Effective Biodegradable Amphiphilic Polycaprolactone Micelles for Drug Delivery Applications

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Background

Cancer and chemotherapy

- Leading cause of death in every country in 21st century
- 35.3 million cancer cases and 18.5 million cancer deaths are projected by 2050

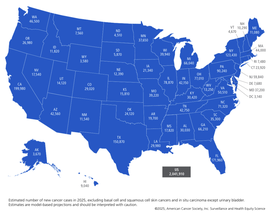


Figure 1. Estimated number of new cancer cases in 2025.

Limitation of chemotherapy

- Commonly used doxorubicin (DOX) is poorly water-soluble
- Poor solubility in the bloodstream.
- Harmful side effects, such as DOX-induced cardiotoxicity

Polymeric Micelles for Drug Delivery

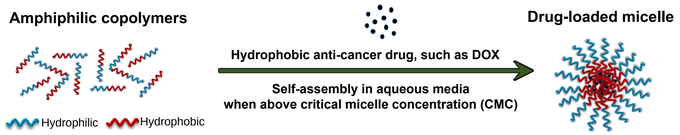
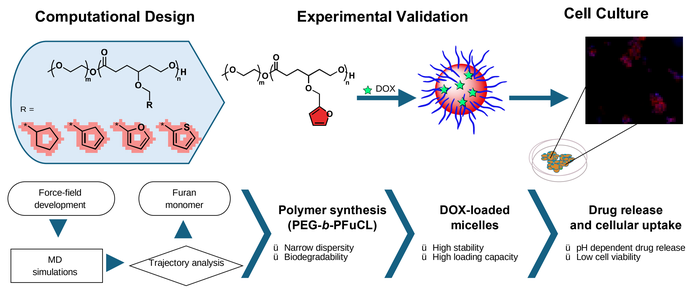


Figure 2. Self-assembly of amphiphilic copolymer to form drug-loaded micelles

Limitations of micellar drug delivery and research gaps

- Low stability, Low drug loading capacity and longer development time
- Ambiguity regarding micellization, drug encapsulation and drug-polymer interaction
- Lacking mechanistic insights at the atomic level behavior

Simulation Workflow



Model Preparation

- The polymer chains were optimized, and the resultant polymer chains were multiplied (n = 25) and arranged with hydrophobic blocks facing inward using packmol.
- Drug-loaded micelles were prepared in the same manner with 12 DOX molecules

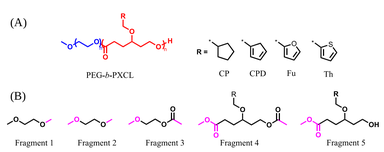


Figure 3. Structures of (A) simulated amphiphilic block copolymers and (B) the structural representation of the fragments for force field parametrization

Table 1. Summary of Simulations and Analysis

Functional Group	Box Size (Å³)	Total Atoms	Total Simulation time (ns)	Analysis
Cyclopentane (CP)	181 × 168 × 195	524, 719	300	SASA, Water contact, H-bond, R_g, lie, NCI
Cycolpentadiene (CPD)	164 × 180 × 165	426, 961	300	
Furan (Fu)	186 × 152 × 182	446, 134	300	
Thiophene (Th)	137 × 155 × 141	256, 162	300	

Molecular Dynamics Simulations

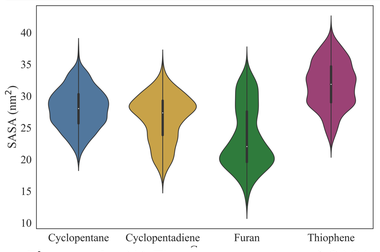


Figure 4. (A) Time progression of SASA of micelles

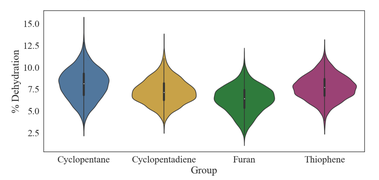


Figure 5. Violin plots of Dehydration % of micelles

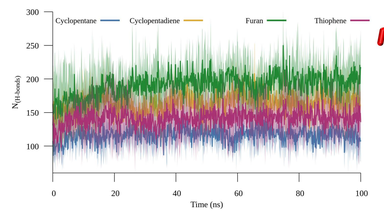


Figure 6. Time evolution of H-bonds between the hydrophobic core of the micelles and DOX molecules.

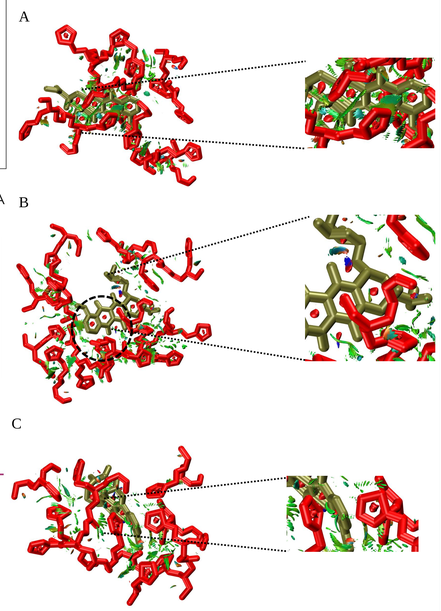
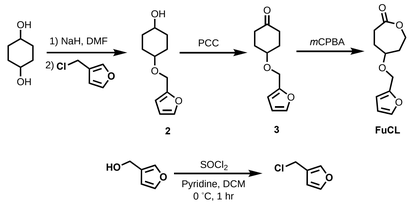


Figure 7. Representative non-covalent interaction (NCI) between DOX molecules and micelles with (A) cyclopentadiene, (B) furan, and (C) thiophene functional groups at the hydrophobic core.

Monomer and Polymer Synthesis



Scheme 1. Synthesis of FuCL monomer

Table 2. Properties of obtained polyesters

Polymer	PFuCL	PEG-*b*-PFuCL
M:I	100:1	50:1
M_n[a] (g mol⁻¹)	14200	9800
M_n[b] (g mol⁻¹)	8900	6700
Dispersity[b]	1.402	1.436

[a]*calculated* from NMR, [b]Calculated from SEC analysis

Acknowledgements

The authors acknowledge Prof Steven O. Nielsen for suggestions on charge scaling. The authors acknowledge the Texas Advanced Computing Center (TACC) at the University of Texas at Austin and the Office of Information Technology and Cyberinfrastructure Research Computing (CIRC) department at the University of Texas at Dallas for providing HPC resources that have contributed to the research results reported.

Micelle Characterization

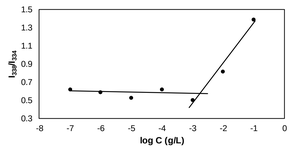


Figure 8. CMC of PEG-*b*-PFuCL micelles

Table 3. Size, DLC and DLE of the PEG-*b*-PFuCL micelles with Polymer DOX ratio (10:1)

Micelle	Size (nm)		DLC(wt%)	DLE(wt%)
	Empty	Loaded		
PEG-*b*-PFuCL	54.28 (0.173)	58.07 (0.243)	4.25	42.5

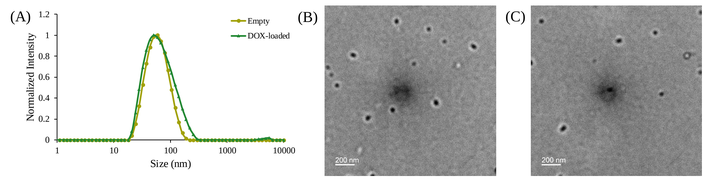


Figure 9. A) DLS of empty and drug-loaded PEG-b-PFuCL micelles. TEM images of (B) empty and (C) drug-loaded PEG-b-PFuCL micelles.

Biological Studies

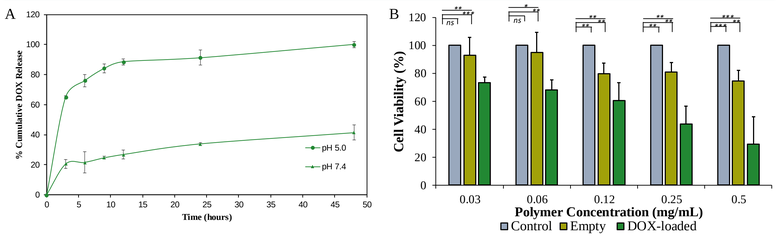


Figure 10. (A) Cumulative drug release and (B) Cytotoxicity of empty and DOX-loaded PEG-*b*-PFuCL micelles incubated at 37 °C for 24 h.

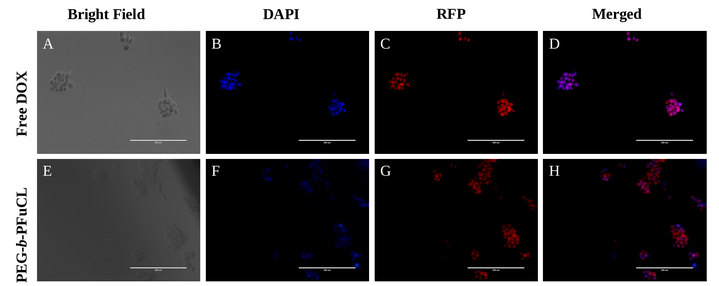


Figure 11. Cellular uptake of free DOX and PEG-b-PFuCL micelles into MDA-MB-231 cells at 37 °C after 4 h of incubation

Conclusions

- The MD simulations of four polymeric micelles were performed by optimizing the hydrophilic charge and characterized drug-polymer interactions.
- The FuCL monomer was synthesized and polymerized using PEG as initiator
- The micelles of PEG-*b*-PFuCL were shown to be thermodynamically stable and higher DLC
- The micelles are non-cytotoxic and readily uptaken by MDA-MB-231 breast cancer cells

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