Bottlebrush Copolymer Excipients to Non-Covalently Sequester and Solubilize Active Pharmaceutical Ingredients

Bottlebrush polymers have great potential as vehicles to non-covalently sequester, stabilize, and deliver hydrophobic small molecule active pharmaceutical ingredients. To this end, we synthesized a poly(N-isopropylacrylamide-stat-N,N-dimethylacrylamide) bottlebrush copolymer using reversible addition-fragmentation chain-transfer polymerization followed by ring-opening metathesis polymerization. Post-polymerization end-group modification was then used to control the thermoresponsive properties of the bottlebrush copolymer in solution. Solubility enhancement of the anti-seizure medication, phenytoin, increased with the hydrophilicity of the end-group moiety. Notably, carboxylic acid functionalized bottlebrush copolymers outperformed linear copolymer controls at higher drug loadings because they existed as unimolecular nanoparticles that were more stable in solution. In addition, the top-performing bottlebrush copolymer excipients were used to solubilize an orally administered breast cancer therapeutic, GDC-0810, with which we visualized how the drug-polymer nanostructures formed during dissolution are distinct between linear and bottlebrush copolymer excipients using cryogenic transmission electron microscopy. These insights could allow us to better interpret how the formation of liquid-liquid phase separated nanodroplets versus amorphous drug-polymer nanoparticles impacts the bioavailability of small molecule actives. This work provided the first investigation of bottlebrush copolymers for the hydrophobic non-covalent sequestration and solubilization of small molecule pharmaceuticals.

Wednesday, May 18 • 10 AM CDT • Zoom Link
Meeting ID: 958 6172 3631 • Password: mse_FLS

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