ 0.8 µmol) were also evaluated. Rats in four groups (n = 3 in each group) were injected intravenously with 0.2 mL of individual NPs or pure BLM, at the same BLM dose (A Model: 1.95 mg/kg, B Model: 0.72 mg/kg). As depicted in Fig. S6a, the SiO_2-BLM NPs demonstrated a slow release of BLM to reach the maximum concentration at about 24 hrs and to be eliminated from the body with the half-life of about 16 hrs. On the other hand, the BLM-SiO_2-MB NPs (Fig. S6b) showed a relatively quick initial drug release with the T_{max} at about 8 hrs, and a rapid elimination with the half-life of about 11 hrs. In comparison (Fig. S6c), BLM-SiO2-BLM NPs, which combined the features of both A model and B model, demonstrated a controllable release of BLM to reach the maximum concentration at about 8 hrs, afterwards, a sustained release feature was observed for 3 days with the plasma elimination half-life of about 28 hrs.

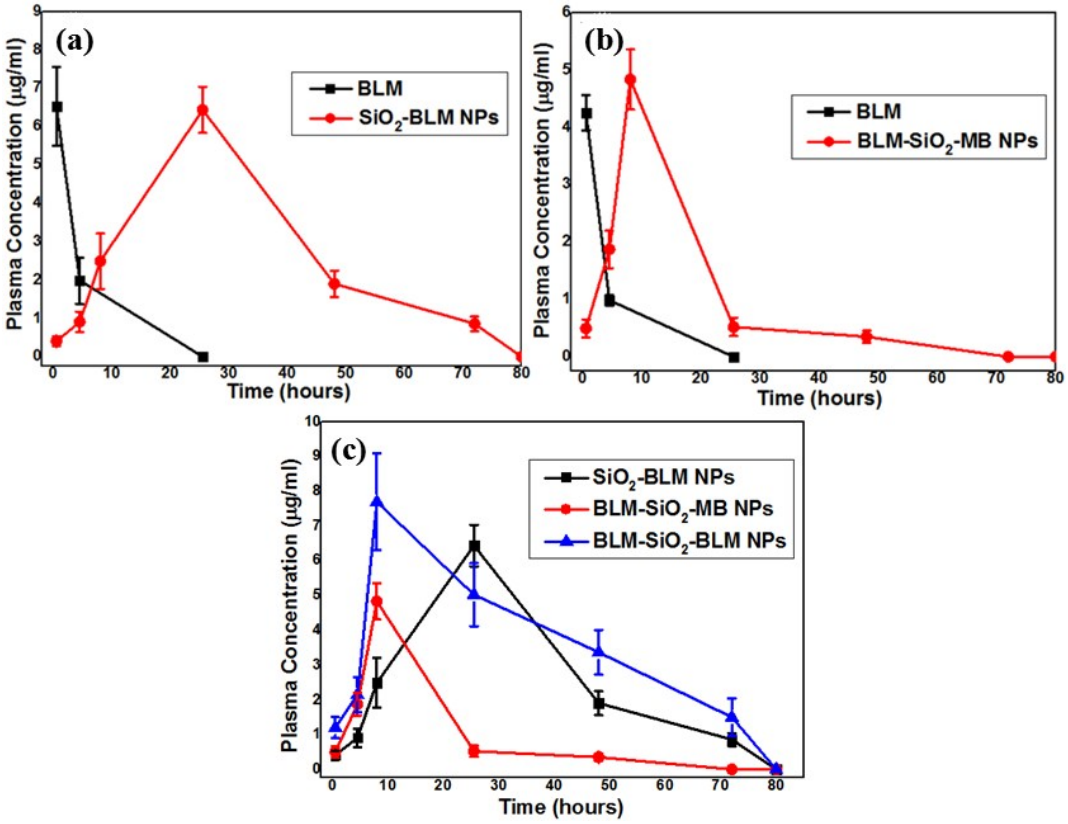

Figure S6. The BLM concentration in plasma after the injection of (a) pure BLM and SiO_2-BLM (A model), (b) pure BLM and BLM-SiO_2-MB (B model), and (c) A, B and D Model NPs. Each data point represents the mean ± SD of three rats.

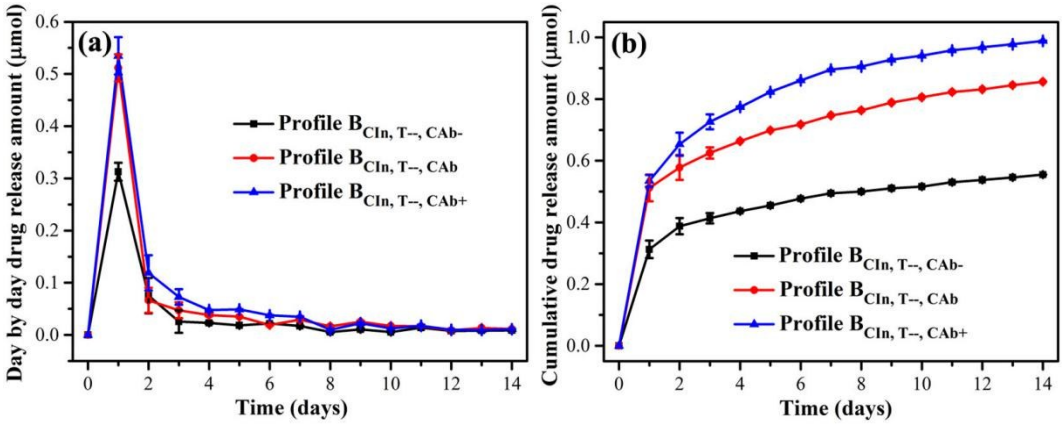

Figure S7. (a) Day-by-day and (b) cumulative release profiles of BLM taken from three BLM-SiO_2-MB NP samples with different absorbed BLM amount (CAb-= ~0.5 μmol, CAb= ~0.8 μmol, and CAb+= ~1.0 μmol), but the same MB load amount CIn=~2.2 μmol, and the same TEOS amount T--= 0.15 mL.

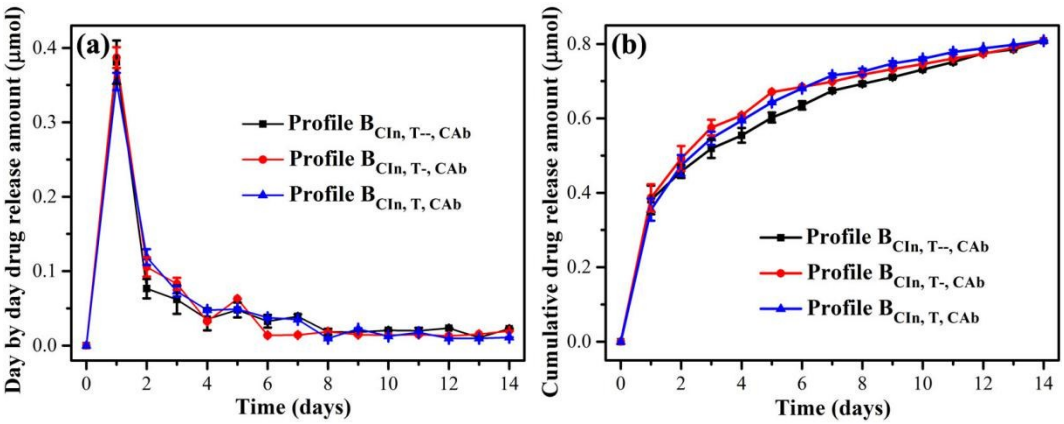

Figure S8. (a) Day-by-day and (b) cumulative release profiles of BLM taken from three BLM-SiO_2-MB NP samples at different TEOS amount (T--= 0.15 mL, T-= 0.2 mL, and T= 0.23 mL), the same MB load amount CIn=~2.2 μmol, and the same absorbed BLM amount CAb= ~0.8 μmol.

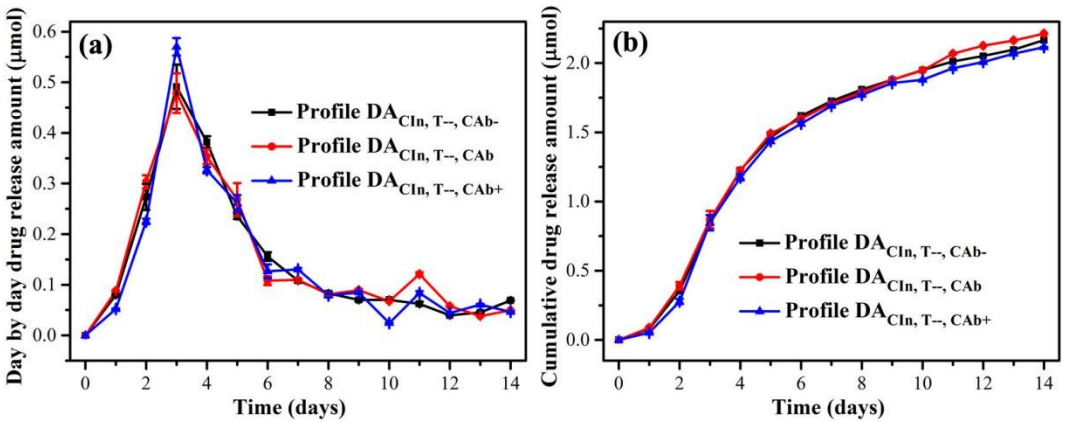

Figure S9. (a) Day-by-day and (b) cumulative release profiles of delayed MB from three BLM-SiO_2-MB NP samples at the same MB load amount CIn=~2.2 μmol, different absorbed BLM amount (CAb-= ~0.5 μmol, CAb= ~0.8 μmol, and CAb+= ~1.0 μmol), and the same TEOS amount T--= 0.15 mL.

Quick elimination of the nanoparticles themselves (when drugs were not released) from the circulation is not likely, as one can see that the "grown-in" drug MB in the BLM-SiO2-MB NPs was released from the NPs to the plasma. This is supported by *in vivo* results taken from the B model (Fig. S10).

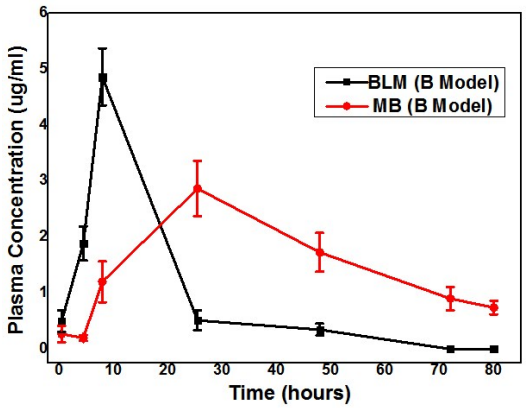

Figure S10. The MB and BLM concentration in plasma after the injection of BLM-SiO_2-MB NPs (B model). Each data point represents the mean ± SD of three rats.

The role of the first-loaded drug was revealed by the characterization of the A model, where there is only "the first-loaded drug" in the SiO_2. One can observe a rather slow release profile in A model (Fig. 3e in manuscript)—it took a while for the drug release to reach its peak at day 6 and then gradually decreased. Together with the drug release, carriers underwent decomposition (Fig. S11). Further evidence came from another control experiment, i.e., by dispersing the SiO_2-BLM NPs into acetone, in which BLM was not soluble, neither the BLM release nor the SiO_2 NP decomposition occurred (Fig. S12). In fact, the SiO_2-BLM NP was very stable after being dried—neither BLM escape nor SiO_2 decomposition occurred after months when they were stored in the powder form.

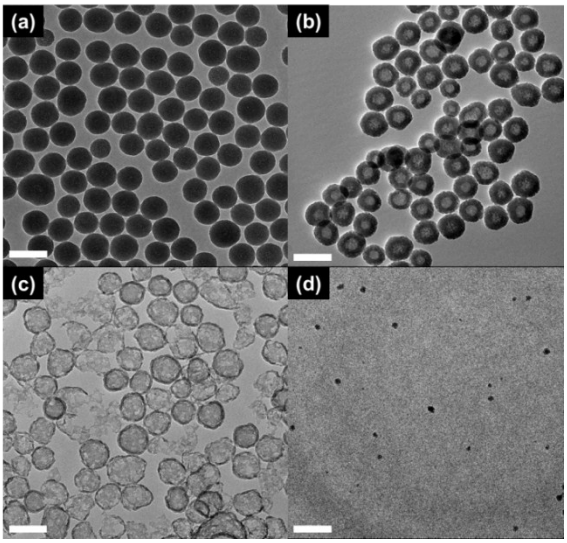

Figure S11. TEM images of the SiO_2-BLM NPs after being immersed in deionized water at 37 ^oC for (a) 1, (b) 4, (c) 10, and (d) 16 days. The scale bars are 100 nm.

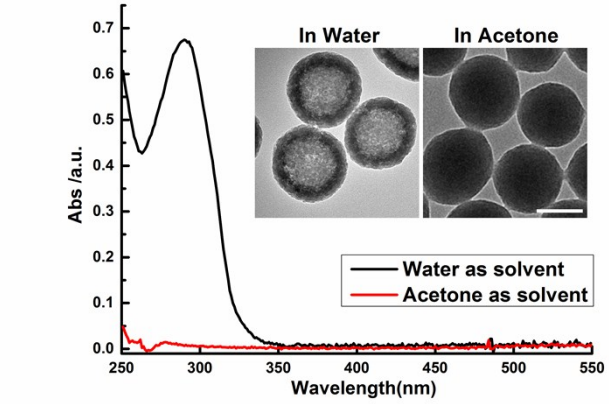

Figure S12. Comparison of BLM release and carrier decomposition when NPs were dispersed in different solvents. TEM images of the NPs and corresponding absorbance spectra of the supernatants after SiO_2-BLM NPs soaking in water or acetone for 6 days. As BLM is not soluble

in acetone, diffusion of BLM from the NP to the solvent is prohibited, and consequently the decomposition of NPs does not occur. The scale bar is 50 nm for both images.