

## ABSTRACT

Block copolymer micelles have proven to be a viable method for drug delivery because they can increase circulation time in the body and they can enhance passive and active targeting in the body. It has been shown that drug loaded micelles must be in the range of 100-300 nm in diameter for the most effective targeting. Current limitations in this area of study include low ratios of drug to polymer in the micelle core and poor efficiency in the overall incorporation of drug into the micelles. Johnson and Prud'homme of Princeton University have improved these problems through the design of an impingement mixing apparatus. However, Johnson is limited to very low concentrations and low molecular weights of block copolymers. The aim of this research project is to improve upon Johnson's method by developing a new process for *in situ* block copolymer formation for the encapsulation of drugs.

This thesis presents a new method to reactively couple end-functionalized homopolymers *in situ* to form an amphiphilic block copolymer and simultaneously encapsulate a hydrophobic drug in an aqueous environment. Drug loaded BCP micelles were formed by dispersing a hydrophobic polymer A with end functionality X (along with the drug) in an organic solvent and a hydrophilic polymer B with end functionality Y in water. Upon mixing, the reactive pair X-Y rapidly combines to form a covalently bonded block copolymer A-b-B *in situ* and simultaneously micellized to encapsulate the drug as it began to aggregate but before it precipitated from solution. The ability to reactively form the BCP *in situ* permitted higher concentrations of drug, provided higher concentrations of steric stabilizing polymers in the mixing stream, and allowed for higher molecular weights of

polymer. This resulted in higher drug concentrations in the micelle core, better particle size control, and a more versatile process for preparing nanoparticles in drug delivery.

Polystyrene-b-poly(ethylene glycol) was prepared from polystyrene with either a single isocyanate or acid chloride end functionality and poly(ethylene glycol) with a single amine end functionality in THF and THF/water mixing streams using an impingement mixer developed at Princeton University. Mixing experiments and investigations of block copolymer micellization were conducted with and without the presence of  $\beta$ -carotene. Block copolymers were formed both *in situ* and before mixing to determine the effectiveness of this process. Characterization was performed using gel permeation chromatography, nuclear magnetic resonance spectroscopy, dynamic light scattering, cryogenic transmission electron microscopy, and ultraviolet-visible spectrometry. All of the successful micelle systems investigated provided micelle sizes less than 300 nm with at least 80% drug encapsulation.

The acid chloride and amine reaction, unlike the isocyanate and amine reaction, was proven to be fast enough for the formation of polystyrene-b-poly(ethylene glycol) in the impingement mixer. In the shortest residence time used for this study, 20 ms, approximately 70% block copolymer formed by the *in situ* process. The optimal concentrations for effective  $\beta$ -carotene encapsulation with 2000 g/mol-b-5000 g/mol polystyrene-b-poly(ethylene glycol) are: block copolymer concentration  $> 1.3$  wt%,  $\beta$ -carotene concentration  $\leq 2.6$  wt%, and jet velocity  $> 2.0$  m/sec. This system has proven to be a promising alternative to premade block copolymers for drug encapsulation.