Supporting Information

Reverse Microemulsion-Based Synthesis of (Bis)phosphonate-Metal Materials with Controllable Physical Properties: An Example Using Zoledronic Acid-Calcium Complexes

Xu Li, Youssef W. Naguib[†], Solange Valdes, Stephanie Hufnagel, and Zhengrong Cui[*]

The University of Texas at Austin, College of Pharmacy, Division of Pharmaceutics, Austin, Texas, 78712.

*Author of correspondence：Tel: (512) 495-4758, Email: Zhengrong.cui@austin.utexas.edu.

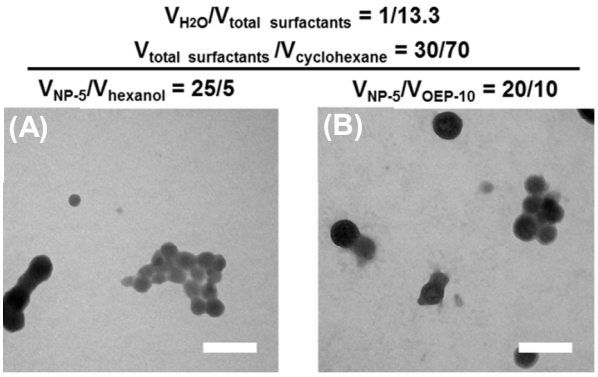

Figure S1. Representative TEM micrographs of Zol-Ca complexes synthesized using RM with a co-surfactant hexanol ($V_{NP-5}/V_{Hexanol}$ of 25/5) **(A)** or OEP-10 (V_{NP-5}/V_{OEP-10} of 20/10) **(B)**. The $V_{H2O}/V_{total\ surfactants}$ and $V_{total\ surfactants}/V_{cyclohexane}$ ratios were fixed at 1/13.3 and 30/70, respectively (bars = 100 nm).

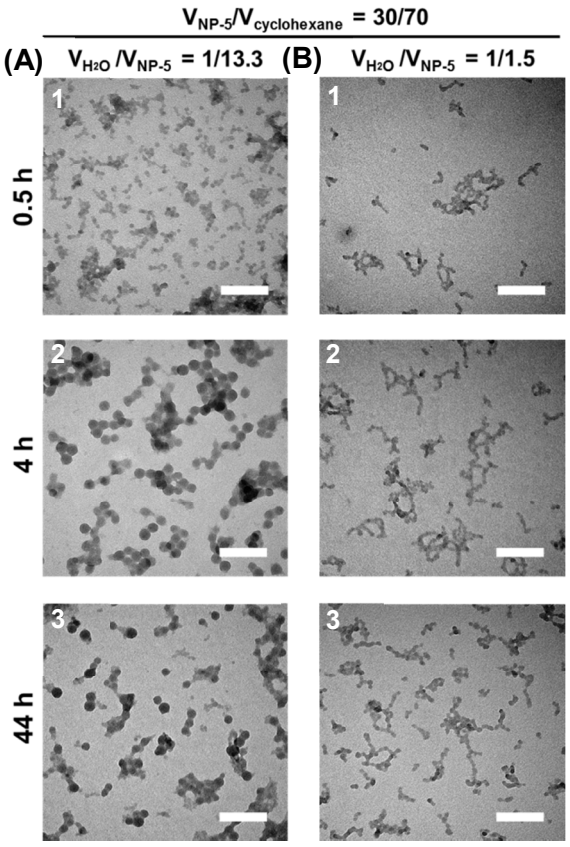

Figure S2. Effects of reaction time on the physical properties of Zol-Ca complexes synthesized in RM. Representative TEM images of Zol-Ca complexes prepared in RM with $V_{NP-5}/V_{cyclohexane}$ ratio fixed at 30/70 and **(A)** V_{H2O}/V_{NP-5} ratios of 1/13.3 or **(B)** $V_{NP-5}/V_{cyclohexane}$ ratio of 1/1.5 (bars = 100 nm).

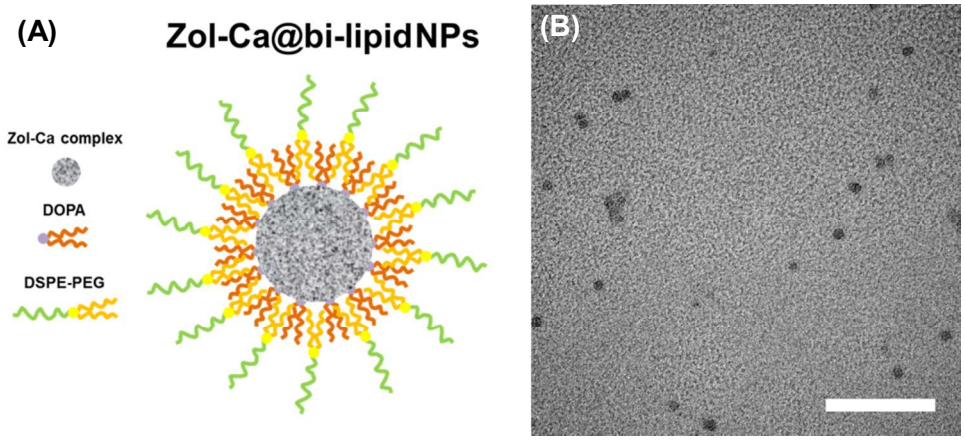

Figure S3. (A) The proposed structure of Zol-Ca@bi-lipid NPs. **(B)** The representative TEM micrograph of the Zol-Ca@bi-lipid NPs prepared with a Zol/DSPE-PEG_{2K} weight ratio of 20 μg/mg (bar = 200 nm).

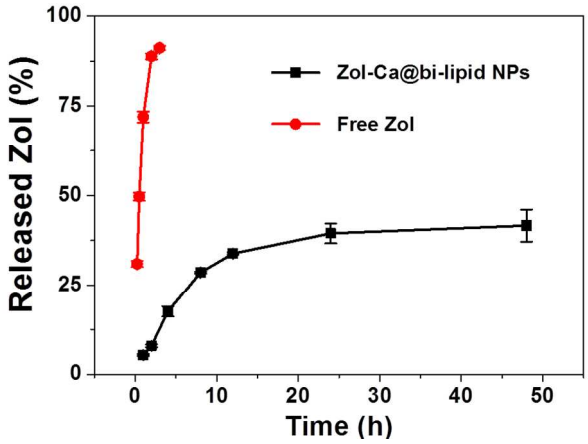

Figure S4. The Zol release profiles of Zol-Ca@bi-lipid NPs or free Zol in 10 mM sodium phosphate buffers with pH value of 7.4. Data are mean ± S.D. (n = 3).

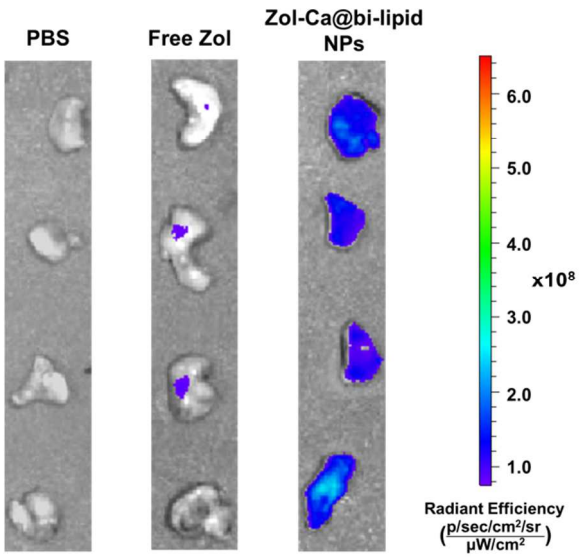

Figure S5. Fluorescent images of orthotopic M-Wnt tumors collected 24 h after i.v. injection of PBS, free Zol or Zol-Ca@bi-lipid NPs (2% of Zol was labelled with AF647) into C57BL/6 mice (n=4).

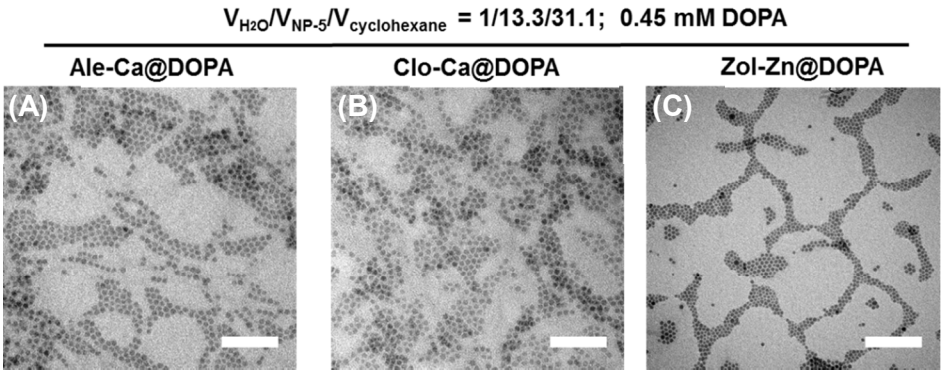

Figure S6. Representative TEM micrographs of DOPA-coated **(A)** alendronic acid-calcium (Ale-Ca@DOPA), **(B)** clodronic acid-calcium (Clo-Ca@DOPA) and **(C)** zoledronic acid-zinc (Zol-Zn@DOPA) prepared using 0.45 mM DOPA-containing RM with $V_{H2O}/V_{total\ surfactants}$ and $V_{total\ surfactants}/V_{cyclohexane}$ ratios of 1/13.1 and 30/70, respectively (bars = 100 nm).

Table S1. The molar ratio of Ca to Zol (Ca/Zol) in Zol-Ca complexes prepared in RM system with different conditions (such as the V_{H2O}/V_{NP-5} ratio or presence of DOPA).

Samples		molar ratio of Ca/Zol	Average molar ratio of Ca/Zol (Mean ± SD, n = 3)
Spherical Zol-Ca complexes ($V_{NP-5}/V_{cyclohexane}$ of 30/70; V_{H2O}/V_{NP-5} of 1/13.3)	1#	3.59	3.60 ± 0.14
	2#	3.46	
	3#	3.75	
Pearl-necklace-like Zol-Ca complexes ($V_{NP-5}/V_{cyclohexane}$ of 30/70; V_{H2O}/V_{NP-5} of 1/1.5)	1#	2.60	2.41 ± 0.17
	2#	2.34	
	3#	2.29	
Zol-Ca@DOPA composites ($V_{NP-5}/V_{cyclohexane}$ of 30/70; V_{H2O}/V_{NP-5} of 1/1.13.3)	1#	6.36	6.62 ± 0.55
	2#	6.24	
	3#	7.24	