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[Faculty of Science
Pharmaceutical Sciences]

Stability of Drug-Loaded Polymeric Micelles

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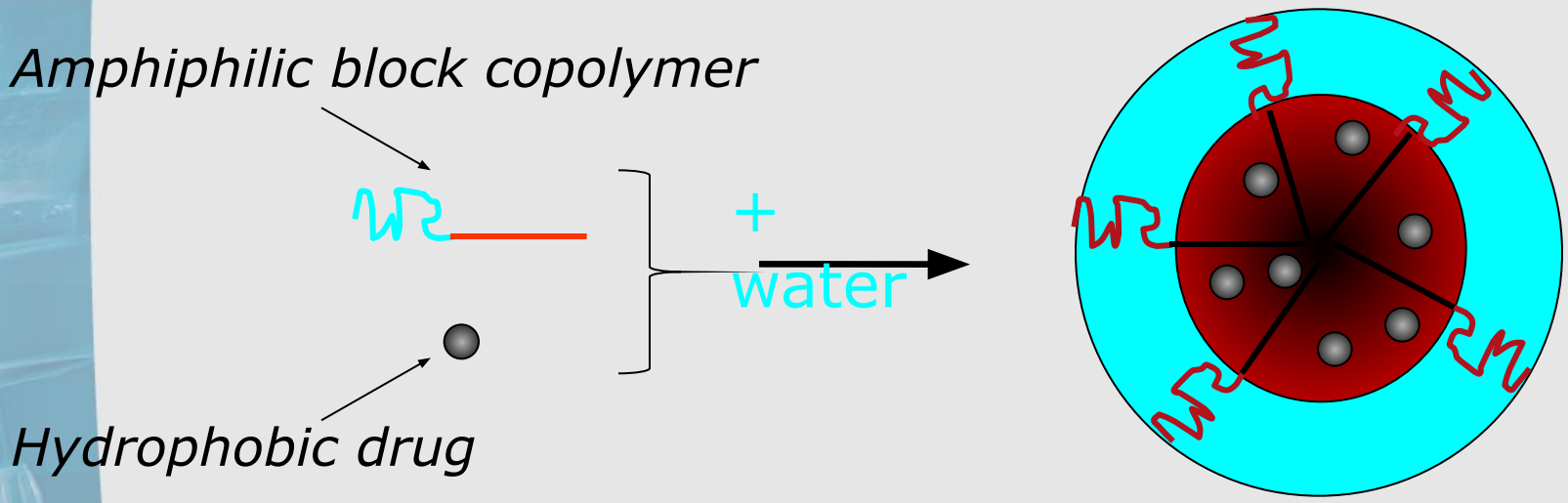
CRS Annual Meeting, Montreal, Canada, July 13th, 2022

Block copolymers as drug carrier



"DRUG CARRIER"

- Incorporation of hydrophobic drugs
- Long circulation in the blood stream after i.v. administration
- Accumulation in e.g. tumor tissues

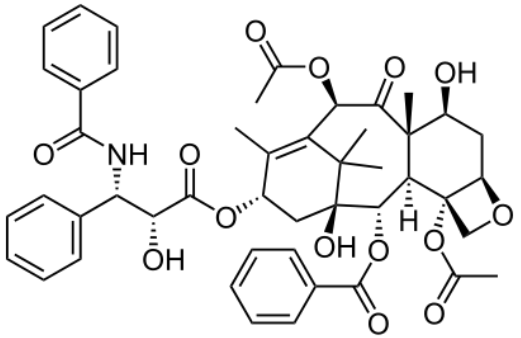
Polymeric Micelles are dynamic systems!

- In the blood stream:
  - micelles rapidly dissociate when:
    - concentration drops below CMC
    - Unimers interact with plasma proteins
    - Micelles are stable but the loaded drug is rapidly released due to solubilization by plasma proteins

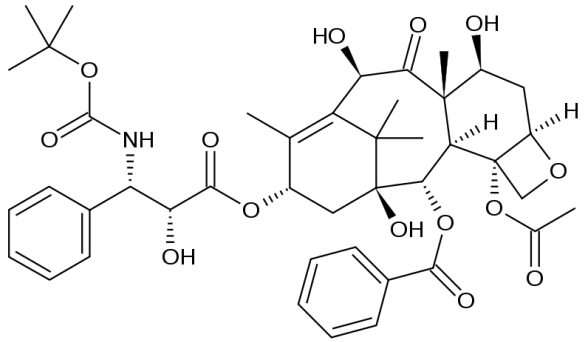
How to stabilize Polymeric Micelles?

- Crosslinking of the core preferable via reversible bonds (e.g. ester or disulfide bonds)
- Covalent linkage of the drug to the core
- Exploiting non-covalent interactions:
  - Ionic
  - Crystalline domains
  - Inclusion complexes
  - Π–Π interactions

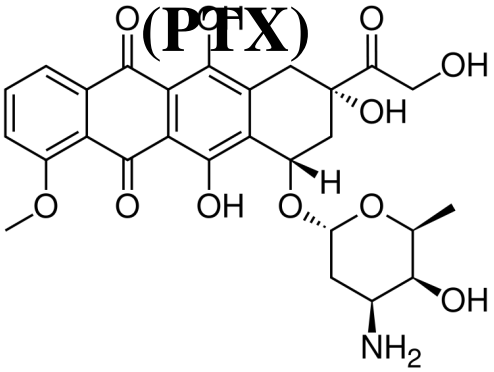
Aromatic anti-cancer drugs



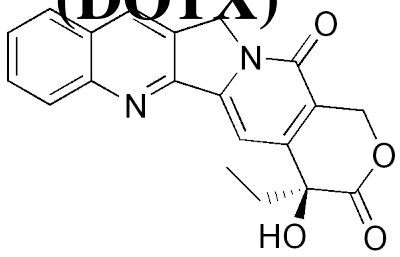
Paclitaxel (PTX)



Docetaxel (DOTX)

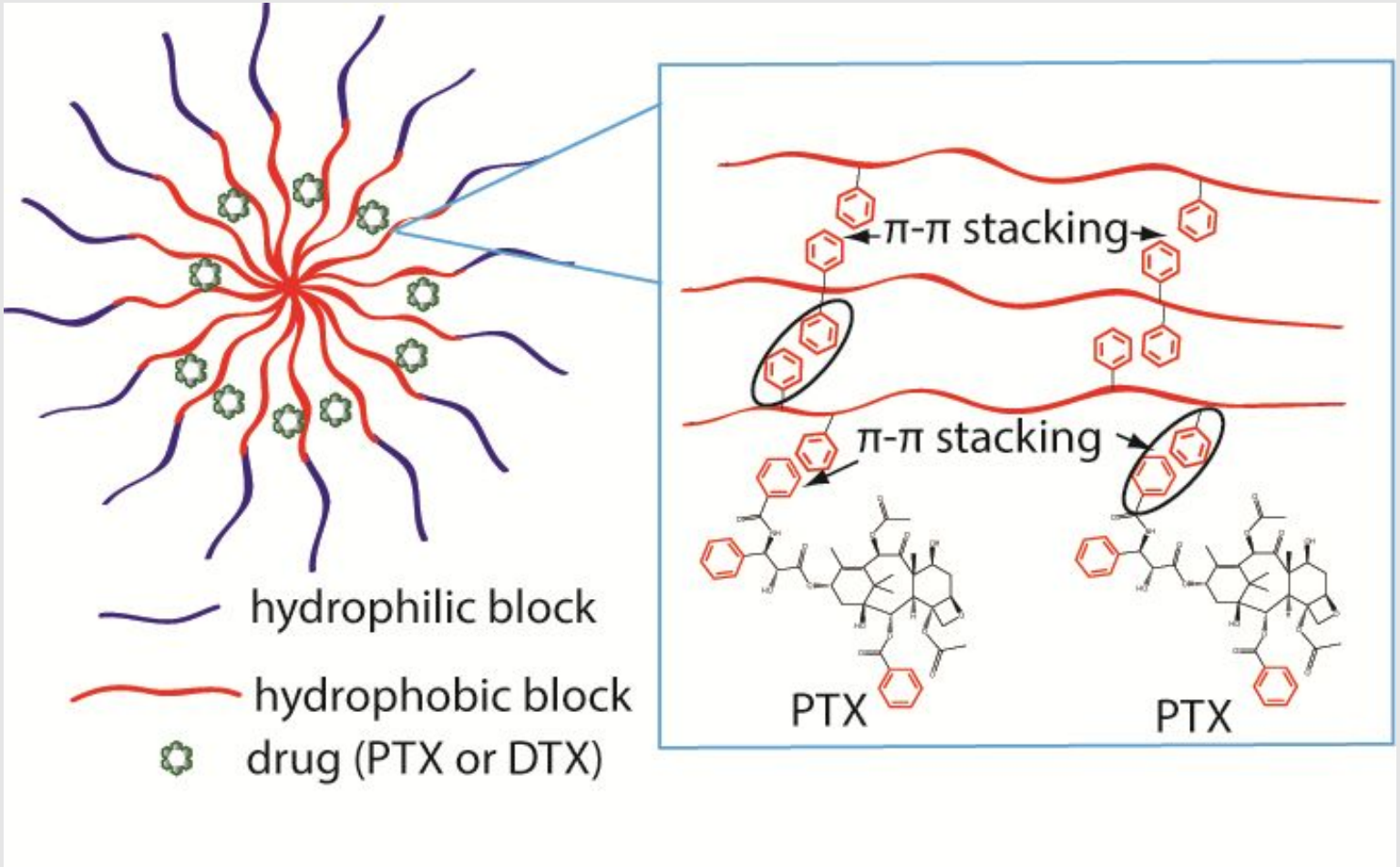


Doxorubicin

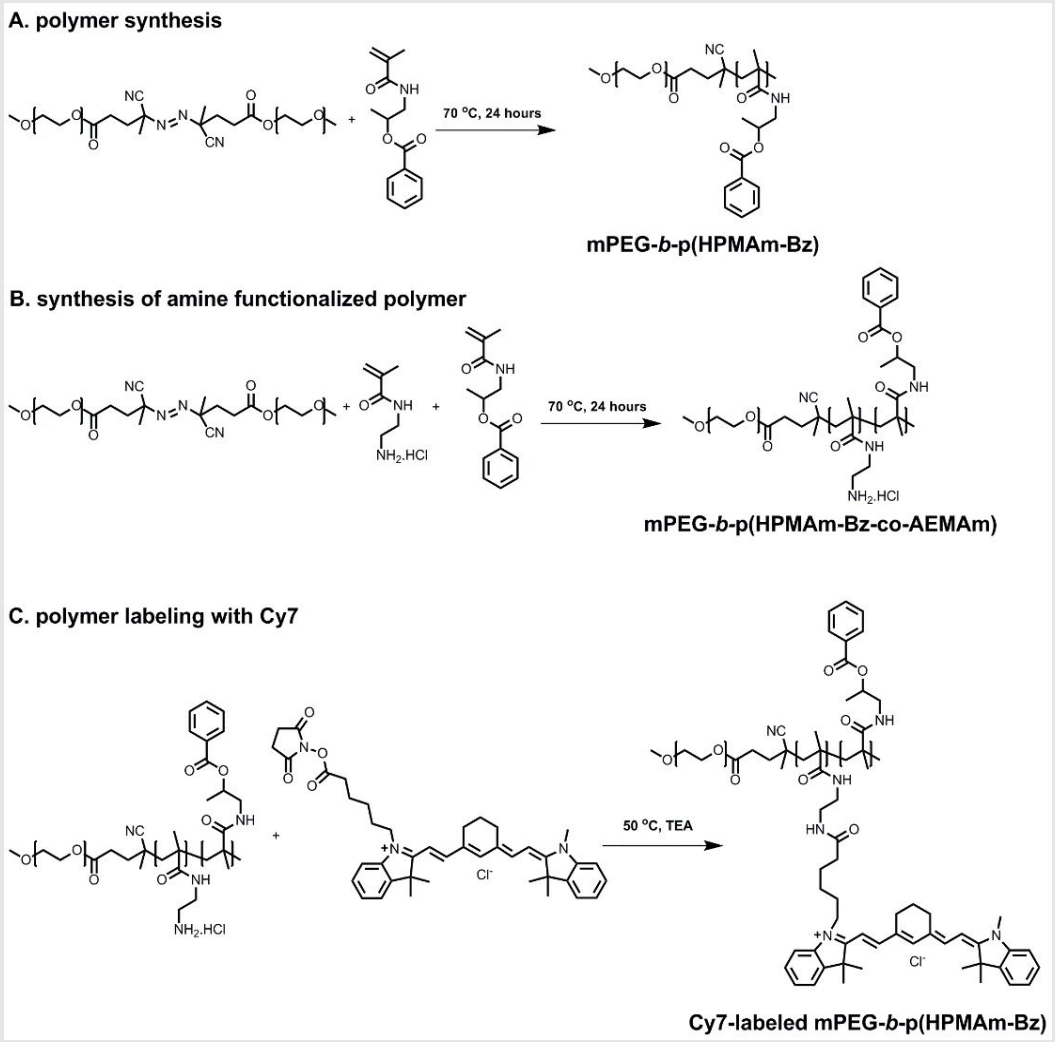


Camptothecin

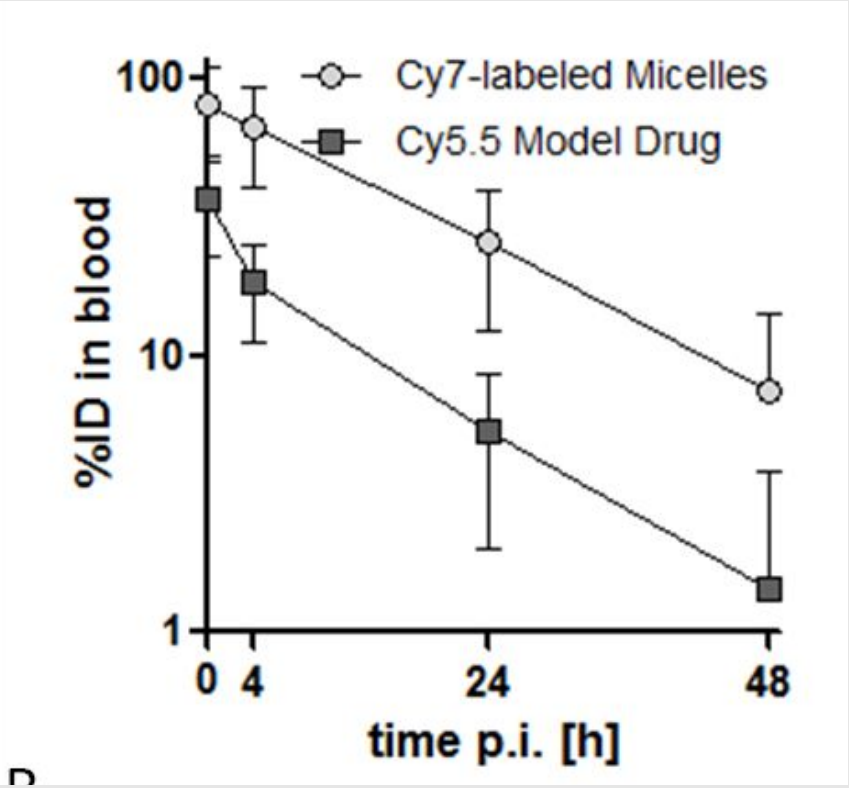
Polymeric micelles with π-π stacking



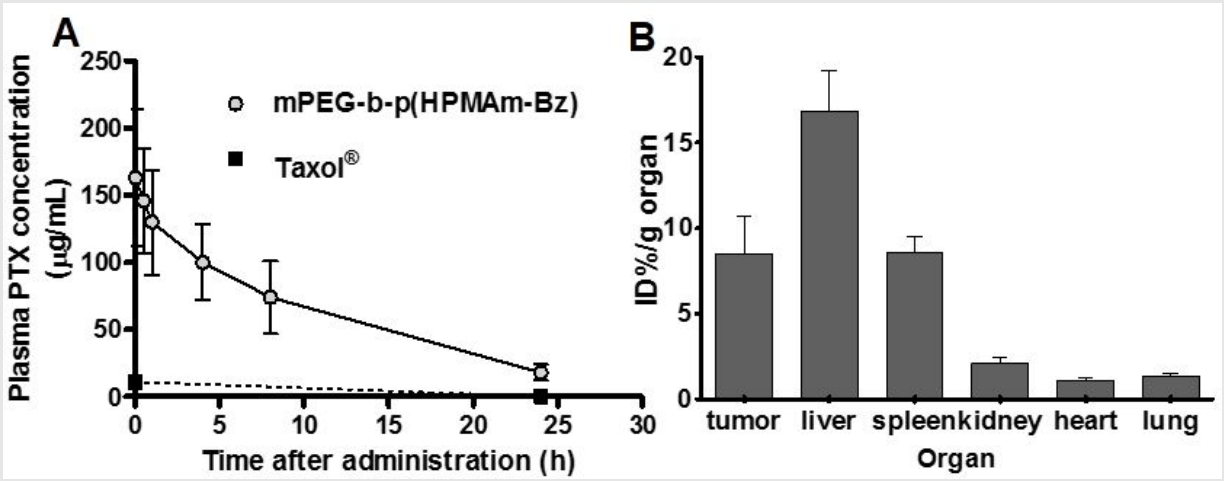
Synthesis of PEG-pHPMAm-Bz



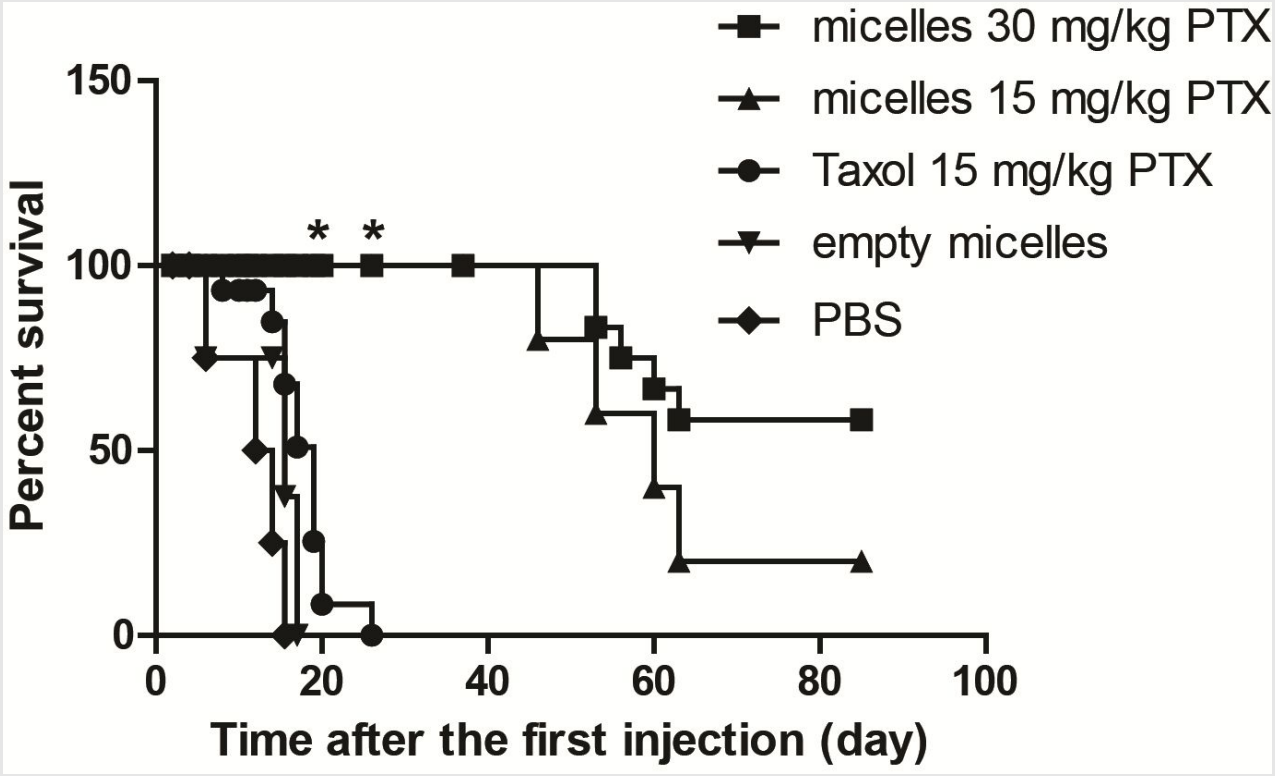
Circulation kinetics of labelled micelles



Pharmacokinetics and biodistribution of PTX: PEG-pHPAMa-bz versus Taxol formulation

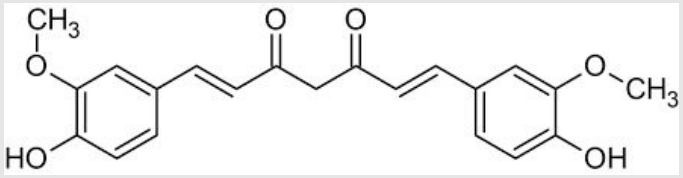


Survival of A431 tumor-bearing mice treated with PTX-loaded micelles



Development of curcumin loaded micelles

Curcumin structure:

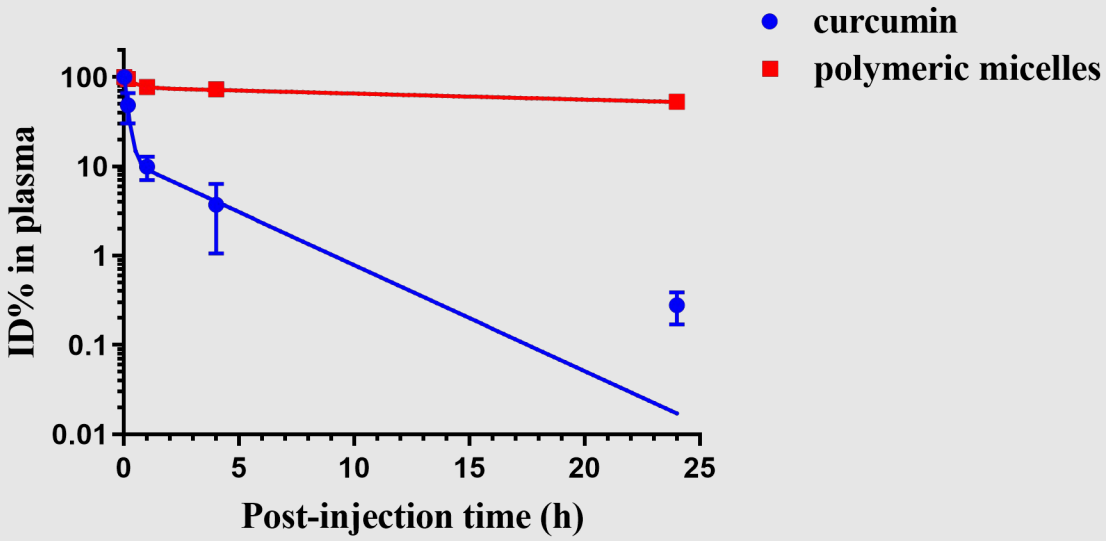


Natural compound, low aqueous solubility, rather instable molecule, extremely low bioavailability

Many pharmacological activities: anti-inflammatory, antioxidant, anti-cancer

'popular' molecule for the development of nanoformulations

Circulation kinetics of curcumin loaded-cy7 labeled micelles in healthy mice



Component	$t_{1/2}$ (h)		$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg·h/mL)	V_1 (mL/kg)	V_2 (mL/kg)	V (mL/kg)	CL (mL/h/kg)
	α-phase	β-phase						
curcumin	0.11	2.5	-	319	86	344	-	157
micelles	-	-	42	6713	-	-	70	1.2

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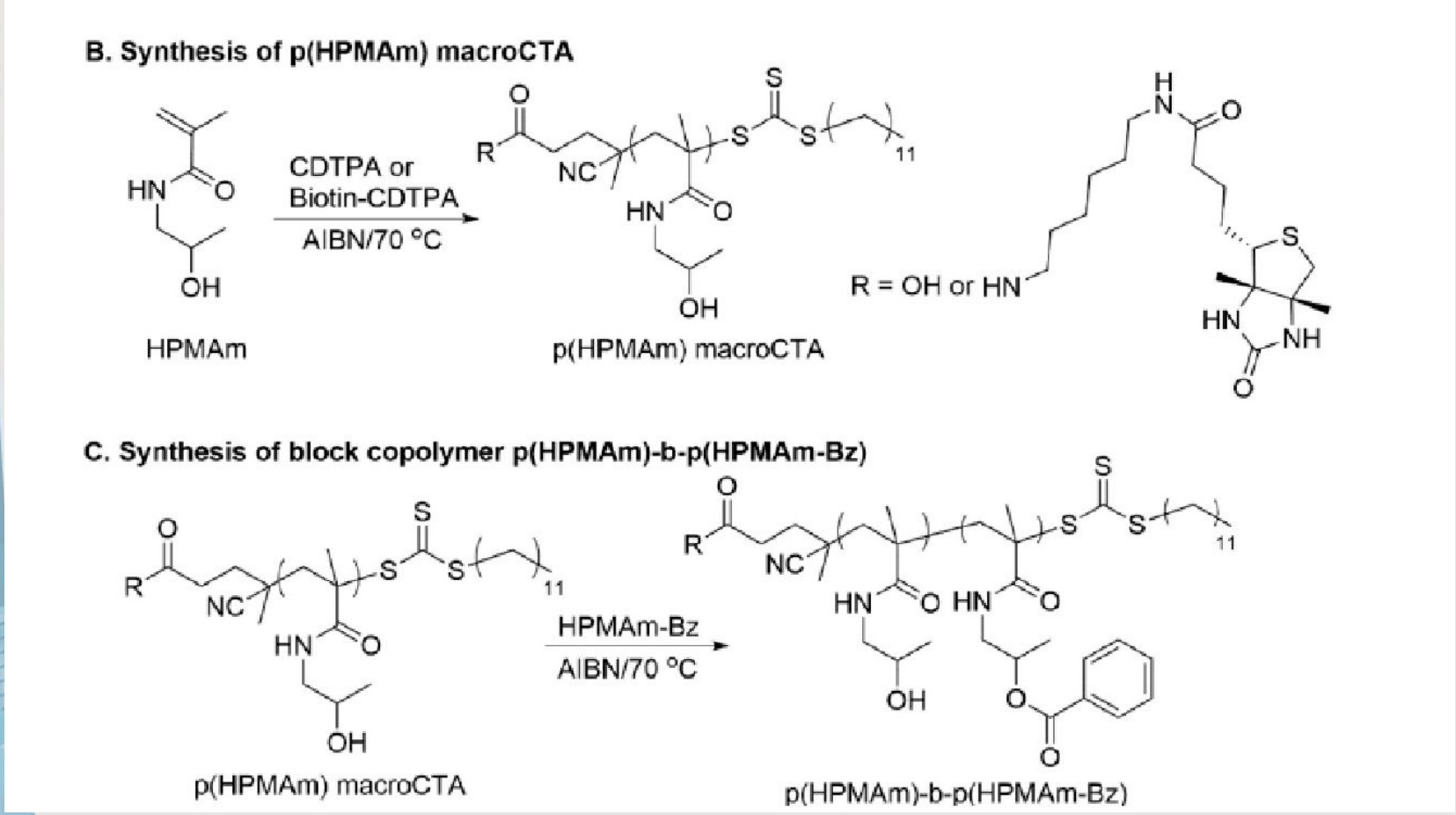
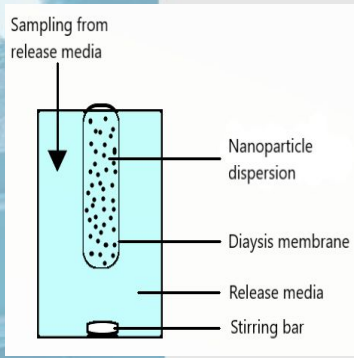
Synthesis of all pHPMA-based micelles with and without biotin terminus via RAFT

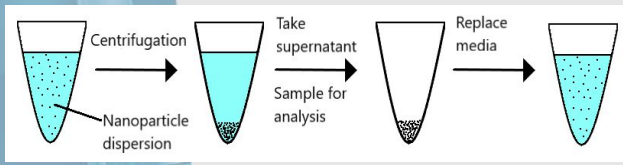


Biotinylated polymeric micelles: Drug release

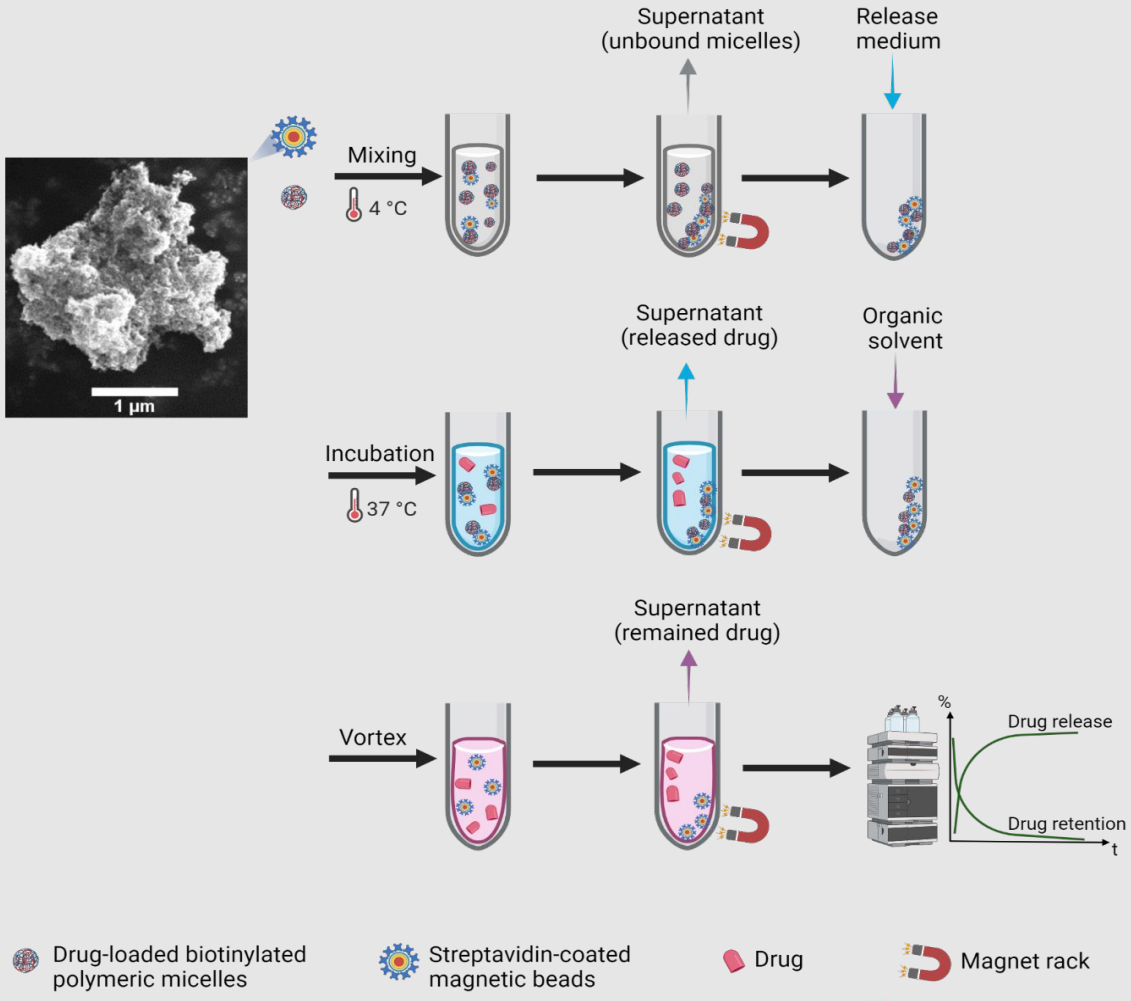
Dialysis method



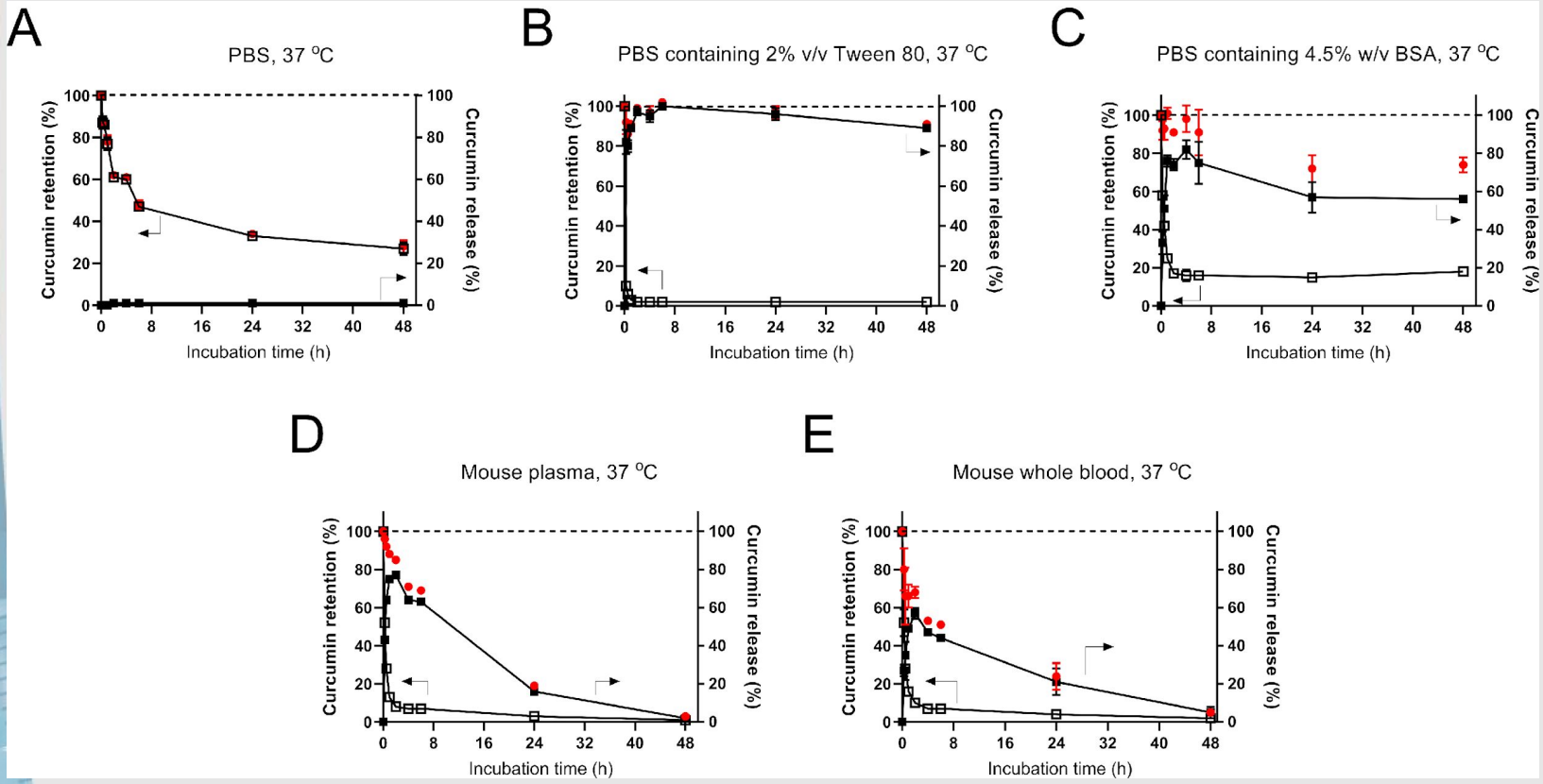
Centrifugation method



'Fishing' method



Curcumin release from pHPMAm-pHPMam-bz micelles in different media



Conclusions

- Polymeric micelles are attractive systems to solubilize and deliver hydrophobic drugs
- Stability can be improved exploiting Π–Π interactions
- These interactions do not guarantee good drug retention
- Biotinylated micelles are good systems to study retention of drugs in biological media including plasma and blood