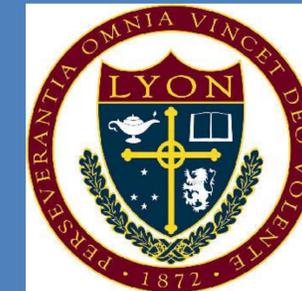




Synthesis and Characterization of Polyester Nanosponges for Drug Delivery



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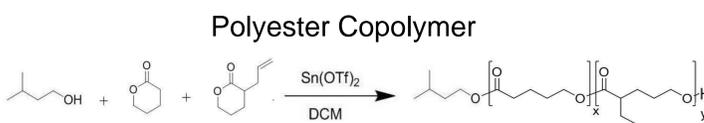
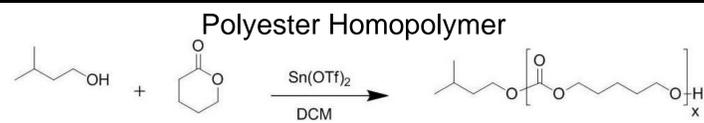
Research Directions

- Poor water solubility is a major hurdle for many promising therapeutics, preventing many drugs from being clinically accepted.
- A recent approach uses nanoparticles to encapsulate therapeutics, increasing solubility without altering the drug¹
- Our research is focused on the synthesis of polyester nanoparticles, or nanosponges, formed by covalently cross-linking polymers
- These biodegradable particles have tunable sizes based on the amount of cross-linker and can be functionalized, allowing targeted drug delivery or imaging

Goals

- We propose a method using tin triflate, a catalyst rarely used due to difficulty removing tin from the final product
- Our goal was to optimize this process, allowing for fast, efficient, and controlled creation of polyester polymers and nanoparticles
- We required a method that would greatly reduce the synthesis time while maintaining a controlled linear polymerization and efficiently removing the tin
- We specifically wanted to optimize copolymer synthesis, a process we can now control by varying the amount of solvent used in the reaction

Synthesis

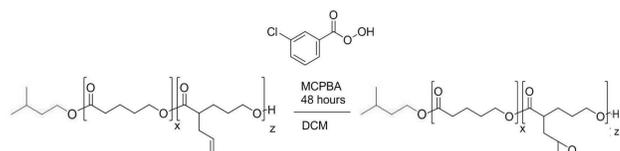


Polymers were made with the ratio
([monomer]:[initiator]:[catalyst]) = (1250:4:50)

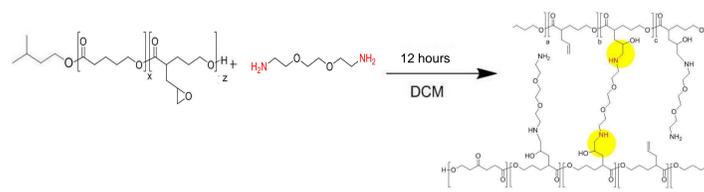
After the reaction is complete, polymerization is stopped by precipitating the polymer twice in 200 mL cold methanol –

this also removes the tin triflate leaving less than 90 ppm

Polyester Oxidation

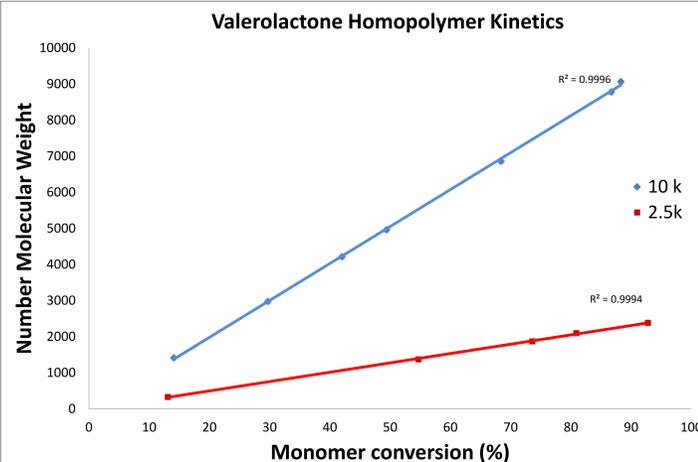


Nanoparticle Formation



Reaction Kinetics

- Increasing the amount of tin triflate catalyst reduces the reaction time
- Reaction time dependent on polymer size, percentage of varying monomers, and solvent concentration
- Polymers made at room temperature with preparation taking less than thirty minutes



The advantage of using tin triflate is that it allows the reaction to be carried out quickly at room temperature. Organic catalysts require glove box preparation, greatly increasing preparation time and difficulty.

The kinetics of the polymer synthesis show a controlled linear growth of the polymer, regardless of the polymer size. Time points were taken from 0-360 minutes, with the 10 k polymer completing in 120 minutes and the 2.5 k polymer completing in 360 minutes

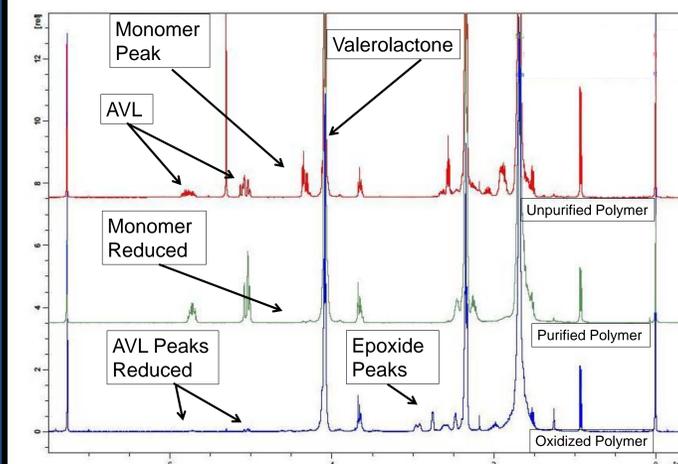
Copolymer Synthetic Variations

Size	% AVL Predicted	Time	Mn predicted	Mn NMR	% AVL	Notes
4k	20	Overnight	4,000	5,083	16.0	Standard (8.7M)
4k	10	Overnight	4,000	4,648	8.5	Dilute (6.6 M)
3k	10	Weekend	3,000	3,754	10.5	Dilute (6.6 M)
3k	10	1 hr	3,000	3,550	6.8	Standard (8.7 M)
3k	10	1 hr	3,000	3,110	4.4	Standard (8.7M)
3k	10	Overnight	3,000	3,909	8.6	Dilute (6.6 M)
2k	10	Overnight	2,000	2,464	8.7	Dilute (6.6 M)
2k	20	Overnight	2,000	2,817	16.2	Dilute (6.6 M)

Systematic copolymer series using allyl-valerolactone (AVL)

- Reactions run in bulk (not shown), standard (8.7 M) or dilute conditions (6.6 M)
- Varying solvent amount changed reaction time and AVL incorporation
- We can use this to prioritize time or material use making this a flexible synthetic pathway
- Bulk conditions finish fastest, typically under an hour, but with very low AVL incorporation
- Standard conditions provided a good balance of reaction time to AVL incorporation
- Dilute conditions are much slower, running for over 12 hours, but allow much higher AVL incorporation

Characterization



By NMR we are able to follow the progress of the reaction

- The top spectra shows an unpurified copolymer
 - Note the presence of the monomer peak
- The middle spectra shows the polymer after two precipitations in cold methanol
 - Note the reduction of the monomer peak, as only the polymer precipitates
 - Tin also removed in this step
- The bottom spectra shows the oxidized polymer
 - Note the reduction of the AVL peaks and the emergence of the epoxide peaks

Conclusions and Future Directions

We have successfully optimized the synthesis of polyester polymers for use in nanoparticle formation. Not only have we been able to reduce the synthesis time **from three days to six hours**, we are able to efficiently remove the tin from the product. This allows us to oxidize the polymer before finally cross-linking to create nanoparticles.

With this process optimized we can now optimize the cross-linking step before testing the nanoparticles ability to encapsulate various drugs, starting with the insoluble breast cancer drug thiostrrepton. Finally we will test the targeting ability of the nanoparticle in vivo.

Acknowledgements

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Principle Investigator: Dr. Eva Harth, Department of Chemistry
Harth Lab



Reference

1. Van der Ende, A.E.; Kravitz, E.J.; Harth E. Approach to Formation of Multifunctional Polyester Particles in Controlled Nanoscopic Dimensions, *Journal of the American Chemical Society*, 2008, 130, 8706-8713.