Synthesis and Characterization of Nanosponges for Drug Delivery and Cancer Treatment

William Kornahrens, Benjamin Spears and Eva Harth*

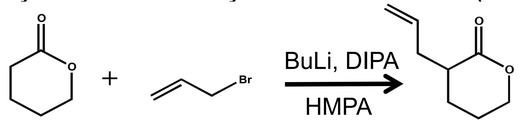
Department of Chemistry, Vanderbilt University, 7210 Stevenson Center, Nashville, TN 37235-1822

Abstract

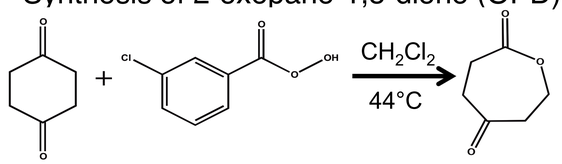
Degradable 3-D polyester nanoparticles, or nanosponges, have been receiving more attention for their potential biomedical applications. Conventional cancer treatments involve the use of drugs that are toxic to healthy cells as well as tumor cells. A more ideal form of treatment could be facilitated through the use of nanoparticles crosslinked with targeting units, such as peptides, that selectively recognize receptors on the surfaces of tumor cells. Unlike other delivery systems, nanosponges have the advantage of enabling a controlled, linear release of a large amount of drug over a defined period of time. In addition, post modification strategies can be utilized to alter several properties of nanosponges, such as hydrophobicity, morphology, particle size, and functionality. We utilized two different linear copolymers for nanoparticle formation: one is poly(valerolactone-allylvalerolactone) and the other is poly (valerolactone-allylvalerolactone–oxepanedione). These two linear polymers have different morphologies and will be investigated with future *in vivo* and *in vitro* drug release studies. In particular, temozolomide, a chemotherapeutic used to treat advanced brain tumors, was encapsulated inside these nanoparticles and the rate of drug release was measured with UV-visible spectroscopy. Furthermore, the nanoparticles have been labeled with a fluorescent dye in order to conduct biodistribution studies to determine if they are capable of crossing the blood-brain barrier.

Monomer Synthesis

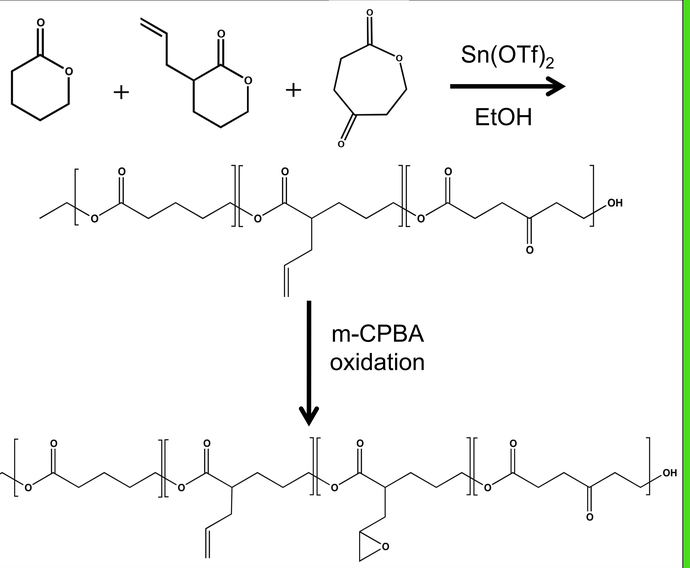
Synthesis of α-allyl-δ-valerolactone (AVL)



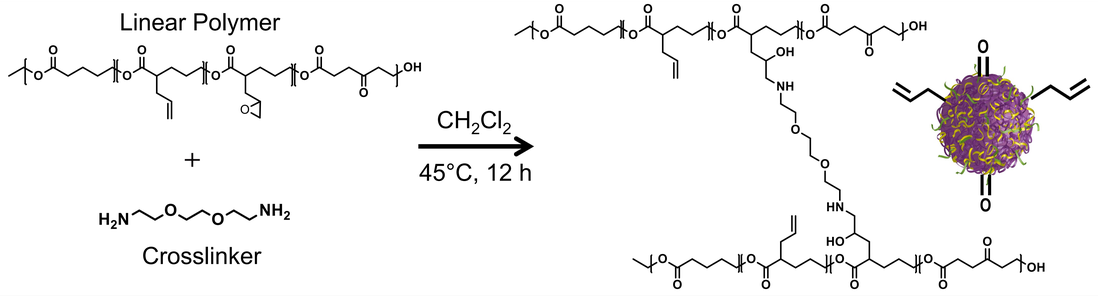
Synthesis of 2-oxepane-1,5-dione (OPD)



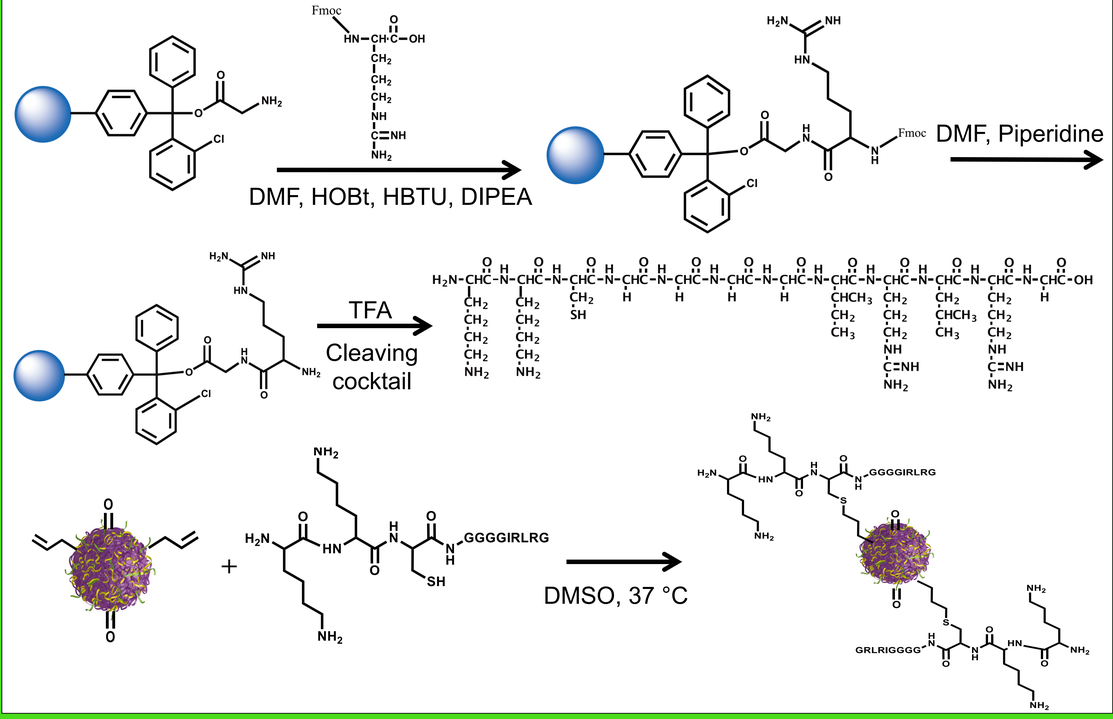
Ring-Opening Polymerization



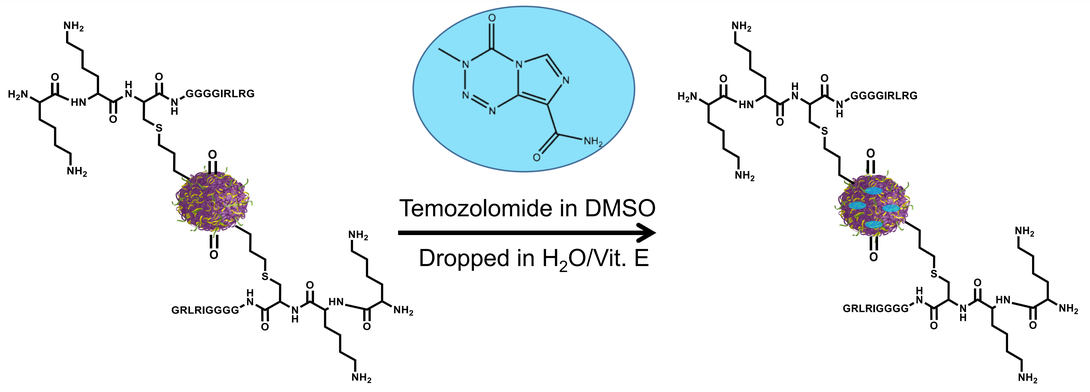
Nanoparticle Formation



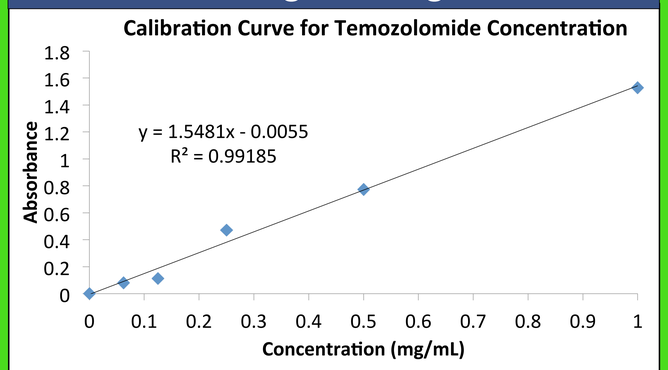
Synthesis and Attachment of Targeting Peptide



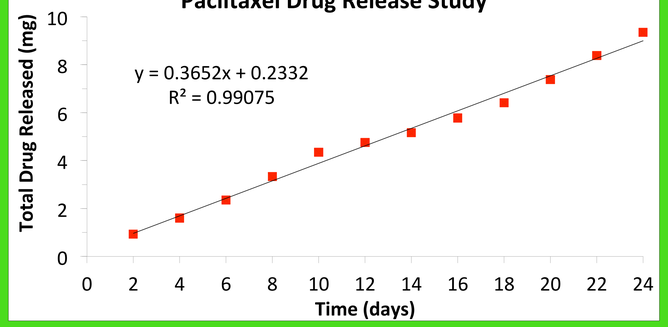
Drug Encapsulation



Drug Loading



Drug Release



Conclusion

Individual monomers (AVL, VL, and OPD) were synthesized and used to make two different copolymers. The synthesis of the polymers was optimized by using tin triflate rather than tin octanoate as a catalyst to increase reaction rate and thereby decrease PDI. Poly (VL/AVL) and poly (VL/AVL/OPD) were synthesized to determine how the presence of OPD in the nanoparticle affected hydrophobicity. The allyl functional groups were then partially oxidized to allow for a crosslinking reaction to form the nanoparticle. A peptide known to bind to cell receptors on tumor cell surfaces was synthesized and attached to the nanoparticle to allow for targeted drug delivery. Preliminary results show that drugs such as paclitaxel have a linear release profile as the nanoparticle degrades.

References

1. van der Ende, A.; Kravitz, Evan J.; Harth, Eva. *J. Am. Chem. Soc.* **2008**, 130, 8706-8713.
2. Passarella, R. J.; Spratt, D. E.; van der Ende A. E.; Phillips J. G.; Wu, Hongmei; Sathiyakumar, V.; Zhou, Li; Hallahan, D. E.; Harth, E.; Diaz, R. *Cancer Res* **2010**, 70(11), 4550-9

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