ADVANCED MATERIALS

Supporting Information

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Nanoparticle Shape Improves Delivery: Rational Coarse Grain Molecular Dynamics (rCG-MD) of Taxol in Worm-Like PEG-PCL Micelles

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Supplemental Information

CG Model Development: As described in cited references, the short range interactions, are described by a Lennard Jones potential of a 9-6 type, $\nu(r)_{9-6}$, where σ and ε are fixed by a combination of surface tension and density for the chemical mapping of each bead type, $\nu(r)_{9-6} = \frac{27}{4}\varepsilon\left(\frac{\sigma^9}{r^9} - \frac{\sigma^6}{r^6}\right)$. Mixing is defined using the conventional combination rule where $\sigma_{AB} = \frac{\sigma_{AA}+\sigma_{BB}}{2}$ and $\varepsilon_{AB}=\varepsilon_A\varepsilon_B$. The CG mapping consists of 3-5 heavy atoms per site. The mapping for PEG consists of that already described by Shinoda et al., while the mapping for PCL consists of 3 different CG beads for every CL monomer as shown in **Figure 1A** and as defined explicitly in **Table S1**. Paclitaxel is divided into 23 beads, of chain type, benzene type, and ring type, and individual molecular mappings are found for each bead, with some simplifications between them being made, as explicitly defined in **Table S2.** However, we note in these systems significant hydrogen bonding is of course an additional consideration for all interactions, including: the PEG-PEG, PEG-water, PCL-drug [1], and may add additional complexities to the phase behavior and partitioning of the system, particularly for the temperature dependence. In this case, all beads are uncharged. Bond and angular interactions between CG beads are obtained from all-atom simulations using a potential based on the CHARMM27 force-field of a short PCL melt (see Supplement), while intramolecular interactions for paclitaxel are obtained from simulations in all-atomistic octanol (all-atom force field for paclitaxel parameterized by David Sept [2]) . In these cases, the intramolecular interactions are modeled via harmonic potentials given by $V(r)_{bond} = K_b(r - r_o)^2$ and $V(r)_{angle} = K_a(\theta - \theta_o)^2$. Here, K_b and r_o represent the equilibrium force constant and distance for bonds, and K_a and θ_o represent the equilibrium force constant and angle for angles. These constants are obtained from the respective simulations using an inverse Boltzmann technique, such that:

$$U_{bond}(r) \propto -k_B T ln \frac{P(r)}{r^2} \qquad (1)$$

$$U_{angle} \propto -k_B T ln \frac{P(\theta)}{sin\,\theta} \quad (2)$$

PEG-PCL Simulations: All CG simulations were run using LAMMPS, a parallel molecular dynamics code developed by Sandia National Laboratory, with a timestep of 10 fs. The temperature and the pressure were controlled using the Nose-Hoover algorithm at 300K and 1atm.

Octanol Water Setup: In order to test the octanol water exchange free energy, we set up a simulation box containing 3000 CG octanol molecules and 1000 CG waters, with one CG paclitaxel. All CG simulations were run using LAMMPS, a parallel molecular dynamics code developed by Sandia National Laboratory. A two level RESPA multitime step integrator was used, with the bond and angle potentials were evaluated with the inner time step of 2 fs, and the nonbonded interactions were evaluated with the outer time step of 10 fs. The temperature and the pressure were controlled using the Nose-Hoover algorithm at 300K and 1atm. Using the NPT thermostat, an interface spontaneously forms between the water and octanol, with the paclitaxel sampling locations in the bulk octanol, as well as close to the interface. The size of the box at equilibrium was approximately 96 Å x 96 Å x 192 Å. We pull paclitaxel across the octanol water interface at a constant velocity of .000002 Å/fs 20 times using a constraint with spring constant of 1000.0 g/mol fs^2, and average the force across 20 pulls to find the work and thus the change in free energy using Jarzynski's relation.

Thermodynamic Integration Setup: In order to test the change in free energy from the inside of the micelle to the outside or bulk solution water, we set up two simulation boxes—one containing a slice of a periodic worm micelle, and the other containing a spherical micelle composed of the same molecular weight copolymers as shown in **Figure 1**. Parameters for the simulation are the same as described for the octanol water setup, except the size of the two simulation boxes at equilibrium are approximately 340 Å x 340 Å x 90 Å and 260 Å x 270 x 270 Å respectively. In addition, we next start by setting up thermodynamic integration calculations for CG paclitaxel by confining the drug at a radial distance, allowing free angular

rotation and movement in the angular plane, from the inside to the outside of the micelle, starting at the center of mass of the worm micelle and by increasing each simulation point by 5 Å respectively, until the paclitaxel distance from the center of mass of the micelle is inside of the bulk water in solution. We constrain paclitaxel at each point using a harmonic force with spring constant of 10.0 g/mol fs^2. In addition we constrain the center of mass of the micelle with a harmonic force with spring constant of 1000.0 g/mol fs^2. At each distance, we simulate the system for 25 ns, for a total of 250 ns simulation time for each micelle.

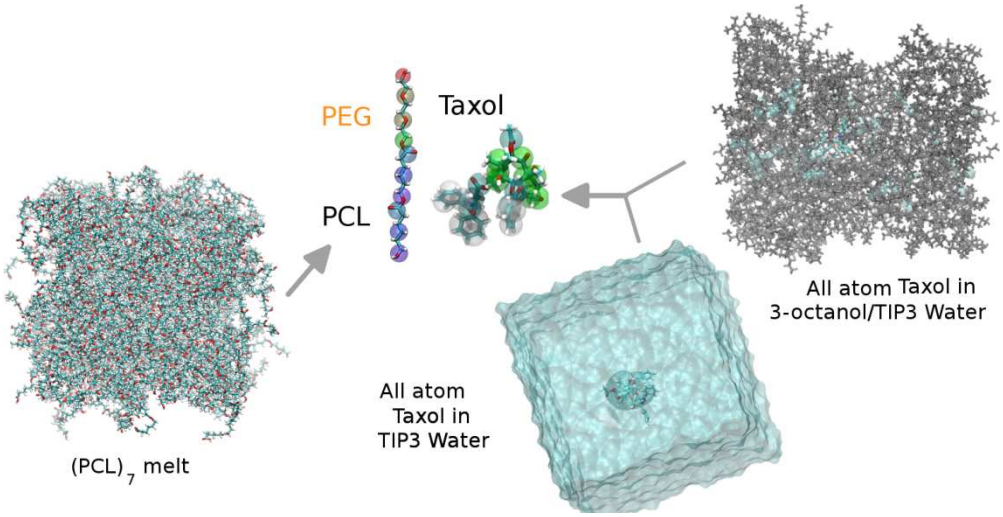
Higher Concentrations Setup: Two sets of simulations were run for approximately 300ns, one of a PEG_{2000}-PCL_{5000} worm micelle at 3wt% taxol loading, one of a worm micelle at 9 wt% taxol loading. The simulation box size is 320 Å by 320 Å by 500 Å.

Weak segregation and the diffuse interface: The smallest monomer volume of the two respective polymers is used, by convention to calculate the interaction parameter:

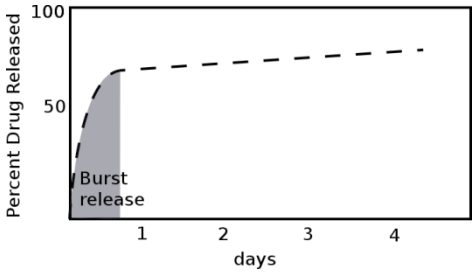
$$\chi = \frac{V_m}{k_B T(\delta_i - \delta_j)^2}. \qquad (3)$$

The difference in Hildebrand solubility parameters δ_i and δ_j is for PEG and PCL. The monomer volume (V_m) for PEG is 41.4 cm^3/mol, for PCL is 59.9 cm^3/mol (obtained from all-atom molecular dynamics), and for PBD is 31.1 cm^3/mol. The approximate Hildebrand solubility parameter (δ) for PEG is 14.1cal/cm^3, for PCL is 11.2 cal/cm^3 [3]. From this value of $\chi_{PEG\text{-}PCL}$, we can estimate the interfacial tension and width assuming SST (strong segregation theory), as 2.7mN/m and 15 Å. Additionally, scaling of the hydrophobic core size, R_{core}, with the length of the hydrophobic tail, M_h, fits the power law $R_{core} \sim M_h^{1/2}$ as shown in **Figure S1**, with the molecular weight of the tail increasing from 5000, 7500, to 1000 Da's in the worm micelle phase. This is an indication of weak segregation, or a random polymer chain.

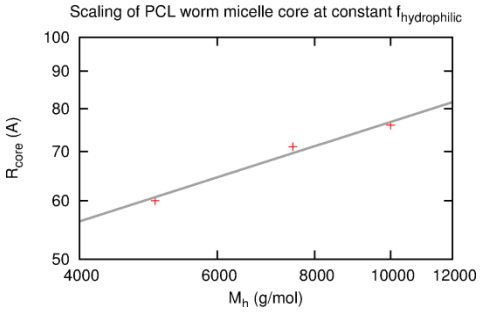
[1] D. Sutton, S. Wang, N. Nasongkla, J. Gao and E. E. Dormidontova, *Exp Biol Med (Maywood)* **2007**, *232*, 1090.
[2] D. Sept and F. C. MacKintosh, *Phys Rev Lett* **2010**, *104*, 018101.
[3] J. Liu, Y. Xiao and C. Allen, *J Pharm Sci* **2004**, *93*, 132.



Supp. Fig S1. Process of creating the CG model for PCL and Taxol. Bonds and angles are obtained from all-atom simulations of a PCL_7 melt. Taxol bonds and angles are likewise obtained from all-atom simulations of drug in TIP3 water and also a mixture of 3-ocanol and water. Short range, or Lennard Jones type interactions, are mapped from small chemical groups, which are defined in Supp. Table 1. and Supp. Table 2. Bonds and angles are obtained using an inverse Boltzmann technique and are defined in Supp. Table 4 for PCL



Supp. Fig S2. Schematic illustrating burst release. Solute loaded close to the interface of a micelle is quickly released in less than 24 hours, followed by the rest of the solute at a much slower rate.



Supp. Fig S3. Scaling of the hydrophobic core size R_{core} of Worm micelles with the length of the hydrophobic tail M_h fits a power law $R_{core} \sim M_h^{0.5}$. This scaling is appropriate for random polymer in a melt and this indicates minimal effects of interfacial tension on chain configurations and thus weak segregation.

Supp. Table 1. PEG-PCL CG Mapping. The mapping for PEG that of Shinoda et al., while the mapping for PCL consists of 3 different CG beads for every CL monomer as shown in Figure 1A.

CG Monomer	Chemical Structure
W	$(H_20)_3$
EO	$-CH_2-0-CH_2-$
OA	$H0CH_2-$
CM	$-CH_2CH_2CH_2-$
M1	$-C0\ CH_2-$
M2	$-CH_2\ O-$

Supp. Table 2. Taxol CG Mapping as shown in Figure 1A. Taxol is divided into 23 beads, of chain type, benzene type, and ring type, and individual molecular mappings are found for each bead, with some simplifications being made.

CG Monomer	Chemical Structure
W	$(H_20)_3$
CC1	formamide
CC2	ethanol
CC3	ester
CC4	acetate
CC5	ester
CC6	acetate
R1a	½ benzene
R1b	CH3-CH2-CH3
R1c	CH2-CH2-OH
R2a	ethanol
R2b	1/2 benzene
R3	ethanol
R4a	1/3 benzene
R4b	OA
B1a	1/3 benzene
B1b	1/3 benzene
B1c	1/3 benzene
B2a	1/3 benzene
B2b	1/3 benzene
B2c	1/3 benzene
B3a	1/3 benzene
B3b	1/3 benzene
B3c	1/3 benzene

Supp. Table 3. Summary of PEG-PCL simulations for study of phase behavior. Simulation morphology ranges from loose aggregates to a frustrated bilayer assembly to the worm or spherical micelle case. Higher molecular weight aggregates are pre-formed in the experimental morphology and the simulation is run for several hundred nanoseconds.

Diblock	Diblock (g/mol)	Experimental Morphology	Simulation Morphology	Agg. Core Thickness (Simulation)
PEG_{23}-PCL_4	PEG1000-PCL500	undetermined	Loose aggregates	N/A
PEG_{23}-PCL_9	PEG1000-PCL1000	Spherical (dominant)	Sphere	~
PEG_{23}-PCL_{26}	PEG1000-PCL3000	Bilayer(dominant) + Sphere	Bilayer / Sphere	42 Å (bilayer)
PEG_{45}-PCL_{44}	PEG2000-PCL5000	Worm (dominant by weight %) + Sphere	Worm / Sphere	60 Å (worm)
PEG_{46}-PCL_{67}	PEG2000-PCL7700	Bilayer	Bilayer	50 Å (bilayer)
PEG_{111}-PCL_{66}	PEG4800-PCL7500	Worm	Worm	71 Å (worm)
PEG_{148}-PCL_{88}	PEG6500PCL10000	Worm	Worm	76 Å (worm)