MIXING AND REACTION IN THE FORMATION OF BLOCK COPOLYMER SELF-ASSEMBLY OF NANOPARTICLES

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INTRODUCTION

The formation of block copolymer micelles and their applications in drug delivery have been actively investigated because polymer-based carriers have been shown to incorporate hydrophobic drugs.[1,2] In particular, polymer-based drug nanoparticles have revealed many advantages, including stability and long circulation times in vivo.[3] The drug loading efficiency, size, and stability of drug nanoparticles depend on the method used to form them. Commonly used techniques for the production of nanoparticles include salting out, solvent-evaporation, and emulsification-based methods.[4] However, many of these methods have serious limitations, including long processing times, process scale-up, low nanoparticle drug loading, and lack of controlled nanoparticle size. In order to overcome these limitations, an easily scalable[5] Flash Nano Precipitation process to produce stable, high concentration, and high drug loading nanoparticles using amphiphilic diblock copolymers was developed.

EXPERIMENTAL METHODS

Flash Nano Precipitation uses Confined Impinging Jets (CIJ) to provide micromixing of the copolymer and drug. Amphiphilic diblock copolymers dissolved in a good solvent can form micelles when the solvent quality for one block is decreased. The CIJ mixer is used to achieve such a solvent quality change. The use of impinging jets provides mixing timescales that are shorter than the timescale for nucleation and growth of particles, which allows for the formation of nanoparticles with size distributions, morphologies, and drug loading efficiencies not provided by other technologies.[6] The rapid mixing in CIJ mixers offers a uniform residence time distribution, and creates a high energy dissipation region provided by the turbulence generated through the collision of the incoming jet streams at high velocity and equal momentum in a confined volume.

In the CIJ mixer, an amphiphilic diblock copolymer and drug are dissolved in a water-miscible solvent such as tetrahydrofuran (THF), and sent in a stream through the CIJ mixer chamber, where it collides with an opposing water stream, leading to the formation of nanoparticles, collected at the mixer outlet. When producing the nanoparticles via impinging jets, precipitation occurs under conditions of high supersaturation, which favors nucleation over growth processes, yielding smaller size particles.[7]

RESULTS AND DISCUSSION

Using the CIJ mixer, -carotene nanoparticles were formed by mixing with poly(styrene)-b-poly(ethylene glycol). The nanoparticles size was easily controlled by varying the drug concentration, and the resulting -carotene particle size was varied between 450 and 47 nm, as determined by dynamic light scattering (Figure 1). The particle size smaller than 100nm achieved here is within the optimal size range for arterial uptake of drug nanoparticles.[4]

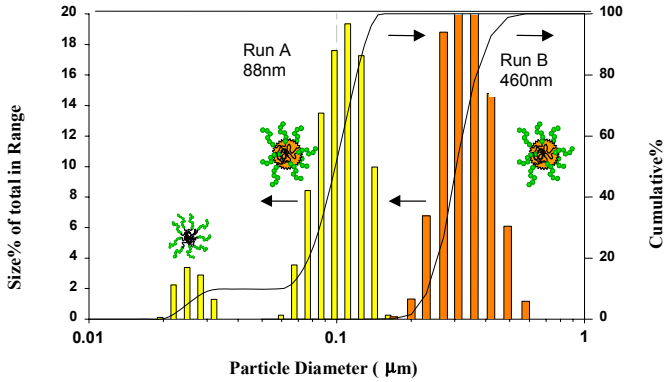

Figure 1: Formation of -carotene nanoparticles with PS-PEG (1,000-3,000 g/mole, respectively) using the CIJ mixer. The particle size can be controlled by changing the drug concentration in the mixing process. Run A consists of 0.52 wt% of -carotene and 0.52 wt% of PS-PEG, and resulted in 88 nm particles. Run B consists of 2.6 wt% of -carotene and 0.4 wt% of PS-PEG, and resulted in 460 nm particles.

The process was improved with end-functionalized reactive precursor homopolymers that form copolymers and nanoparticles during mixing using the CIJ mixer. A minimum copolymer concentration is required to provide stability of the nanoparticles, and arrest further growth of the drug particles. Above the minimum copolymer concentration, the nanoparticles size changes little with copolymer content for both premade and reactively formed block copolymer nanoparticles (Figure 2).

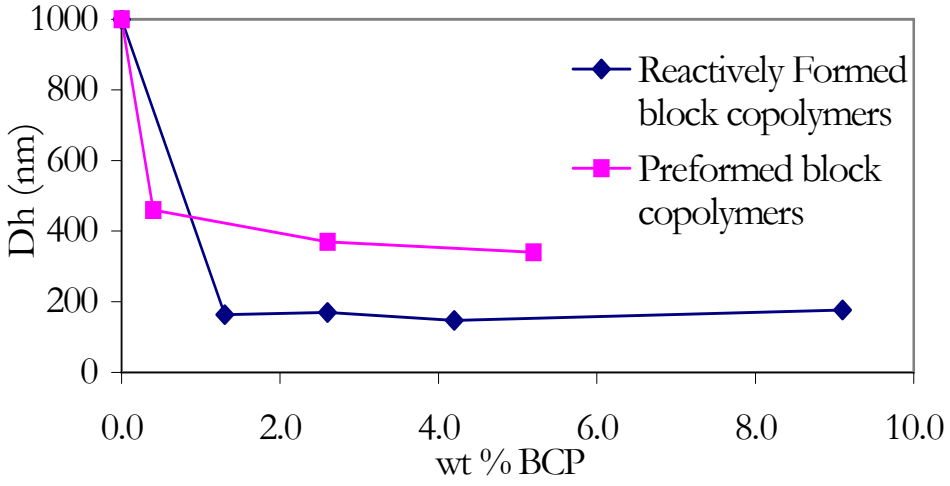

Figure 2: Effect of block copolymer concentration on nanoparticle size. Above a minimum copolymer concentration, the amount of block copolymer used has little effect on nanoparticle size.

CONCLUSION

Flash Nano Precipitation is a novel and efficient process to encapsulate hydrophobic drugs. The high yield, controlled particle size, and high loading provided by this process have been demonstrated using -carotene as a model drug. The use of reactive precursor homopolymers provided a novel alternative to efficiently encapsulate hydrophobic drugs using the CIJ mixer.

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