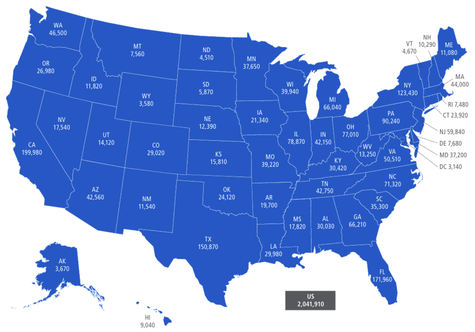
Optimizing Polymeric Micelles for Drug Delivery: Role of Disubstituted Amide Functionalized Polycaprolactone as Hydrophobic Block

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Cancer

- Expected to be the leading cause of death in every country in the 21st century.
- 35.3 million cancer cases and 18.5 million cancer deaths are projected by 2050.[1]



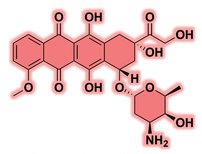
Estimated number of new cancer cases in 2025, excluding basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates are model-based projections and should be interpreted with caution.

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Figure 1. Estimated number of new cancer cases in 2025.[2]

Limitation of chemotherapy

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



Doxorubicin (DOX)

Polymeric Micelle for Drug Delivery

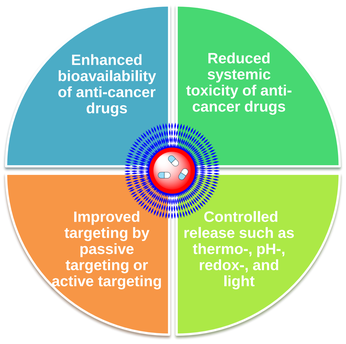


Figure 2. Advantages of drug delivery by polymeric micelle carriers.

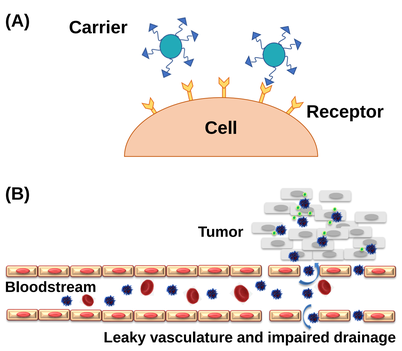


Figure 3. (A) Active targeting and (B) passive targeting.

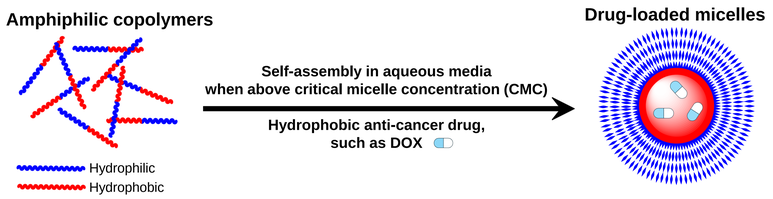


Figure 4. Self-assembly of amphiphilic diblock copolymer into polymeric micelles.

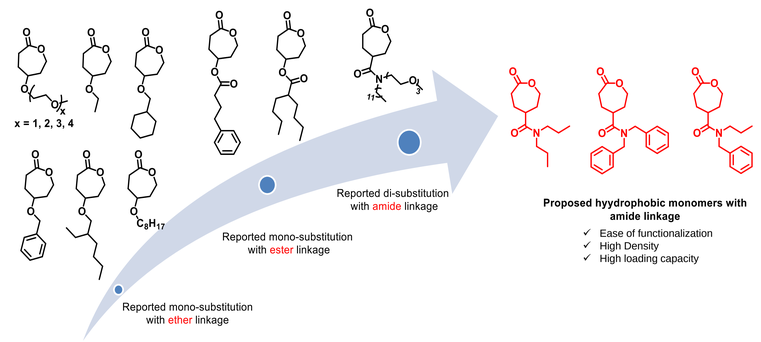
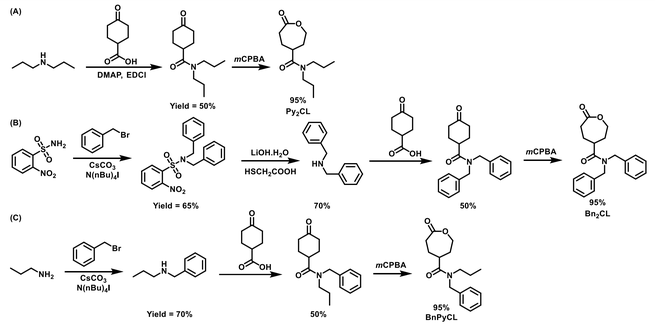


Figure 5. The development of γ-functionalized ε-caprolactone monomers.[3-6]

Synthesis and Characterization



Scheme 1. Synthesis of disubstituted γ-amide functionalized ε-caprolactones (ε-CL).

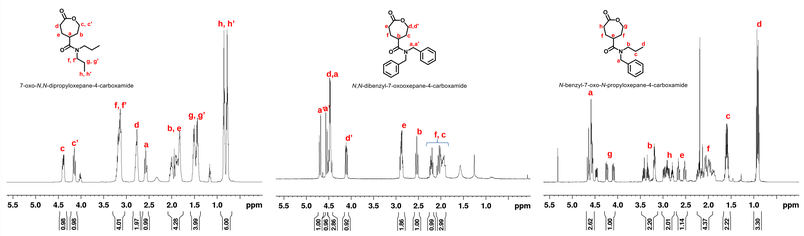
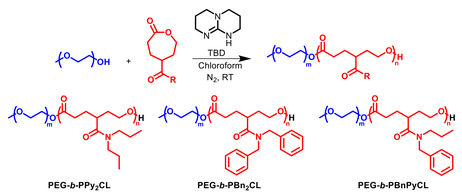


Figure 6. ^{1}H NMR of synthesized hydrophobic monomers; Py_2CL, Bn_2CL, and BnPyCL (left to right).



Scheme 2. Ring-opening polymerization of ε-CL monomer using poly(ethylene glycol) (PEG) as an initiator and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as a catalyst.

Table 1. Summary of molecular weights, compositions of synthesized block copolymers, and their relative drug loading capacities.

Polymer	mol% Hydrophilic : Hydrophobic	M_n, g/mol (NMR)	M_n, g/mol (SEC)	PDI (SEC)	CMC (g/L)	Size (dispersity) (nm) Empty	Size (dispersity) (nm) DOX-loaded	Ratio Polymer : DOX	DOX loading capacity (wt%)
PEG-*b*-PPy_2CL	53:47	7,900	4,200	1.1	6.00 x 10^{-4}	83.40 (0.131)	139.6 (0.091)	10:1	3.70
PEG-*b*-PBn_2CL	49:51	18,550	6,300	1.3	1.16 x 10^{-3}	120.2 (0.129)	134.0 (0.149)	10:1	5.55
PEG-*b*-PBnPyCL	52:48	16,600	4,600	1.9	1.50 x 10^{-4}	121.0 (0.105)	137.9 (0.164)	10:1	7.33

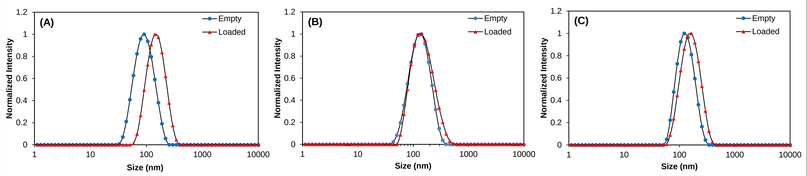


Figure 7. Hydrodynamic sizes of empty and DOX-loaded micelles of PEG-*b*-Py_2CL, PEG-*b*-PBn_2CL, and PEG-*b*-BnPyCL (left to right).

In-vitro Drug Release

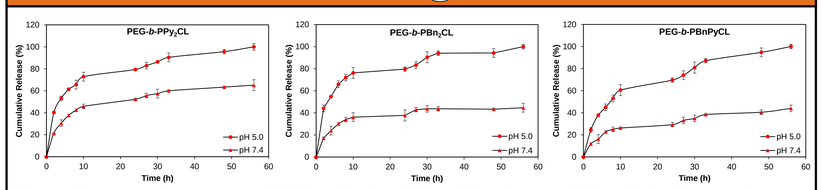


Figure 8. *In-vitro* drug release of PEG-*b*-Py_2CL, PEG-*b*-PBn_2CL, and PEG-*b*-BnPyCL at acidic and physiological pH.

Biological Studies

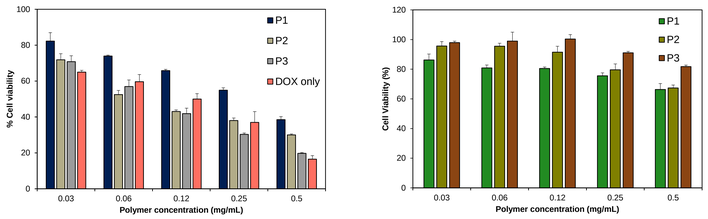


Figure 9. Cell Viability of Empty and DOX-loaded micelles in MDA-MB-231 breast cancer cells. P1; PEG-*b*-Py_2CL, P2; PEG-*b*-PBn_2CL, P3; PEG-*b*-BnPyCL.

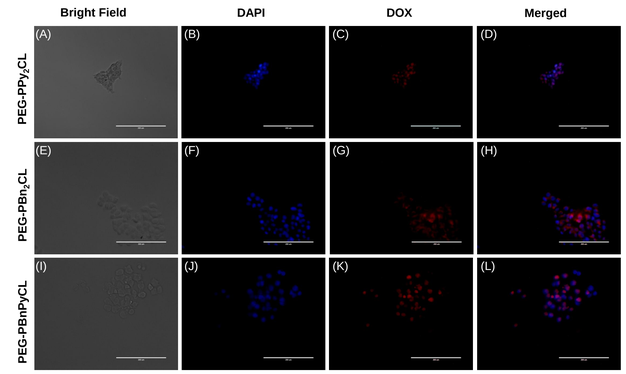


Figure 10. Cellular uptake of DOX-loaded micelles in MDA-MB-231 breast cancer cells.

Summary

- Designed various γ-functionalized ε-caprolactones for ring-opening polymerization, generating amphiphilic diblock copolymers used in micellar drug delivery.
- Employing an amide linker allows the attachment of two aryl groups to each ε-CL monomer; hence, it doubles the functional group density per polymeric unit.
- PEG-*b*-PBnPyCL exhibited the highest DLC (7.33 wt%) among the functionalized PCL-based micelles and sustained pH-responsive drug release in a tumor-mimicking environment (pH 5.0). In addition, PEG-b-PBnPyCL exhibited nearly 20% cell viability in MDA-MB-231 breast cancer cells, comparable to the anticancer drug itself.

Summary of Key Elements and Findings of Research

Novel γ-functionalized ε-caprolactone monomers to generate amphiphilic diblock copolymers with tunable composition, molecular weight, size, and drug loading capacity of micelles.

Potential for Positive Impact

The synthetic platform developed for caprolactone monomers can be modified to synthesize amide-functionalized caprolactone monomers. This can result in polymers with high drug loading capacity and better cellular uptake with ease of functionalization.

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