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Quantifying Drug Cargo Partitioning in Block Copolymer Micelle Solutions

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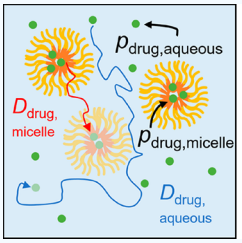
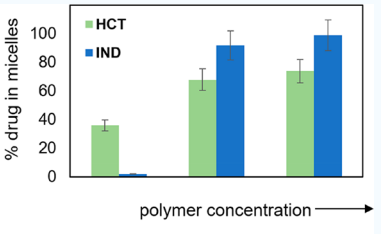
ABSTRACT: Understanding molecular partitioning in solution is crucial for the design of micelle-based formulations. We investigate PEO−PPO−PEO triblock copolymer micelles and their solubilization of three hydrophobic drugs: hydrochlorothiazide, indomethacin, and paclitaxel. Using NMR diffusometry, we quantify the diffusion coefficients of different species in solution, including polymers, drug cargo molecules, and solvent molecules. Polymer concentration and drug chemistry changes cause effects such as increasing partition percentages of hydrochlorothiazide and indomethacin within micelles as the F127 concentration increases from 1 to 5% w/v. This facile methodology enables quantification of drug distribution in micelles without perturbation of the solution, thus opening opportunities to understand broader processes of cargo partitioning.





KEYWORDS: *Pluronic, hydrophobic drugs, NMR diffusometry, biodistribution, F127, PFG NMR*

Block copolymer micelles (BCMs) have been favored in numerous applications such as drug delivery, nanoreactors, and tissue engineering.[1] In particular, they are used as targeted drug delivery vehicles because of the long solution residence time for cargo, low critical micelle concentration (CMC), and in vivo degradability.[2] Poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide) (PEO−PPO−PEO) triblock copolymers provide wide-ranging possibilities to build microenvironments for incorporation of various cargos because of their amphiphilicity. Therefore, PEO−PPO−PEO triblock copolymers are used in a wide range of applications, such as pharmaceutical formulations, foaming agents, and advanced coatings. Commercially available PEO−PPO−PEO copolymers manufactured by BASF are named Pluronic polymers. They have been applied as drug delivery media for the solubilization and delivery of poorly water-soluble drugs in order to reduce toxicity. Researchers have probed the micellization and gelation of Pluronic polymers by neutron scattering,[3] rheology,[4] fluorescence spectroscopy,[5] and NMR spectroscopy.[6] Above the CMC, entropy-driven micellization occurs by the formation of a hydrophobic interior of PPO blocks and a water-swollen exterior layer of PEO blocks. At even higher concentrations of polymer (above the critical gelation concentration), a thermoreversible gel forms as a result of intermolecular associations between the polymer chains.[7]

The particular polymeric material used in drug delivery can greatly affect the pharmacological properties of a drug, including its pharmacokinetics, biodistribution, and sustained release. Broad distribution of drugs in the body can result in dose-limiting side effects and affect normal tissues. Using drug delivery carriers, such as PEO−PPO−PEO copolymer micelles, can help to reduce those effects by encapsulation of the drugs in hydrophobic reservoirs. Therefore, it is important to understand and quantify how drugs are distributed in the delivery carriers and in the surrounding aqueous environment. The partition coefficient (K) defines the distribution of drugs in different phases, which is critical to estimating the release rate and residence time in the organism as well as other aspects of biological activity. Knowledge of K also provides insight into the nature and strength of molecular interactions between drug molecules and micelles, for example, van der Waals forces, hydrophobic interactions, and hydrogen bonding.[8] Several factors have been determined to affect the solubilization capacity of micelles, including compatibility between the core-forming polymers and the cargo, micellar size, aggregation number, interfacial tension between water and the cargo, and the molecular volume of the cargo. K can sometimes be obtained experimentally from UV−vis spectroscopy,[9] high-performance liquid chromatography (HPLC),[10] differential scanning calorimetry (DSC),[11] and fluorescence spectroscopy.[12] Those methods require either additional separation (filtration or dialysis) of micelle−drug solutions or fluorescent probe labeling, which can involve possible drug loss,

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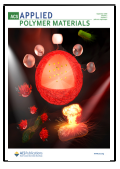

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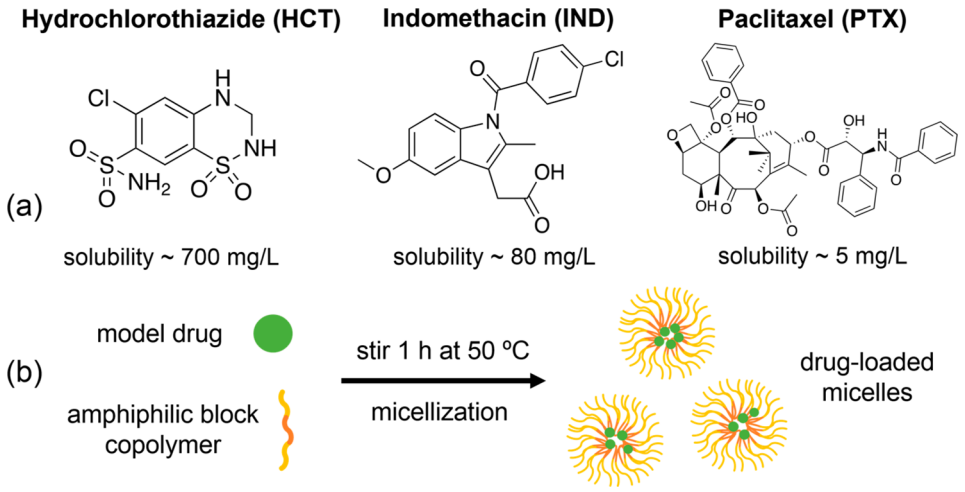

Figure 1. (a) Chemical structures and measured water solubilities of the model drugs HCT, IND, and PTX. (b) Preparation of drug-loaded Pluronic BCMs.

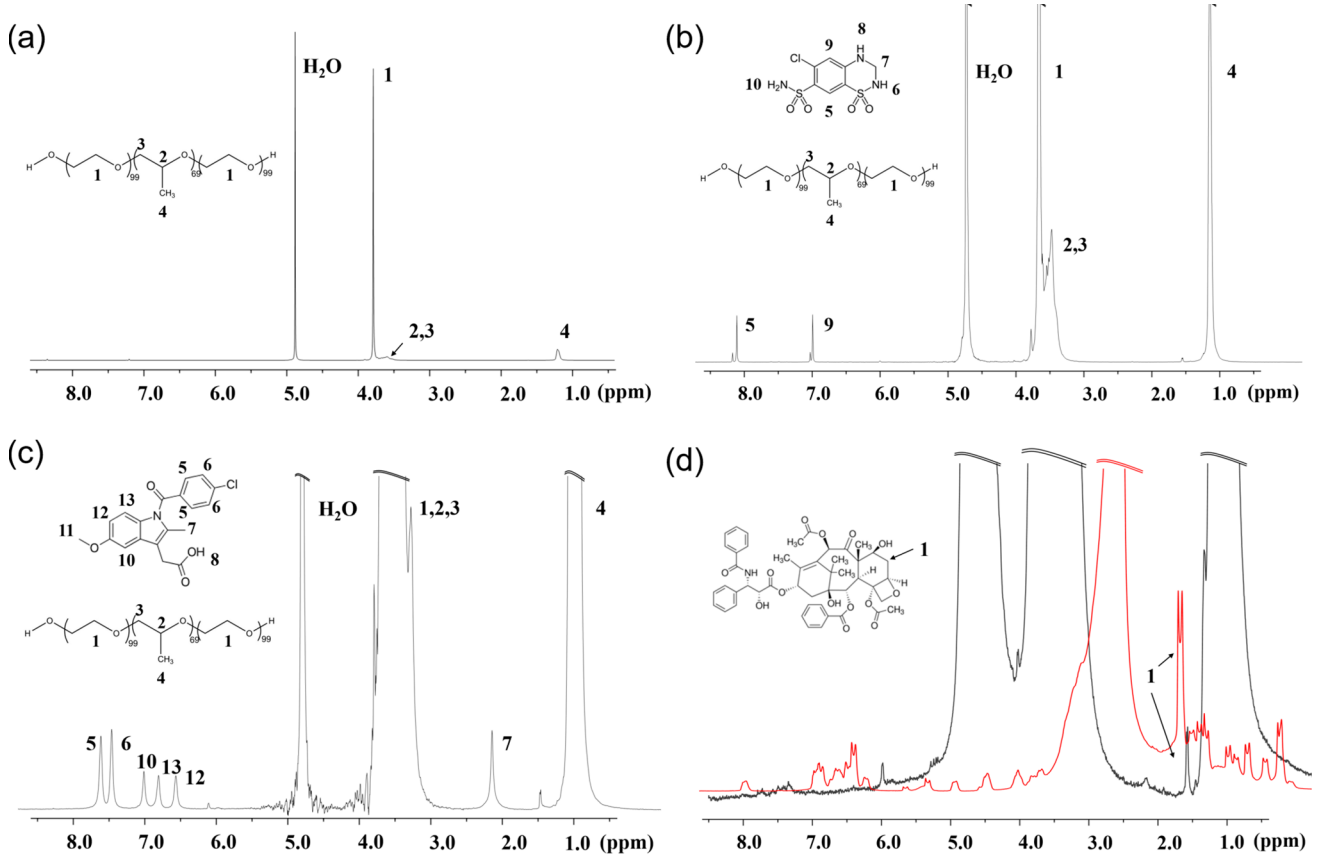

Figure 2. ^{1}H NMR spectra of F127 micelles with and without drug loading. (a) 1% w/v F127 BCM without drug. (b) 0.3% w/v HCT solubilized in 2% w/v F127 BCMs. Peak 7 overlaps with the residual solvent H_2O (HOD) peak, and peaks 6, 8, and 10 are weak because of deuterium exchange. (c) 0.3% w/v IND solubilized in 3% w/v F127 BCMs. Peaks 9 and 11 overlap with the PEO peak, and peak 8 is weak because of deuterium exchange. In (b) and (c), we have magnified the spectral intensity (peaks 1, 4, and water are off-scale) to observe the drug peaks. (d) 0.2% w/v PTX dissolved in DMSO-d_6 (red) and 0.06% w/v PTX solubilized in 5% w/v F127 BCMs (black). We have magnified the intensity (polymer and solvent off-scale) in both spectra to observe drug peaks.

measurement perturbations, and/or complicated preparation procedures.

On the basis of our and others' investigations of polymeric micelle structure and dynamics, in this article we present a simple and nondestructive NMR diffusometry approach to investigate the drug partitioning behaviors of Pluronic F127 BCM solutions. In short, NMR diffusometry can quantify the fractions of drug encapsulated in micelles and free in solution.

We can define the drug encapsulated in BCMs as the *micellar phase* (for the drug) and the drug dissolved in the surrounding solvent as the *aqueous phase*. We assume that the activity coefficient of the drug is equal to 1 in both phases (as

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in a dilute system), and thus, the partition coefficient is given by the ratio of the model drug concentrations in the two phases:

$$K = \frac{[M]_{micelle}}{[M]_{aqueous}} \quad (1)$$

where $[M]_{micelle}$ is the concentration of the model drug M in the micellar phase and $[M]_{aqueous}$ is the concentration of model drug in the aqueous phase. In this study, we investigated three hydrophobic model drugs with different solubilities—hydrochlorothiazide (HCT), indomethacin (IND), and paclitaxel (PTX)—to understand their solubilization and partitioning behaviors in Pluronic F127 BCMs. Pluronic F127 formulations have been widely applied to enhance drug solubilization and prolong the release profile for poorly water-soluble drugs.[13] HCT is a diuretic and antihypertensive drug that is also used to treat side effects of diabetes and can be used to treat edema (excess fluid held in body tissues) caused by medical problems such as heart, kidney, and liver diseases or by estrogen and corticosteroid therapies.[14] IND is an anti-inflammatory drug that reduces fever, pain, and inflammation and relieves symptoms of arthritis and gout.[15] PTX is a chemotherapy agent with activity against lung, breast, prostate, and other types of solid tumor cancers.[16] The water solubilities of these three model drugs follow the order HCT > IND > PTX (Figure 1a).[16−18]

Common methods of incorporating water-insoluble drugs into micelles include chemical conjugation and physical entrapment.[19] Drugs can generally be encapsulated into BCMs to enable intravenous injection with a lower overall drug dose, increasing the probability that the drug will reach its intended target tissue or organ. The quantity of drug loaded depends on the drug and polymer structures and the resulting intermolecular interactions, which include influences from the block copolymer composition, hydrophobic (block) ratio, and molecular weight. In this study, we prepared HCT- and IND-loaded Pluronic F127 micelles by a direct dissolution method (Figure 1b) and PTX-loaded micelles by a solid dispersion method.

Employing an NMR methodology that can be applied using common NMR spectrometers, we are able to gain new insights into the dynamics and distribution of drug cargo in polymeric micelle solutions. These studies and methods also show promise for shedding new light onto understanding of molecular interactions between small-molecule cargos and micellized polymers. Such new understanding will enable the rational design of drug delivery formulations as well as other micelle encapsulation technologies, e.g., micelle-phase "nanoreactor" synthesis.

RESULTS AND DISCUSSION

To initially understand the molecular structure and solubility of drug−micelle solutions, we present ^{1}H NMR spectra of BCMs with and without drug loading (Figure 2). The spectral intensity is scaled to better observe peaks associated with drug molecules. Notably, PTX is one of the most efficient and widely applied anticancer drugs, yet it has extremely low water solubility (~5 mg/L).[20] The solubility of PTX in F127 micelles, quantified from the data in Figure 2d (0.06% w/v or 600 mg/L, as verified by NMR peak integration), represents an increase of more than 2 orders of magnitude over the intrinsic aqueous solubility of PTX, which reinforces the use of polymeric micelles to increase the solubility of hydrophobic drugs.

To further explore micelle and drug dynamics and partitioning of drugs into micelles and into the solution, we investigate a range of Pluronic F127 and drug compositions using NMR diffusometry. Because of the separate NMR spectral peaks assigned to the drugs and block copolymer molecules (Figure 2), we can separately and simultaneously characterize micelle diffusion (via the polymer peaks) and drug diffusion. In Pluronic F127 micellar solutions, NMR diffusometry demonstrates a decrease in the self-diffusion coefficient of the polymer (D_{poly}) with increasing concentration (see section 4 in the Supporting Information (SI)). We can also quantify the drug diffusion coefficients both in micellar solutions and in pure water. We can then use the combination of diffusion coefficients to extract the percentages of the drugs *encapsulated inside micelles* versus *in the surrounding aqueous solution*, and the micelle solution can be effectively modeled as a two-phase system.[23] The time scale of exchange (τ_{ex}) between the two phases (i.e., in the micelle core and free in solution) is an important parameter influenced by drug cargo size, hydrophobicity, and other specific molecular (thermodynamic) interactions with the solvent and with the micelle core. If solubilized drug molecules are in the "slow exchange" regime relative to the NMR observation time, then we can quantify the drug concentrations in the two phases from a two-component fit to a Stejskal−Tanner (NMR signal decay) plot.[24,25] In this case, one component is the drug freely diffusing in the aqueous solution, and the other component is the drug present in the micellar cores.

In the present work, however, both HCT and IND exhibit only one diffusion coefficient (see SI section 4 and Figure S4). This signifies that *these drugs are in fast exchange between the aqueous and micellar phases* (i.e., $\tau_{ex} \ll \Delta$), and thus, the lifetime of drug residing in the hydrophobic core is shorter than the smallest NMR observation time (i.e., the diffusion encoding time) of 10 ms. We discuss further implications of this for drug delivery and for quantification of drug partitioning by various methods below.

We can, however, still quantify the partitioning of the drug molecule by using the single-component diffusion coefficient of the drug molecule (D_{drug}), which is a weighted average of contributions from drug encapsulated in the micellar phase and drug dissolved in the aqueous phase in this fast-exchange regime. This drug diffusion coefficient is given by the following equation:[26]

$$D_{drug} = p_{drug,micelle} \cdot D_{drug,micelle} + p_{drug,aqueous} \cdot D_{drug,aqueous} \quad (2)$$

where $D_{drug,micelle}$ and $D_{drug,aqueous}$ are the diffusion coefficients of drug encapsulated in the micellar phase and drug in the aqueous phase, respectively, and $p_{drug,micelle}$ and $p_{drug,aqueous}$ are the populations (mole fractions) of drug molecules encapsulated in micelles and diffusing freely in the aqueous phase, respectively. The total mole fraction must equal unity ($p_{drug,micelle} + p_{drug,aqueous} = 1$).

In order to quantify the populations of a model drug in these two phases using eq 2, we assume that (1) $D_{drug,micelle}$ is the same as the diffusion coefficient of the polymer chains in micelles (D_{poly}) and (2) $D_{drug,aqueous}$ is the same as the diffusion coefficient of the drug dissolved in the solvent in the absence of micelles ($D_{drug,soln}$). We can do the following experiments to assess these assumptions. For assumption (1), it should be reasonable to use the observed polymer diffusion coefficient

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Table 1. Diffusion Coefficients, Partition Percentages, and Equivalent Partition Coefficients (K) of Drug (HCT or IND) and Polymer (F127) in Drug-Loaded Micelles at Different Polymer Concentrations[a]

	HCT-loaded BCMs				IND-loaded BCMs			
F127 conc. (% w/v)	D_{poly} (10^{-11} $m^2 \cdot s^{-1}$)	D_{drug} (10^{-11} $m^2 \cdot s^{-1}$)	p_{drug} (%)[b]	K	D_{poly} (10^{-11} $m^2 \cdot s^{-1}$)	D_{drug} (10^{-11} $m^2 \cdot s^{-1}$)	p_{drug} (%)[b]	K
5	1.7	20	70	2.4	1.8	2.0	99	100
3	2.6	25	62	1.7	1.5	4.7	93	13
2	4.4	35	48	0.93	2.4	11	79	3.8
1	4.1	44	33	0.49	3.7	44	3	0.03
0	N/A	63	0	N/A	N/A	45	0	N/A

[a]The HCT and IND concentrations in F127 micelle solutions (1−5% w/v polymer) were 0.25 ± 0.05 and 0.30 ± 0.05% w/v, respectively. HCT and IND were added to aqueous solutions (without polymer) to obtain a concentration of 0.5% w/v, and measurements were made after precipitation of excess drug. All of the diffusion measurements were performed at 25 ± 1 °C, and the errors in the D values are less than or equal to ±4%. [b]$p_{drug} = 100 \times p_{drug,micelle}$ from eq 2.

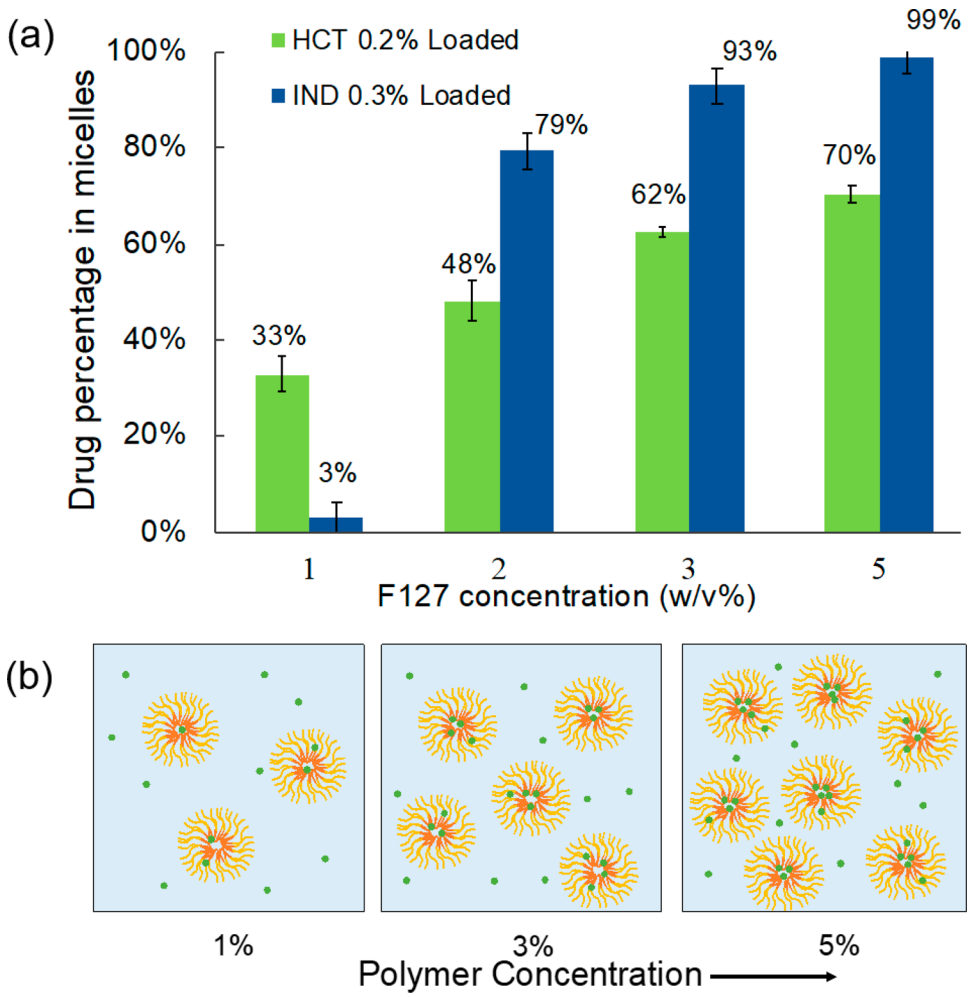

Figure 3. (a) Drug (HCT and IND) partition percentages in F127 BCMs. The increased amount of drug solubilized results from the increased number of amphiphilic chains in solution, providing increased reservoirs for hydrophobic drugs. (b) Representation of micelle size evolution and distribution of HCT-loaded BCMs as a function of polymer concentration. The micelles at higher F127 concentration encapsulate more drug in the micelle cores.

(D_{poly}) in micellar solution to represent the diffusion coefficient of model drugs in the micellar phase ($D_{drug,micelle}$). This is supported by characterizing the diffusion of IND in F127 micelles at 5% w/v. Whereas pure IND in aqueous solution (with no F127 present) has a diffusion coefficient of 4.5×10^{-10} $m^2 \cdot s^{-1}$, IND in the F127 micellar solution shows $D_{drug} = 2.0 \times 10^{-11}$ $m^2 \cdot s^{-1}$. This value is nearly equal to D_{poly} (1.8×10^{-11} $m^2 \cdot s^{-1}$). This result strongly indicates that nearly all of the drug molecules are successfully trapped in micelles and that the drug moves along with the micelles for this "fully encapsulated" IND-F127 sample. For assumption (2) to be correct, the addition of model drugs should not affect the bulk viscosity and hence the diffusion of solvent molecules. In this case, we used the diffusion of an internal standard (residual solvent HOD) to track the bulk viscosity. Clearly this dilute species will not influence cargo encapsulation and release. Overall, the viscosity of the 1−5% w/v F127 micelle solutions as determined using the Stokes−Einstein equation (see SI

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sections 2 and 3) does not vary in solutions that are saturated with these drugs (up to 1% w/v).

Using these assumptions and eq 2, we can extract the populations of the drugs in micelles for all of the samples and therefore probe how the drug hydrophobicity and polymer concentration affect the partitioning (population) of drugs in the micelles. Table 1 contains the measured diffusion coefficients and partition percentages of HCT, IND, and polymer (F127) in micellar solutions.

On the basis of the above assumptions and results, we can compare the measured partition percentages of the HCT and IND model drugs in F127 BCMs (Figure 3a). IND has a lower aqueous solubility than HCT, which contributes to a higher compatibility between the drug and core-forming blocks relative to free solution and thus an increased preference for IND to reside in the micelle phase. As the F127 concentration increases, the partitioning of IND into BCMs rises sharply, and all of the IND (99%) resides in micelles in 5% w/v F127. The less hydrophobic HCT, on the other hand, is not as strongly encapsulated by the BCMs since the drug is substantially soluble in water, and the partition fraction of HCT exhibits a steady monotonic rise as the F127 concentration increases. Here one can consider that the relative size of the model drugs HCT and IND might affect their partitioning into micelles. In this case, IND (molecular weight 358 g/mol) should occupy a slightly larger molecular volume than HCT (molecular weight 298 g/mol), which also may contribute to its lower loading capacity in micelles. However, we still expect the most significant difference to lie in the hydrophobicity.

For 1% w/v F127 IND-loaded BCMs, we note that the drug partition percentage is low, possibly because of the phase behavior of the BCMs. The CMC and critical micelle temperature of F127 were reported to be 0.97% w/v and 20 °C,[21,22] and therefore, at 1% F127 the micelles are on the edge of stability at room temperature.[27] Thus, the core may be effectively less hydrophobic under these conditions, and the interactions between the drug and the polymer chains may destabilize the micelles. However, for 1% w/v F127 HCT-loaded BCMs, it is still possible to incorporate a certain amount of HCT (33%), as HCT is less hydrophobic than IND. Multiple molecular interactions such as hydrophobic interactions, hydrogen bonding, and van der Waals forces can all impact cargo loading in micelles. Future work will investigate more specifically the molecular and thermodynamic effects that give rise to these differences.

These results show that NMR diffusometry offers a convenient and quantitative method to investigate the micellar dynamics of F127 at varied concentrations as well as the micellar solubilization of different cargo molecules, such as the model hydrophobic drugs HCT and IND. For both drugs, the partition fractions increase with increasing F127 concentration, as we have introduced more hydrophobic reservoirs to encapsulate cargos by increasing the micelle core volume and/or the total number of micelles. We are beginning to apply small-angle neutron scattering to obtain more structural information such as aggregation number and core volume in micelles to better understand the drug loading process. In Figure 3b, we conceptually summarize how drug solubilization depends on the polymer concentration.

As a preliminary study, we also prepared PTX-loaded micelles by a solid dispersion method. Our NMR results show that 0.06% w/v PTX is fully encapsulated within 5% w/v Pluronic micelle cores (>99%), which is sensible on the basis of its strongly hydrophobic nature. This presents a significant increase in solubility of PTX and can shed light on the rational design of anticancer drug formulation. Further studies will continue to investigate chemotherapy drug−micelle interactions.

It should be noted that previous measurements of drug partition coefficients using UV−vis or fluorescence spectroscopy or HPLC[9−12] relied on filtration or dialysis of the micelle sample combined with spectroscopy before and after the separation procedure. Since τ_{ex} for the hydrophobic drugs is shorter than such experimental measurement and separation procedure times, a new equilibrium state is reached before spectroscopy measurements are performed, which would give rise to different partition percentages measured before and after any separation procedures. NMR diffusometry has a clear advantage for drug partition measurements because it does not require any separation procedures after micelle−drug formulation. This enables the determination of more reliable (equilibrium) partition percentages in as-formulated drug delivery systems.

In summary, this investigation provides insights into the molecular interactions between polymer chains, drug cargo molecules, and solvent molecules in a Pluronic F127 triblock copolymer micelle system. HCT, IND, and PTX are hydrophobic drugs with different aqueous solubilities that display drastically different solubilization and partitioning properties in F127 BCM solutions. Increasing polymer concentration gives rise to increased drug loading capacity. By understanding the structures, exchange kinetics, and solubilization properties of micelles and hydrophobic cargo molecules, we can better understand and modulate drug formulations as well as more reliably predict in vitro release profiles of candidate drugs.

EXPERIMENTAL SECTION

Sample Preparation. HCT, IND, and Pluronic F127 were purchased from Sigma-Aldrich, and PTX was obtained from Prof. D. G. I. Kingston. In the case of BCM solutions containing HCT and IND, drug-loaded BCM solutions were prepared by mixing the drug, triblock copolymer, and deuterated solvent (D_2O) at 50 °C for 60 min. After cooling, the transparent solutions were transferred to a 5 mm NMR tube for data acquisition. Each sample tube was equilibrated at room temperature (25 °C) prior to obtaining NMR diffusometry data in order to ensure that the sample was at thermal equilibrium. PTX-loaded BCMs were prepared by a solid dispersion method, where PTX and F127 polymer were dissolved separately in 2 mL of DMF solvent to obtain transparent solutions, followed by fully mixing the two solutions and drying under vacuum overnight to obtain homogeneous solid dispersions. D_2O was then added to the solid dispersions under the same conditions as mentioned above to prepare PTX-loaded BCMs.

Pulsed-Field-Gradient (PFG) NMR Diffusometry. Our previous studies have shown the utility of NMR in the measurement of diffusion coefficients and relative populations of unimers and micelles.[24,25] The pulsed-field-gradient stimulated echo (PGSTE) sequence was employed to measure diffusion of the various species in solution.[28,29] The signal amplitude I was measured as a function of gradient strength (g) and was fit with the Stejskal−Tanner equation,[30]

$$I = I_0 \exp[-\gamma^2\delta^2 g^2(\Delta - \delta/3)D] \quad (3)$$

where I_0 is the signal amplitude at $g = 0$, γ is the gyromagnetic ratio, δ is the effective gradient pulse length, Δ is the diffusion time between gradient pulses, and D is the self-diffusion coefficient. Detailed experimental parameters are given in SI section 2.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsapm.0c00694.

Materials used for analysis, molecular weight characterization for the F127 polymer, detailed NMR diffusometry experimental parameters, diffusometry analysis for bulk solution viscosity and micelle diameter estimation, and explanation of partition percentages with varying drug concentration (PDF)

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Notes

The authors declare no competing financial interest.

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