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Spatial Distribution of Hydrophobic Drugs in Model Nanogel-Core Star Polymers

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Abstract

Star polymers with a cross-linked nanogel core are promising carriers of cargo for therapeutic applications due to the synthetic control of amphiphilicity of arms and stability at infinite dilution. Three nanogel-core star polymers were investigated to understand how the arm-block chemical structure controls loading efficiency of a model drug, ibuprofen, and its spatial distribution. The spatial distribution profiles of hydrophobic core, hydrophilic corona, and encapsulated drug were determined by small-angle neutron scattering (SANS). SANS provides the nanometer-scale sensitivity to determine how the arm-block chemistry enhances the sequestering of ibuprofen. Validated molecular dynamics simulations capture the trends in drug profile and polymer segment distribution with further details on drug orientation distribution. This work provides a basis to study structure–function relationships in macromolecular-based carriers of cargo and represents a path toward validated and predictive simulation.

Graphical Abstract

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ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.macromol.7b02061](https://doi.org/10.1021/acs.macromol.7b02061). Scattering length density (SLD), modeling of small-angle neutron scattering, SANS fit results, transmission electron microscopy (TEM), Flory–Huggins parameter χ , UV–vis calibration curve (PDF)

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INTRODUCTION

Polymer nanoparticles provide advanced materials for the encapsulation and targeted delivery of drugs. The loading characteristics depend on several design criteria including thermodynamic compatibility, size characteristics, and interfacial energy. Block copolymer micelles represent model structures that take advantage of relative affinity of cargo for one component, often the hydrophobic core. However, block copolymer micelles, due to their self-assembled state, upon incorporation of cargo may influence the overall micelle aggregation number—the average number of polymers forming the micelle above the critical micelle concentration. For instance, the small-angle neutron scattering (SANS) results of Foster et al.¹ and Alexander et al.² studied the uptake of ibuprofen and flurbiprofen, respectively, in Pluronic block copolymer micelles. They observed that drug loading into the micellar core increases the fraction of micellization and aggregation number. Akiba et al. measured the encapsulation of the hydrophobic retinoid antagonist drug (LE540) into the micellar core formed by poly(ethylene glycol)-*block*-poly-(partially benzyl-esterified aspartic acid), PEG-P(Asp(Bzl)), diblock copolymers.³ In this case, LE540 was uniformly distributed within the core with simultaneous increase in aggregation number. A slightly different behavior in the same system was observed by Sanada et al., whereby hydrophobic tetrabromocathecol distribute at the core–corona interface without changing the aggregation number.⁴ These sensitive anomalous X-ray scattering experiments, quantified by a model, demonstrate the coupled spatial distribution of cargo and block copolymer micelle aggregation characteristics.

Even slight changes in drug polarity alters the spatial distribution. Nakanishi et al. found 4-bromobenzyl alcohol was homogeneously dispersed in the hydrophobic core of block copolymer micelles while bromobenzene formed a depletion layer at the core–shell interface.⁵ Similarly, an extensive study by Valero et al.⁶ found that the drug chemical

structure has a strong correlation with the spatial localization of drugs in F127 Pluronic block copolymer micelles. Therefore, the uniformity of the hydrophobic molecules distributed within polymeric micelles is affected by polarity.

One approach to decouple the polymer micelle aggregation characteristics and solute loading is to use a covalently bonded polymer nanoparticle. Recent synthetic advancements have led to increased interest in star and branched polymers as micelle replacements.^{7–9} Nanogel-core star polymers offer a covalently cross-linked core surrounded by water-soluble radiating arms.^{9–12} The cross-linked nanogel core is hydrophobic, and additional hydrophobic segments are incorporated via blocks on the star arms with outermost hydrophilic segments providing stabilized nanostructures in water. Since this covalently assembled macromolecule does not have a critical micelle concentration, upon infinite dilution under delivery conditions it will not revert to unimers like block copolymer micelles. The hydrophobic cross-linked core and flexible hydrophobic star-arm segments are rationalized to serve as the cargo space.

We study the effect of homopolymer, diblock, and terpolymer star arms on the spatial distribution of a model hydrophobic drug, ibuprofen. n Gel-(EG₁₁₄)_{*f*} is composed of *f* homopolymer arms of poly(ethylene glycol) (EG₁₁₄), with degree of polymerization of 114, that radiate from the cross-linked hydrophobic caprolactone (CL) nanogel core (*n*Gel). The diblock arms of n Gel-(VL₂₃-EG₁₁₄)_{*f*} consists of an inner hydrophobic block of poly(valerolactone) (VL₂₃) and an outer hydrophilic block of EG₁₁₄. The terpolymer arms of n Gel-(VL₁₁-*t*BuCL₁₀-EG₁₁₄)_{*f*} consist of an inner hydrophobic poly(valerolactone)-*c*o-poly(4-*tert*-butylcaprolactone) (VL₁₁-*t*BuCL₁₀) and an outer hydrophilic block of EG₁₁₄. SANS measurements are combined with Pedersen's spherical micelle scattering model to study how the star arm chemistry controls the loading and spatial distribution of ibuprofen. SANS enables us to determine the spatial distribution profiles of the hydrophobic core, hydrophilic corona, and encapsulated drugs. The experiments and analysis make simplifying assumptions that were tested by independent molecular dynamics (MD) simulation and drug loading estimates by ultraviolet (UV)–vis spectroscopy.

MATERIALS AND METHODS

Nanogel-core star polymers were synthesized and characterized as reported previously.¹² The synthetic conditions for the cross-linked caprolactone nanogel-core preparation were kept constant in order to achieve core structures and average number of arms fixed. Inhibitor-free tetrahydrofuran (THF) was purchased from Sigma-Aldrich. Deuterium oxide (D₂O, 99.9 D atom %) and *d*-tetrahydrofuran (*d*-THF, 99.95 D atom %) were purchased from Cambridge Isotope Laboratories. Ibuprofen was purchased from Spectrum Chemical Mfg. Corp. and used as received. Poly(ethylene glycol) methyl ether (number-average relative molecular mass, M_n = 5000 Da, PDI = 1.01) was purchased from Sigma-Aldrich. Deuterated poly(ethylene glycol) methyl ether (M_n = 5000 Da, PDI = 1.08) was obtained from Polymer Source. Both polymers were kept under vacuum at 50 °C for 24 h prior to use and characterized by the manufacturer for their relative number-average molar mass (M_n) and polydispersity index (PDI). Table 1 shows the chemical structures of nanogel-core star polymers studied in this work.

Sample Preparation.

Nanogel-Core Star Polymer in d-THF.—Nanogel-core star polymers were dissolved directly in inhibitor free *d*-THF as clear solutions of 0.4 mass % with stirring at 40 °C for 30 min. After approximately 24 h at room temperature, the solutions were diluted to the required concentrations of 0.1%–0.4%.

Nanogel-Core Star Polymer in D₂O.—For *n*Gel-(*d*-EG₁₁₄)_f and *n*Gel-(EG₁₁₄)_f 40 mg of nanogel-core star polymer was dissolved in 2 mL of D₂O directly. The solution was filtered through 0.45 μm PVDF syringe filter after stirring at room temperature overnight. For *n*Gel-(VL₂₃-EG₁₁₄)_f and *n*Gel-(VL₁₁-*t*BuCL₁₀-EG₁₁₄)_f 40 mg of nanogel-core star polymer was dissolved in 0.4 mL of inhibitor-free THF. 2 mL of D₂O was added, while stirring, and left at room temperature overnight. The mixture was filtered through a 0.45 μm PTFE syringe filter, and the obtained solution was sparged in a nitrogen stream to remove THF. The sparging process was stopped when 250 mass % of the added THF had been removed, and the solution was diluted to 2% by D₂O assuming no polymer loss. Precipitate was observed for *n*Gel-(VL₂₃-EG₁₁₄)_f.

Ibuprofen Loaded Nanogel-Core Star Polymer in D₂O.—Ibuprofen loading was accomplished by adding 4 mg of ibuprofen to 40 mg of *n*Gel-(*d*-EG₁₁₄)_f, *n*Gel-(EG₁₁₄)_f, *n*Gel-(VL₂₃-EG₁₁₄)_f, and *n*Gel-(VL₁₁-*t*BuCL₁₀-EG₁₁₄)_f before dissolution in 0.4 mL of inhibitor-free THF and following an identical procedure to *n*Gel-(VL₂₃-EG₁₁₄)_f and *n*Gel-(VL₁₁-*t*BuCL₁₀-EG₁₁₄)_f in D₂O.

UV–Vis Spectroscopy.

The amount of loaded ibuprofen in nanogel-core star polymers was determined using a Varian Cary 5000 UV–vis–near-infrared spectrophotometer at room temperature with quartz cuvettes of 10 mm path length. In short, 150 μL of 2% ibuprofen loaded nanogel-core star polymer in aqueous solution was first air-dried under room temperature and then redissolved in 3 mL of inhibitor-free THF to release ibuprofen into solution. The amount of loaded ibuprofen was determined by UV–vis absorbance at 264 nm referenced to a calibration curve of ibuprofen in THF over the concentration range of 12.5–400 μg/mL. The polymer absorbance at 264 nm was subtracted. Free ibuprofen was also subtracted at an amount equal to the equilibrium solubility in water, which is 0.0127 mg/mL at 25 °C.¹³ Ibuprofen loading efficiency (%) was calculated by amounts of ibuprofen loaded/amounts of ibuprofen fed × 100.

Small-Angle Neutron Scattering (SANS).

SANS measurements were performed at the National Institute of Standards and Technology, Center for Neutron Research (NCNR) NG7 SANS and NGB 10m *n*SOFT beamlines with cold neutrons. The scattered intensity $I(q)$ was measured as a function of the wave vector (q) defined by $q = (4\pi/\lambda) \sin(\theta/2)$, where θ is the scattering angle and λ is the neutron wavelength. For the NG7 instrument, λ was 6 Å with $\lambda/\lambda \approx 0.14$ and used three sample-to-detector distances (1, 4, and 13 m) to provide a q range of 0.04–5 nm^{−1}. For the NGB instrument, the two wavelength settings were used across three sample–detector distances: $\lambda = 10$ Å at 5.2 m and $\lambda = 5$ Å at both 5.2 and 1.2 m with fixed $\lambda/\lambda \approx 0.15$ leading to similar

q ranges. All samples were measured in 1 or 2 mm path length Hellma quartz cells at 25 °C. Data were placed on an absolute intensity scale via direct beam flux measurement, detector sensitivity and element size, transmission, sample-to-detector distance, and sample scattering volume considerations. Standard data reduction routines and scaling to absolute intensity measurements were applied.¹⁴ Background intensity due to incoherent scattering contributions from protons and solvent scattering was experimentally estimated and subtracted using established methods.¹⁵ Uncertainties (error bars) are estimated by one standard deviation of the mean by least-squares minimization of fits to the SANS data. Modeling details of SANS data are provided in the Supporting Information.

Differential Scanning Calorimetry (DSC) Measurements.

DSC measurements were carried out with a Shimadzu DSC 7 calorimeter at a heating rate 10 °C/min. Samples were first subjected to heating to 150 °C and then cooled down to 40 °C at the maximum cooling rate. The glass transition temperature (T_g) was measured in the second heating ramp.

Molecular Dynamics Simulations.

All-atom MD simulation of the nanogel core with 16 emanating star arms of VL₁₆-EG₂₄ with explicit water were performed using the LAMMPS simulation software package¹⁶ on an IBM BlueGene/Q supercomputer. The force field used OPLS-AA parameters^{17,18} for ibuprofen, OPLS-AA with slight modification for the star polymer, and TIP4P-Ew for water,¹⁹ as described previously.²⁰ The simulations included 106 950 water molecules in a cubic simulation cell with an edge length of approximately 14.9 nm. Simulations were performed at 350 K using NVT ensemble, with a production phase of 50 ns after equilibration.

SANS Model Background.

In order to understand the nanogel-core star polymer structure, we utilize the model developed by Pedersen for spherical micelles.^{21,22} This model provides a molecular analysis of the micelle with a spherical core surrounded by f_{arm} Gaussian chains at the core surface, as depicted in Figure 1a. The details are in the original papers, but we provide a brief account relevant to the discussion. As shown in eq 1, $P(q)$ is Pedersen's form factor that contains contributions to the total particle scattering from self-correlations and pair-correlations

$$P(q) = \beta_{\text{core}}^2 P_{\text{core}}(q) + f_{\text{arm}} \beta_{\text{chain}}^2 P_{\text{chain}}(q) + 2f_{\text{arm}} \beta_{\text{core}} \times \beta_{\text{chan}} S_{\text{core-chain}}(q) + f_{\text{arm}}(f_{\text{arm}} - 1) \beta_{\text{chain}}^2 S_{\text{chain-chain}}(q) \quad (1)$$

The self-correlations from the core and chain are within $P_{\text{core}}(R_{\text{core}}, \sigma, q)$ and $P_{\text{chain}}(R_g, q)$ that are modeled by a spherical core and a Debye chain, respectively; the parameters in these functions are core size (R_{core}), core-corona interfacial width (σ), and chain radius of gyration (R_g) as indicated within the function and defined in Figure 1a. The cross-correlations within the micelle between chains at the core surface are determined by $S_{\text{chain-chain}}(A_{\text{chain}}, \sigma, q)$ while chain-core correlations by $S_{\text{core-chain}}(A_{\text{chain}}, R_{\text{core}}, \sigma, q)$. In this case the scattering amplitude (A_{chain}) of corona chains are modeled by the Fourier transform of a *Spline* 2 chain segmental density profile (eqs 9 and 35 in ref 22). The total

excess scattering lengths of the hydrophobic block in core (β_{core}) and hydrophilic block in corona (β_{chain}) are calculated based upon the specific volumes and scattering length density (SLD) differences with the solvent. The details of the SLD calculations are displayed in the Supporting Information.

The monodisperse form factor, $P(q)$, was averaged over a Schulz–Zimm distribution of average core radius ($\bar{R}_{\text{core}}$) and polydispersity index $\rho = \sigma_R / \bar{R}_{\text{core}}$, where σ_R is the variance. The experimental absolute SANS intensity of $I(q)$ is given by

$$I(q) = \frac{c}{M} P_{\text{poly}}(q) S(q) \quad (2)$$

where P_{poly} is the polydispersity-averaged form factor, c is the mass concentration of polymer, and M is the mass-average molecular mass of a nanogel-core star polymer. $S(q)$ is the hard sphere structure factor to account for interparticle correlations characterized by hard sphere volume fraction and effective radius. The average radial concentration distribution $\phi(r)$, as shown in Figure 1b, is obtained using the method outlined by Pedersen via the Fourier transform of the combined core and corona amplitudes, A_{mic} , as expressed by eq 3 (also see eq 16 in ref 23 and eq 18 in ref 24). The amplitudes of A_{mic} for the core and corona weighted by the molar volumes are described in the Supporting Information.

$$\phi(r) = \frac{1}{2\pi^2} \int_0^\infty A_{\text{mic}}(q) \frac{\sin qr}{qr} q^2 dq \quad (3)$$

Pedersen's micelle model was programmed into the Igor Pro software using available libraries from the NCNR data analysis packages. In organic solvent of *d*-THF, a global fitting method within the Igor Pro software was used to simultaneously fit the SANS data sets with common $\bar{R}_{\text{core}}$, R_g , f_{arm} , and f_{solv} for each nanogel-core star polymer at different polymer concentrations. In the solvent D₂O, f_{arm} of each polymer is set to be the same as the value in *d*-THF, since the star arms are covalently bonded. The strategy of isotopic substitution of hydrogen for deuterium is used to increase the sensitivity to different parts of the micelle. D₂O was used in conjunction with hydrogenous polymers to observe the whole micelle structure; select deuteration of the PEG chain in the presence of D₂O increased the sensitivity to the core–PEG interface. Common $\bar{R}_{\text{core}}$ and f_{arm} are used for *n*Gel-(EG₁₁₄)_{*f*} and *n*Gel-(*d*-EG₁₁₄)_{*f*} in the global fitting method. MD simulations of methoxypoly(ethylene glycol)-*block*-polycaprolactone (MePEG-*b*-PCL) found the PCL core excludes water.²⁵ Similarly, nuclear magnetic resonance spectra found water does not solvate VL.¹² Based on these, no solvent of D₂O was allowed ($f_{\text{solv}} = 0$) to swell the core during SANS model fit.

Several alternative analytic SANS models are available,¹⁴ and a question may be raised regarding the curve fitting uniqueness. However, few systematically treat the correlations as outlined by Pederson. The regression results are least-squares solutions and tested for self-consistency among the core size, arm radius of gyration, organic versus aqueous solvent, and polymer concentration. The internal consistency of the parameters with independent measurements appears favorable and is discussed.

RESULTS AND DISCUSSION

Drug–Polymer Interactions and Loading Efficiency.

The thermodynamic solubility of drug in the hydrophobic core may be estimated by the Flory–Huggins parameter (χ), such that the smallest χ indicates highest compatibility.^{26,27} Table 2 shows the predicted compatibility of the different polymer segments with ibuprofen and solvent (D₂O). The group contribution method of Hoftyzer and Van Krevelen^{28,29} shows that ibuprofen compatibility is highest (smallest χ) for *t*BuCL, suggesting ibuprofen has a higher solubility within *n*Gel-(VL₁₁-*t*BuCL₁₀-EG₁₁₄)_f than *n*Gel-(VL₂₃-EG₁₁₄)_f. Interestingly, as shown in Table 1, the drug loading efficiency of *n*Gel-(VL₁₁-*t*BuCL₁₀-EG₁₁₄)_f is 110% higher than *n*Gel-(VL₂₃-EG₁₁₄)_f, which is consistent with the trend of χ parameter. However, this approach reflects only compatibility arguments, not additional interfacial packing effects. For instance, the 6% loading efficiency of *n*Gel-(EG₁₁₄)_f shown in Table 1 may be due to less bulk cargo space because of the smaller core (bulk loading limited) or less interfacial area for drug packing (surface area limited). To explore this, SANS quantified by a detailed scattering molecular model are used to find the drug profile. These results are then compared to MD simulations.

Structures in *d*-THF.—The star arms of EG₁₁₄ and VL₁₁-*t*BuCL₁₀-EG₁₁₄, as well as the cross-linked caprolactone nanogel core, are swollen by *d*-THF. In dilute solutions of *d*-THF, nanogel-core star polymers provide a rigorous test of Pedersen's model. Figure 2 shows a concentration-dependent fit to *n*Gel-(EG₁₁₄)_f and *n*Gel-(VL₁₁-*t*BuCL₁₀-EG₁₁₄)_f. The f_{arm} of each star polymer is shown in Table 1. The agreement of f_{arm} between SANS and GPC light scattering confirms the validity of the model for nanogel-core star polymers. The value of f_{arm} obtained in *d*-THF may then be used in D₂O. The volume fraction of *d*-THF in the cross-linked caprolactone nanogel core is $f_{\text{solv}} \approx 13\%$, indicating the caprolactone nanogel core is highly cross-linked.

Model-independent Zimm plots are also shown in the insets of Figure 2. H is the neutron optical constant and k an arbitrary scaling factor. The molecular mass of the overall star polymer are in Table 1. In this case, the number of star arms per polymer was estimated by $f_{\text{arm}} = M_w/M_{w,\text{arm}}$ which ignores the molecular mass of the cross-linked nanogel core. M_w and f_{arm} in *d*-THF by SANS are qualitatively in agreement with the values by GPC light scattering. This provides the confidence to extend Pedersen's model to D₂O, where quality GPC light scattering was unavailable.

Structure in D₂O.—In D₂O, cross-linked caprolactone nanogel core, VL₂₃ and VL₁₁-*t*BuCL₁₀ blocks become insoluble and collapse.³⁰ Representative SANS data of *n*Gel-(*d*-EG₁₁₄)_f, *n*Gel-(EG₁₁₄)_f, *n*Gel-(VL₂₃-EG₁₁₄)_f and *n*Gel-(VL₁₁-*t*BuCL₁₀-EG₁₁₄)_f before and after drug encapsulated are displayed in Figure 3. The data have several prominent features. All curves of protonated polymers (Figure 3b–d) follow $\approx q^{-2}$ dependence at higher q due to the Gaussian chain scattering.³¹ A peak becomes pronounced at $0.7 \text{ nm}^{-1} < q < 1.5 \text{ nm}^{-1}$ as the arm structure changes from EG₁₁₄ to VL₂₃-EG₁₁₄ to VL₁₁-*t*BuCL₁₀-EG₁₁₄. This peak results from the dense hydrophobic core with narrow size distribution. The peak shifts to lower q with added drugs that may reflect bulk core swelling or packing of drugs at the

core–arm interface. The curves of deuterated $n\text{Gel}-(d\text{-EG}_{114})_f$ in Figure 3a show deviation from q^{-2} dependence at higher q , resulting from the low contrast between $d\text{-EG}_{114}$ and D_2O . The scattering contribution of $d\text{-EG}_{114}$ chains is lower, leading to a higher resolution of the hydrophilic and hydrophobic interphase. Further analysis by the model quantifies the behavior.

Hydrophobic Core Structure: Before and after Ibuprofen Loading.—For $n\text{Gel}-(\text{EG}_{114})_f$ and $n\text{Gel}-(d\text{-EG}_{114})_f$ the cross-linked caprolactone nanogel core provides a cargo space for partitioning of hydrophobic drugs based upon solubility parameters. The size and polydispersity of the cross-linked nanogel core and the subsequent packing of the hydrophobic segments from the emanating arms change the overall hydrophobic core size, as shown in Table 3. $n\text{Gel}-(\text{EG}_{114})_f$ shows an average $\bar{R}_{\text{core}} = 2.54 \pm 0.9$ with polydispersity index of $\sigma_R/\bar{R}_{\text{core}} = 0.53 \pm 0.20$ from a Schulz–Zimm distribution. The polydispersity eliminates any expected SANS peaks from the spherical core. However, the peak becomes more pronounced in $n\text{Gel}-(\text{VL}_{23}\text{-EG}_{114})_f$ and $n\text{Gel}-(\text{VL}_{11}\text{-}t\text{BuCL}_{10}\text{-EG}_{114})_f$ as the total size of the hydrophobic core increases to 5.62 ± 0.07 and 4.95 ± 0.05 nm with lower polydispersity of 0.16 ± 0.01 and 0.14 ± 0.01 . Transmission electron microscopy on $n\text{Gel}-(\text{VL}_{23}\text{-EG}_{114})_f$ estimates an average core size of ≈ 5.3 nm, consistent with SANS (Supporting Information). The fractional increase in the hydrophobic core size is from the packing of the VL_{23} and $\text{VL}_{11}\text{-}t\text{BuCL}_{10}$ hydrophobic segments. These results verify recent MD simulations that show segmental packing of VL blocks upon a small cross-linked CL core.^{25,32,33} MD simulations further suggest $t\text{BuCL}$ segments pack less effectively than VL.³² This poorer packing may enhance the mobility within the hydrophobic core to reduce shape anisotropy under the interfacial tension with water.

In Table 3, a significant increase of $\bar{R}_{\text{core}}$ was observed after drug loading. The packing of drug reduces the core polydispersity for $n\text{Gel}-(\text{EG}_{114})_f$ while no effect was observed for $n\text{Gel}-(\text{VL}_{23}\text{-EG}_{114})_f$ and $n\text{Gel}-(\text{VL}_{11}\text{-}t\text{BuCL}_{10}\text{-EG}_{114})_f$. Drug molecules may not swell the cross-linked core, but rather reside at the core–arm interface. The locally rough surface and core interface of $n\text{Gel}-(\text{EG}_{114})_f$ could be smoothed by drug adsorption, since uniform swelling would not affect polydispersity. The z -average R_g of PEG arm chains are obtained from Pedersen's model. As shown in Table 3, all the values of R_g are smaller than the value of 2.3 nm calculated for Gaussian coils of PEG $M_n = 5$ kg/mol.³⁴ After drug loading, R_g of PEG in $n\text{Gel}-(\text{EG}_{114})_f$ remains constant, while it slightly decreases for $n\text{Gel}-(\text{VL}_{23}\text{-EG}_{114})_f$ and $n\text{Gel}-(\text{VL}_{11}\text{-}t\text{BuCL}_{10}\text{-EG}_{114})_f$ in the presence of higher drug loading. This coil contraction effect, while small, may reflect the locally poorer solvent conditions for PEG in the presence of drug and is discussed in the context of quantifying the spatial profiles. R_g of PEG is not shown for $n\text{Gel}-(d\text{-EG}_{114})_f$ because the neutron contrast between $d\text{-EG}$ and D_2O was very low.

Concentration Profiles.—Pedersen's model estimates the average radial concentration distribution $\phi(r)$ via modeling the core and corona in a piecewise manner and then Fourier transforming the combined form factor amplitude $A_{\text{mic}}(q)$. In our case, the *Spline 2* model was used that smoothly connects the polymer segmental profile to the uniform density core

by an interfacial width. Since D₂O did not swell the hydrophobic core ($f_{\text{solv}} = 0$), one may normalize the concentration profiles as described by Pedersen and Gerstenberg.³⁵

Figure 4 shows the total hydrophobic core, $\phi_{\text{core}}(r)$, and PEG, $\phi_{\text{PEG}}(r)$, concentration profiles for nanogel-core star polymer before and after ibuprofen loading. Figure 4a shows the hydrophobic core with unit normalized volume fraction with diffuse core to star arm interface characterized by the interfacial width (σ). After drug loading, the spatial distribution of the hydrophobic core expands with values shown in Table 3. The loaded drugs are considered as a part of $\phi'_{\text{core}}(r)$, since neutrons cannot distinguish drug molecules and hydrophobic segments unless one of them is deuterated. As shown in Figure 4b, the hydrophobic core overlaps with the PEG profile due to the covalent connectivity.

In Figure 4b, the segmental concentration of PEG reaches a maximum of $\approx 10\%$, consistent with highly swollen star arms at relatively low graft density. This level of PEG hydration agrees with SANS results of F127 Pluronic micelles modeled as a core-shell, not by Pedersen's model.⁶ The abscissa is normalized by the total hydrophobic core radius ($\bar{R}_{\text{core}}$) to show how the tethered PEG chains shift as drug is encapsulated. Figure 4b shows $\phi^{\circ}_{\text{PEG}}(r)$ of $n\text{Gel}-(\text{EG}_{114})_f$ has the lowest overlap with $\phi^{\circ}_{\text{core}}(r)$, indicating the cross-linked caprolactone nanogel core is impermeable. As drug is encapsulated, no spatial expansion of the cross-linked core could be permitted thus drugs could only locate at the cross-linked core-arm interface. The anchored end of PEG to the cross-linked core surface does not shift since the cross-linked core does not swell. The encapsulated drugs at the cross-linked Core-arm interface contribute to $\phi'_{\text{core}}(r)$. The total hydrophobic core of $n\text{Gel}-(\text{EG}_{114})_f$ increases, and the anchored ends of PEG chains are buried. When normalized by the total core radius, $\phi'_{\text{PEG}}(r)$ of $n\text{Gel}-(\text{EG}_{114})_f$ shifts toward the interior of the hydrophobic core compared to $\phi^{\circ}_{\text{PEG}}(r)$, as shown in Figure 4b. This result confirms the prediction³⁰ that for $n\text{Gel}-(\text{EG}_{114})_f$ the drug resides at the interface of the core-PEG without substantial swelling of the core by mobile drug molecules. In contrast, $\phi_{\text{PEG}}(r)$ of $n\text{Gel}-(\text{VL}_{23}-\text{EG}_{114})_f$ and $n\text{Gel}-(\text{VL}_{11}-t\text{BuCL}_{10}-\text{EG}_{114})_f$ shows that the anchored ends of PEG chains shift away from the core center spontaneously with the expansion of total hydrophobic core. This is observed by the nearly constant tail of the distribution at $(r - \bar{R}_{\text{core}} \leq 0)$. This does not lead to substantially different PEG swelling or PEG spatial extent profile but corresponds to spatial expansion of mobile hydrophobic blocks (VL₂₃ or VL₁₁-*t*BuCL₁₀) as drug is encapsulated. Based on these results, the drug penetrates to the interior of hydrophobic core enabled by the repartitioning of the VL₂₃ or VL₁₁-*t*BuCL₁₀ segments in $n\text{Gel}-(\text{VL}_{23}-\text{EG}_{114})_f$ and $n\text{Gel}-(\text{VL}_{11}-t\text{BuCL}_{10}-\text{EG}_{114})_f$ while the cross-linked core remains unchanged.

Estimate for Spatial Distribution of Drug.—For $n\text{Gel}-(\text{EG}_{114})_f$ and $n\text{Gel}-(d\text{EG}_{114})_f$ without ibuprofen, the total hydrophobic core concentration profile ($\phi^{\circ}_{\text{core}}(r)$) is the same as the cross-linked caprolactone nanogel core ($\phi^{\circ}_{n\text{Gel}}(r)$), $\phi^{\circ}_{n\text{Gel}}(r) = \phi^{\circ}_{\text{core}}(r)$. As ibuprofen is loaded, the total hydrophobic core ($\phi'_{\text{core}}(r)$) contains two additive-by-volume parts, such that $\phi'_{\text{core}}(r) = \phi'_{n\text{Gel}}(r) + \phi_{\text{IBU}}(r)$, where $\phi'_{n\text{Gel}}(r)$ is the concentration profile of the cross-linked caprolactone nanogel core after ibuprofen loaded, and $\phi_{\text{IBU}}(r)$ is the concentration profile of loaded ibuprofen. Since the nanogel cross-linked caprolactone core does not change in the

presence of ibuprofen $\phi'_{n\text{Gel}}(r) = \phi^{\circ}_{n\text{Gel}}(r)$, the concentration profile of loaded ibuprofen in $n\text{Gel}-(\text{EG}_{114})_f$ and $n\text{Gel}-(d\text{EG}_{114})_f$ may be estimated by the difference in profiles, $\phi_{\text{IBU}}(r) = \phi'_{\text{core}}(r) - \phi'_{n\text{Gel}}(r)$.

For $n\text{Gel}-(\text{VL}_{23}-\text{EG}_{114})_f$ and $n\text{Gel}-(\text{VL}_{11}-t\text{BuCL}_{10}-\text{EG}_{114})_f$, the total hydrophobic core concentration profiles can be generalized in the presence of the hydrophobic copolymer (HCP) arm segments before drug loading, $\phi^{\circ}_{\text{core}}(r) = \phi^{\circ}_{n\text{Gel}}(r) + \phi^{\circ}_{\text{HCP}}(r)$ and after drug loading $\phi'_{\text{core}}(r) = \phi'_{n\text{Gel}}(r) + \phi'_{\text{HCP}}(r) + \phi_{\text{IBU}}(r)$, where $\phi^{\circ}_{\text{HCP}}(r)$ and $\phi'_{\text{HCP}}(r)$ are the concentration profiles of hydrophobic copolymer arm segments before and after drug loading, respectively. For $n\text{Gel}-(\text{VL}_{23}-\text{EG}_{114})_f$ HCP represents VL_{23} , while for $n\text{Gel}-(\text{VL}_{11}-t\text{BuCL}_{10}-\text{EG}_{114})_f$ HCP is $\text{VL}_{11}-t\text{BuCL}_{10}$. As ibuprofen is loaded, the collapsed HCP segments are swollen and spatial distribution of HCP segments changes, but the total numbers of HCP segments and cross-linked nanogel core remain constant. Therefore, by conservation of mass of the cross-linked nanogel core and total HCP segments, $m_{n\text{Gel}} + m_{\text{HCP}}$ are related to the concentration profiles before and after loading by

$$\begin{aligned} m_{n\text{Gel}} + m_{\text{HCP}} &= \int_0^{\xi} [\phi^{\circ}_{n\text{Gel}}(r) + \phi^{\circ}_{\text{HCP}}(r)] r^2 dr \\ &= \int_0^{\xi} [\phi'_{n\text{Gel}}(r) + \phi'_{\text{HCP}}(r)] r^2 dr \end{aligned} \quad (4)$$

where the integration cutoff (ξ) is taken to be the core size plus the core-corona interfacial full width ($\bar{R}_{\text{core}} + 2\sigma$). SANS cannot separate $\phi_{n\text{Gel}}(r)$ and $\phi_{\text{HCP}}(r)$ unless one of them is deuterated. Deuterated VL and $t\text{BuCL}$ monomer were not available. Here, we use $\phi_{n\text{Gel-HCP}}(r)$ to represent $\phi_{n\text{Gel}}(r) + \phi_{\text{HCP}}(r)$. It is observed that the shape of $\phi_{\text{core}}(r)$ in Figure 4a can be approximately described by a tanh function. In order to solve for the final hydrophobic core profile of $\phi'_{n\text{Gel} + \text{HCP}}(r)$, we assume that $\phi'_{n\text{Gel} + \text{HCP}}(r)$ has a similar tanh shape to $\phi_{\text{core}}(r)$. More details of $\phi'_{n\text{Gel} + \text{HCP}}(r)$ calculation are presented in the Supporting Information. After integration by eq 4, the concentration profile of ibuprofen is obtained by difference $\phi_{\text{IBU}}(r) = \phi'_{\text{core}}(r) - \phi'_{n\text{Gel} + \text{HCP}}(r)$. This analysis assumes little to no water is distributed within the nanogel core or hydrophobic copolymer.

Figure 5 shows that the radial spatial distribution of ibuprofen is not homogeneously distributed in the hydrophobic core. The extent of loading is dependent upon the star arm chemistry as predicted by the loading efficiencies. For $n\text{Gel}-(\text{EG}_{114})_f$ and $n\text{Gel}-(d\text{EG}_{114})_f$ due to the nearly impenetrable cross-linked caprolactone nanogel core, the drug appears at the core surface. For $n\text{Gel}-(\text{VL}_{23}-\text{EG}_{114})_f$ the drug is confined to the hydrophobic core region with maximum of $\phi_{\text{IBU}} \approx 34\%$. In contrast, the maximum of $\phi_{\text{IBU}} \approx 62\%$ for $n\text{Gel}-(\text{VL}_{11}-t\text{BuCL}_{10}-\text{EG}_{114})_f$ with majority within the hydrophobic domain.

On the basis of the average radial concentration distribution shown in Figure 5, one may estimate the amount of ibuprofen. However, we found an overestimate of IBU based upon either the volume expansion of the total hydrophobic core or estimates from the concentration distribution, when compared to the model-independent UV-vis loading data.

We attribute the overestimate of the total hydrophobic core after IBU loading as possibly due to EG segments appearing at the core–corona interface. This may reconcile the smaller R_g of PEG in Table 3 after IBU loading, such that PEG adsorbs or associates with the hydrophobic core. This would be consistent with the decrease of R_g after drug loading. The increment of $\bar{R}_{\text{core}}$ is somehow overestimated and not entirely due to the IBU loading. This is not an artifact of Pedersen's model as an independent estimate of the core size by fitting a sphere form factor to the peak feature at $0.7 \text{ nm}^{-1} < q < 1.5 \text{ nm}^{-1}$ in Figure 3d reveals the same core size consistent with the model and consistent with $q\bar{R}_{\text{core}} = 4.493$ at the first form factor minimum as discussed for block copolymer micelles.³⁶ Therefore, we believe that some PEG segments may be preferentially adsorbed to the core/corona interface. The trend of IBU loading amount obtained from SANS qualitatively agrees with the loading efficiency by UV–vis measurement as shown in Figure S2 that the loading extent follows $n\text{Gel}-(\text{VL}_{11}-t\text{BuCL}_{10}-\text{EG}_{114})_f > n\text{Gel}-(\text{VL}_{23}-\text{EG}_{114})_f > n\text{Gel}-(\text{EG}_{114})_f$. In order to better estimate the IBU spatial distribution, the mass density profiles of IBU were normalized by the amounts per particle determined by UV–vis and shown in Figure 6a.

Figure 6a summarizes the probability mass distribution of ibuprofen with abscissa in units of distance from the surface of the cross-linked caprolactone nanogel core to permit comparison. These results show that the probability to observe ibuprofen is peaked at the nanogel-core interface in the homopolymer arm case but then peaked within the interphase formed by the packing of mobile diblock and terpolymer hydrophobic segments. This allows us to compare the trends in ibuprofen distribution with the validated MD simulations.

MD Simulations of Composition Profiles.—In order to test the conclusions based upon SANS and UV–vis, simulations were performed using models for nanogel star polymers prepared as described in previous work.²⁰ These models were constructed in a way that mimics the synthetic process of the formation of the core in order to obtain a realistic core cross-linking topology.²⁰ The nanogel star polymer constructed in this way had 16 diblock arms $n\text{Gel}-(\text{VL}_{16}-\text{EG}_{24})_{16}$ and was simulated in the liquid phase using an atomistic model for water. Two long simulations were performed: one with 24 ibuprofen molecules included in random starting positions within the simulation cell and another without any ibuprofen molecules. In the simulation that included ibuprofen, after only about 40 ns, 23 of the 24 drug molecules became associated with the star polymer and subsequently remained associated, suggesting that significantly greater loading could be possible. The resulting orientationally averaged mass density profile is shown in Figure 7, for comparison with Figures 4 and 5. There are striking similarities even though the simulated system is significantly smaller than the polymers used in experiments. The simulated system has a hydrophobic core with radius of approximately 2.4 nm compared with about 5.62 nm for the actual molecules of $n\text{Gel}-(\text{VL}_{23}-\text{EG}_{114})_f$. Each component of the diblock arms is shorter, and there are fewer arms. Upon addition of the ibuprofen molecules, the core in the simulation does not exhibit as much core expansion as illustrated in Figure 4a, but there is a slight reorganization of the core with enhanced core density in the vicinity of the ibuprofen. The addition of the ibuprofen pushes the PEG away from the core, exactly as is seen in the experimental systems with diblock and terpolymer arms. As seen in Figure 7b, the simulations show that the ibuprofen is rather well localized, inside the PEG layer, slightly

inside the core, but also having significant contact with both PEG and water as well as the core, i.e., at the interface between the hydrophobic core and the PEG–water layer. Figure 6b shows that the simulated system has a very narrow and well-localized ibuprofen layer (approximately 1 nm thick) compared to the experimental system (approximately 4 nm) and that it is nearer to the surface of the core, but this may be due to the much lower ibuprofen loading used in the simulation.

The relative orientation of the ibuprofen molecules can be determined from the simulation results. When the distance from the center of the polymer to the center of the ibuprofen is <2.5 nm, the ibuprofen is considered to be captured by the star polymer. When this distance is >3 nm, ibuprofen is considered free. The relative orientation of ibuprofen and the polymer was analyzed by computing the distribution of angles measured between two vectors: a vector $(\vec{k})$ from the hydrophobic methyl end to the acid end of ibuprofen, defining the axis of the ibuprofen molecules, and a position vector $(\vec{j})$ from the center of the polymer to the center of ibuprofen. The projected angle (θ) varies from 0° to 180° . At 0° , the acid end points out away from the star polymer toward solvent. At 180° , the acid end points toward the interior of the star polymer. If θ is 90° , ibuprofen appears tangential or lying flat to the star polymer surface. The angle distribution is normalized by $\sin(\theta)$ so that it is flat if there is no preferred orientation. Figure 7c shows that for the free, unbound, ibuprofen outside of the interface (>3 nm) no orientation preference is observed. However, an enhanced probability occurs for θ between 45° and 105° (lying flat) and diminished probability for perpendicular to the surface (0° and 180°). However, it is more probable for the acid end to pointing toward the solvent, since the peak is located below 90° .

Comparing the homopolymer, diblock, and terpolymer star arms, the packing of the VL₁₁-tBuCL₁₀ make the hydrophobic core most accessible to ibuprofen loading. This may lead to the highest segmental mobility as supported by DSC results, where the T_g was found to be -17.8 and 36 °C for VL₁₁-tBuCL₁₀-EG₁₁₄ and VL₂₃-EG₁₁₄, respectively. Further, the hydrophobic core is more regular in shape in the diblock and terpolymer arms as easily shown by the SANS peak and by the simulation sequence of structure in Figure 8. Lastly, because of the low rigidity, it is easier for drug to penetrate, and $\phi_{BU}(r)$ is the highest for the terpolymer arms enabled by the lowest Flory–Huggins interaction parameter. These experimental results support the recent consideration by Yamamoto et al.³⁷ on the role of mobility/rigidity of the hydrophobic core on drug incorporation.

Currently, we do not have experimental data on release profiles of the star polymers; the evaluation is underway. However, we anticipate the rate of cargo release will be fastest for the nGel-(EG₁₁₄)_f star polymer and slowest for the nGel-(VL₁₁-tBuCL₁₀-EG₁₁₄)_f star polymer. Our prediction is based on the accessibility of the cargo and the hydrophobic core by water molecules. Two factors come into play: concentration gradient driven release and hydrolytic degradation of the star polymer. Both factors are present in the case of nGel-(EG₁₁₄)_f where cargo molecules are located at the surface of a hydrophobic core and hence readily exposed to the aqueous environment. In addition, this cross-linked core is more susceptible to hydrolytic degradation under basic or acidic conditions. In the case of nGel-(VL₁₁-tBuCL₁₀-EG₁₁₄)_f cargo is buried inside of the hydrophobic core and hence has a

“harder” time escaping. In addition, the presence of a pendant alkyl functionality increases the overall hydrophobicity of the core, driving water molecules away and hence suppressing the hydrolytic degradation.

CONCLUSION

The spatial distribution of ibuprofen can be controlled by the hydrophobic inner-block segments of emanating star arms in cross-linked nanogel core star polymers. Bulkier hydrophobic block substituents (VL and *t*BuCL) improve the loading efficiency as independently confirmed by UV–vis spectroscopy. The loading efficiency also correlates to solubility parameter/interaction parameter compatibility arguments. While the absolute loading of the drug was improved in the presence of the diblock and terpolymer arm substituents, the reason appears to be caused by a thicker and mobile interphase between the cross-linked caprolactone nanogel core and the emanating hydrophilic PEG arms, rather than bulk loading within the nanogel core. This interphase accommodates a few molecular layers of ibuprofen preferentially lying flat to the hydrophobic core with acid end pointing toward the solvent. Therefore, a design criteria worthy of study is the relationship between the projected interfacial area for adsorption of drug. This could be optimized with respect to the loading efficiency, which is of practical interest in formulations. Importantly, calorimetry provides a simple estimate as to the mobility of the bulky segments within the interphase that guides the spatial distribution of ibuprofen. The validated MD simulations recover the spatial distribution of drug at the nanogel core/arm interphase and provide the first step to develop predictive models toward improved polymers for nanomedicine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- (1). Foster B; Cosgrove T; Hammouda B Pluronic Triblock Copolymer Systems and Their Interactions with Ibuprofen. *Langmuir* 2009, 25 (12), 6760–6766. [PubMed: 19374338]
- (2). Alexander S; de Vos WM; Castle TC; Cosgrove T; Prescott SW Growth and Shrinkage of Pluronic Micelles by Uptake and Release of Flurbiprofen: Variation of PH. *Langmuir* 2012, 28 (16), 6539–6545. [PubMed: 22471962]
- (3). Akiba I; Terada N; Hashida S; Sakurai K; Sato T; Shiraishi K; Yokoyama M; Masunaga H; Ogawa H; Ito K; Yagi N Encapsulation of a Hydrophobic Drug into a Polymer-Micelle Core Explored with Synchrotron SAXS. *Langmuir* 2010, 26 (10), 7544–7551. [PubMed: 20361731]
- (4). Sanada Y; Akiba I; Sakurai K; Shiraishi K; Yokoyama M; Mylonas E; Ohta N; Yagi N; Shinohara Y; Amemiya Y Hydrophobic Molecules Infiltrating into the Poly(Ethylene Glycol) Domain of

- the Core/Shell Interface of a Polymeric Micelle: Evidence Obtained with Anomalous Small-Angle X-Ray Scattering. *J. Am. Chem. Soc* 2013, 135 (7), 2574–2582. [PubMed: 23368537]
- (5). Nakanishi R; Machida G; Kinoshita M; Sakurai K; Akiba I Anomalous Small-Angle X-Ray Scattering Study on the Spatial Distribution of Hydrophobic Molecules in Polymer Micelles. *Polym. J* 2016, 48 (7), 801–806.
 - (6). Valero M; Castiglione F; Mele A; da Silva MA; Grillo I; González-Gaitano G; Dreiss CA Competitive and Synergistic Interactions between Polymer Micelles, Drugs, and Cyclodextrins: The Importance of Drug Solubilization Locus. *Langmuir* 2016, 32 (49), 13174–13186. [PubMed: 27951706]
 - (7). Matyjaszewski K; Tsarevsky NV Nanostructured Functional Materials Prepared by Atom Transfer Radical Polymerization. *Nat. Chem* 2009, 1 (4), 276–288. [PubMed: 21378870]
 - (8). Voit BI; Lederer A Hyperbranched and Highly Branched Polymer Architectures-Synthetic Strategies and Major Characterization Aspects. *Chem. Rev* 2009, 109 (11), 5924–5973. [PubMed: 19785454]
 - (9). Lee VY; Havenstrite K; Tjio M; McNeil M; Blau HM; Miller RD; Sly J Nanogel Star Polymer Architectures: A Nanoparticle Platform for Modular Programmable Macromolecular Self-Assembly, Intercellular Transport, and Dual-Mode Cargo Delivery. *Adv. Mater* 2011, 23 (39), 4509–4515. [PubMed: 21901765]
 - (10). Wiltshire JT; Qiao GG Degradable Core Cross-Linked Star Polymers via Ring-Opening Polymerization. *Macromolecules* 2006, 39 (13), 4282–4285.
 - (11). Appel EA; Lee VY; Nguyen TT; McNeil M; Nederberg F; Hedrick JL; Swope WC; Rice JE; Miller RD; Sly J Toward Biodegradable Nanogel Star Polymers via Organocatalytic ROP. *Chem. Commun* 2012, 48 (49), 6163–6165.
 - (12). Miller RD; Yusoff RM; Swope WC; Rice JE; Carr AC; Parker AJ; Sly J; Appel EA; Nguyen T; Piunova V Water Soluble, Biodegradable Amphiphilic Polymeric Nanoparticles and the Molecular Environment of Hydrophobic Encapsulates: Consistency between Simulation and Experiment. *Polymer* 2015, 79, 255–261.
 - (13). Garzón LC; Martínez F Temperature Dependence of Solubility for Ibuprofen in Some Organic and Aqueous Solvents. *J. Solution Chem* 2004, 33 (11), 1379–1395.
 - (14). Kline SR Reduction and Analysis of SANS and USANS Data Using IGOR Pro. *J. Appl. Crystallogr* 2006, 39 (6), 895–900.
 - (15). Hayashi H; Flory PJ; Wignall GD Configuration of the Polyisobutylene Chain According to Neutron and X-Ray Scattering. *Macromolecules* 1983, 16 (8), 1328–1335.
 - (16). Plimpton S Fast Parallel Algorithms for Short-Range Molecular Dynamics. *J. Comput. Phys* 1995, 117 (1), 1–19.
 - (17). Jorgensen WL; Maxwell DS; Tirado-Rives J Development and Testing of the OPLS All-Atom Force Field on Conformational Energetics and Properties of Organic Liquids. *J. Am. Chem. Soc* 1996, 118 (45), 11225–11236.
 - (18). Price MLP; Ostrovsky D; Jorgensen WL Gas-Phase and Liquid-State Properties of Esters, Nitriles, and Nitro Compounds with the OPLS-AA Force Field. *J. Comput. Chem* 2001, 22 (13), 1340–1352.
 - (19). Horn HW; Swope WC; Pitner JW; Madura JD; Dick TJ; Hura GL; Head-Gordon T Development of an Improved Four-Site Water Model for Biomolecular Simulations: TIP4P-Ew. *J. Chem. Phys* 2004, 120 (20), 9665–9678. [PubMed: 15267980]
 - (20). Carr AC; Felberg LE; Piunova VA; Rice JE; Head-Gordon T; Swope WC Effect of Hydrophobic Core Topology and Composition on the Structure and Kinetics of Star Polymers: A Molecular Dynamics Study. *J. Phys. Chem. B* 2017, 121 (13), 2902–2918. [PubMed: 28290691]
 - (21). Pedersen JS Form Factors of Block Copolymer Micelles with Spherical, Ellipsoidal and Cylindrical Cores. *J. Appl. Crystallogr* 2000, 33 (3), 637–640.
 - (22). Pedersen JS; Svaneborg C; Almdal K; Hamley IW; Young RN A Small-Angle Neutron and X-Ray Contrast Variation Scattering Study of the Structure of Block Copolymer Micelles: Corona Shape and Excluded Volume Interactions. *Macromolecules* 2003, 36 (2), 416–433.
 - (23). Pedersen JS Structure Factors Effects in Small-Angle Scattering from Block Copolymer Micelles and Star Polymers. *J. Chem. Phys* 2001, 114 (6), 2839–2846.

- (24). Pedersen JS; Gerstenberg MC The Structure of P85 Pluronic Block Copolymer Micelles Determined by Small-Angle Neutron Scattering. *Colloids Surf., A* 2003, 213 (2), 175–187.
- (25). Huynh L; Neale C; Pomeš R; Allen C Systematic Design of Unimolecular Star Copolymer Micelles Using Molecular Dynamics Simulations. *Soft Matter* 2010, 6 (21), 5491–5501.
- (26). Liu J; Xiao Y; Allen C Polymer–drug Compatibility: A Guide to the Development of Delivery Systems for the Anticancer Agent, Ellipticine. *J. Pharm. Sci* 2004, 93 (1), 132–143. [PubMed: 14648643]
- (27). Kumar V; Prud'Homme RK Thermodynamic Limits on Drug Loading in Nanoparticle Cores. *J. Pharm. Sci* 2008, 97 (11), 4904–4914. [PubMed: 18300278]
- (28). Lindvig T; Michelsen ML; Kontogeorgis GM A Flory–Huggins Model Based on the Hansen Solubility Parameters. *Fluid Phase Equilib* 2002, 203 (1), 247–260.
- (29). Van Krevelen DW; Te Nijenhuis K Properties of Polymers: Their Correlation with Chemical Structure; Their Numerical Estimation and Prediction from Additive Group Contributions; Elsevier: 2009.
- (30). Miller RD; Yusoff RM; Swope WC; Rice JE; Carr AC; Parker AJ; Sly J; Appel EA; Nguyen T; Piunova V Water Soluble, Biodegradable Amphiphilic Polymeric Nanoparticles and the Molecular Environment of Hydrophobic Encapsulates: Consistency between Simulation and Experiment. *Polymer* 2015, 79, 255–261.
- (31). Pedersen JS; Gerstenberg MC Scattering Form Factor of Block Copolymer Micelles. *Macromolecules* 1996, 29 (4), 1363–1365.
- (32). Swope WC; Carr AC; Parker AJ; Sly J; Miller RD; Rice JE Molecular Dynamics Simulations of Star Polymeric Molecules with Diblock Arms, a Comparative Study. *J. Chem. Theory Comput* 2012, 8 (10), 3733–3749. [PubMed: 26593017]
- (33). Felberg LE; Brookes DH; Head-Gordon T; Rice JE; Swope WC Role of Hydrophilicity and Length of Diblock Arms for Determining Star Polymer Physical Properties. *J. Phys. Chem. B* 2015, 119 (3), 944–957. [PubMed: 25254622]
- (34). Riley T; Heald CR; Stolnik S; Garnett MC; Illum L; Davis SS; King SM; Heenan RK; Purkiss SC; Barlow RJ; Gellert PR; Washington C Core–Shell Structure of PLA–PEG Nanoparticles Used for Drug Delivery. *Langmuir* 2003, 19 (20), 8428–8435.
- (35). Pedersen JS; Gerstenberg MC The Structure of P85 Pluronic Block Copolymer Micelles Determined by Small-Angle Neutron Scattering. *Colloids Surf., A* 2003, 213 (2), 175–187.
- (36). Hickl P; Ballauff M; Jada A Small-Angle X-Ray Contrast-Variation Study of Micelles Formed by Poly(Styrene)–Poly(Ethylene Oxide) Block Copolymers in Aqueous Solution. *Macromolecules* 1996, 29 (11), 4006–4014.
- (37). Yamamoto T; Yokoyama M; Opanasopit P; Hayama A; Kawano K; Maitani Y What Are Determining Factors for Stable Drug Incorporation into Polymeric Micelle Carriers? Consideration on Physical and Chemical Characters of the Micelle Inner Core. *J. Controlled Release* 2007, 123 (1), 11–18.

Figure 1.

(a) Schematic of the Pedersen's model parameters as applied to the nanogel-core star polymers. (b) Radial concentration distribution, $\phi(r)$, with length scales pertinent to the model. The total hydrophobic core radius $\bar{R}_{\text{core}}$ includes the cross-linked caprolactone nanogel-core and hydrophobic copolymer (HCP) arm segments.

Figure 2.

Pedersen's model fit to SANS data of $n\text{Gel}-(\text{EG}_{114})_f$ and $n\text{Gel}-(\text{VL}_{11}-t\text{BuCL}_{10}-\text{EG}_{114})_f$ in d -THF with mass % concentrations shown by the legend. The curves are shifted vertically for clarity by factors indicated above the data. Insets show Zimm plots using data $q < 0.15 \text{ nm}^{-1}$.

Figure 3.

SANS data of nanogel-core star polymers at a fixed concentration of 2 mass % with and without ibuprofen. The blue lines represent the best fit to Pedersen's model. Key fit results are displayed in Table 3. Full fit results are shown in Supporting Information. The data with ibuprofen are vertically offset by $\times 8$, for clarity.

Figure 4.

(a) Radial concentration distribution $\phi_{\text{core}}(r)$ of total hydrophobic core, including cross-linked caprolactone nanogel core, VL and *t*BuCL segments, and encapsulated ibuprofen. (b) Radial concentration distribution $\phi_{\text{PEG}}(r)$ of PEG in corona. The abscissa scaling of $(r - \bar{R}_{\text{core}})$ is calculated by subtracting corresponding values of $\bar{R}_{\text{core}}$. The arrows indicate the hydrophobic core-arm interface where the position of $(r - \bar{R}_{\text{core}}) = 0$. In the legend, superscripts degree and prime are used to represent drug free and drug loaded state, respectively.

Figure 5.

Average radial concentration distribution, $\phi(r)$, of hydrophobic core, PEG, and ibuprofen. The concentration profiles are shown after ibuprofen loading for the nanogel core (ϕ'_{nGel}), ibuprofen (ϕ_{IBU}), corona PEG chains (ϕ'_{PEG}), and the nanogel core combined hydrophobic copolymer arm segments ($\phi'_{nGel-HCP}$) for the four systems under study.

Figure 6.

(a) Average radial mass distribution, $\rho_{\text{IBU}} \phi_{\text{IBU}}(r) r^2$, of nanogel-core star polymer studied. ρ_{IBU} is the mass density of ibuprofen. $\rho_{\text{IBU}} = 1.03 \text{ g/cm}^3$. In the x -axis of $(r - \bar{R}_{\text{core}})$, $\bar{R}_{\text{core}} = 2.54 \text{ nm}$, equal to the radius of the cross-linked caprolactone nanogel core. (b) The analogous mass distribution is shown for the simulated system with $\bar{R}_{\text{core}} = 2.4 \text{ nm}$.

Figure 7.

Orientationally averaged mass density as a function of distance from the center of mass of a small simulated nanogel-core star polymer $n\text{Gel}-(\text{VL}_{16}\text{-EG}_{24})_{16}$ without (a) and with (b) ibuprofen. Different material is represented by different line color: black (total hydrophobic core $n\text{Gel-VL}_{16}$), magenta ($n\text{Gel}$), orange (VL_{16}), purple (PEG), cyan (water), blue (ibuprofen), total (red). (c) Relative orientation distribution of ibuprofen defined by the angle between the vector $\vec{k}$ from the center of mass of the polymer and the vector $\vec{j}$ defined along the ibuprofen from the methyl to carboxylic acid group.

Figure 8.

Simulated $n\text{Gel}-(\text{VL}_{16}\text{-EG}_{24})_{16}$ system showing successive layers of (left to right): cross-linked gel core region (pink); hydrophobic region consisting of gel core region and the PVL block of each arm (both pink); entire star polymer consisting of the hydrophobic region (pink) and the PEG block of each arm (gray); entire star polymer (pink and gray) and adsorbed ibuprofen (various colors); star polymer without the PEG block (pink) and the adsorbed ibuprofen (various colors).

Table 1.

Characteristics of Nanogel-Core Star Polymers Studied^a

name	M_w^b (kg/mol)	f_{arm}	A_2^e (mol cm ³ /g ²)	R_g of particle (nm) ^e	$\bar{R}_c$ (nm) ^c	$\sigma_R/\bar{R}_c^c$	f_{sol} vol frac ^c	star arm R_g (nm) ^c	IBU loading efficiency ^f (%)
n Gel-(EG ₁₁₄) _f	120 ^d	27 ^c	9.2×10^{-5}	7.8	1.9 ± 0.3	0.8 ± 0.1	0.17	1.8 ± 0.1	6.0 ± 0.3
	268 ^e	24 ^d							
		53 ^e							
n Gel-(<i>d</i> EG ₁₁₄) _f	109 ^d	21 ^d							
n Gel-(VL ₂₃ -EG ₁₁₄) _f	221 ^d	28 ^d							23 ± 1
n Gel-(VL ₁₁ - <i>t</i> BuCL ₁₀ -EG ₁₁₄) _f	257 ^d	28 ^c	1.9×10^{-4}	13.6	2.4 ± 0.5	0.5 ± 0.1	0.10	1.7 ± 0.5	48 ± 3
	298 ^e	33 ^d							
	38 ^e								

^a n Gel = cross-linked caprolactone core. EG = (–O–CH₂–CH₂–) and *d*EG = (–O–CD₂–CD₂). VL = (–O–(CH₂)₄–CO–). *t*BuCL = (–O–(CH₂)₂–CH(C(CH₃)₃)–(CH₂)₂–CO–). IBU = ibuprofen.^b Relative mass-average molar mass (M_w).^c Small-angle neutron scattering estimate by Pedersen's model in *d*-THF.^d Light scattering GPC in THF.^e Small-angle neutron scattering estimate by the Zimm plot in *d*-THF.^f The value is an average of three independent measurements with uncertainties (±) estimated by one standard deviation of the mean.

Table 2.Flory–Huggins Parameter χ^a

	EG	CL	VL	<i>t</i> BuCL	IBU
D ₂ O	0.63	0.80	0.76	0.90	0.93
IBU	0.090	0.028	0.045	0.025	

^a χ parameter was calculated from the solubility parameter estimated using the group contribution methods.^{28,29} Details are provided in the Supporting Information.

Table 3.

Key Fit Results of Nanogel-Core Star Polymer in D₂O^a

sample	drug free			drug loaded		
	$\bar{R}_{\text{core}}[\text{nm}]$	$\sigma_{\text{R}}/\bar{R}_{\text{core}}$	$R_{\text{g}}[\text{nm}]$	$\bar{R}_{\text{core}}[\text{nm}]$	$\sigma_{\text{R}}/\bar{R}_{\text{core}}$	$R_{\text{g}}[\text{nm}]$
<i>n</i> Gel-(EG ₁₄) _f	2.54 ± 0.9	0.53 ± 0.20	1.67 ± 0.3	3.92 ± 0.09	0.18 ± 0.02	1.85 ± 0.06
<i>n</i> Gel-(<i>d</i> EG _{11,d}) _f	2.54 ± 0.9	0.37 ± 0.10		3.92 ± 0.09	0.18 ± 0.01	
<i>n</i> Gel-(VL ₂₃ -EG ₁₄) _f	5.62 ± 0.07	0.16 ± 0.006	1.50 ± 0.06	6.46 ± 0.1	0.17 ± 0.01	1.11 ± 0.08
<i>n</i> Gel-(VL ₁₁ - <i>t</i> BuCL ₁₀ -EG ₁₄) _f	4.95 ± 0.05	0.14 ± 0.005	1.84 ± 0.08	6.40 ± 0.05	0.13 ± 0.01	1.33 ± 0.08

^aUncertainties (±) are estimated by one standard deviation to the model fit.