# DRUG ENCAPSULATION IN BIODEGRADABLE POLYMER CARRIERS USING A CONFINED TANGENTIAL FLOW MIXER

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## INTRODUCTION

Nanoparticle formulations of organic actives have been explored for various applications, including cosmetics, printing inks, and drug delivery. For instance, block copolymer nanoparticles offer unique advantages in cancer therapy by solubilizing hydrophobic drugs, reducing drug toxicity, and extending drug circulation times in vivo. The control of nanoparticle size and stability are required in these applications, and are greatly affected by the method used for nanoparticle production. Common techniques to form nanoparticles include slow anti-solvent addition and dialysis, and emulsification-based methods. However, most of these methods have serious limitations, including long processing times, process scale-up, low nanoparticle drug loading, and lack of control of nanoparticle size. A novel process, termed Flash NanoPrecipitation, for the production of nanoparticles was recently introduced.[1, 2, 4] Flash NanoPrecipitation is an easily scalable technique that provides high solute loading, controlled size, and stable nanoparticles using amphiphilic diblock copolymer stabilization. The nanoparticle stability is dependent on the solute encapsulated. For example, controlled size β-carotene nanoparticles stabilized with a block copolymer of poly(ethylene glycol)-*b*- poly(styrene) with molecular weight of 3,000-*b*-1,000 g/mole respectively, were prepared by Flash NanoPrecipitation, and demonstrated stability for months. However, some solutes exhibiting hydrophobicities lower than β-carotene resulted in formulations that showed considerable recrystallization 20-30 minutes after nanoparticle formation. In order to stabilize the formulations and limit recrystallization, solutes were conjugated to a hydrophobic "anchor" consisting of a hydrophobic polymer or other organic component prior to mixing by Flash NanoPrecipitation. This resulted in nanoparticles with stable size, and no apparent aggregation or particle growth for over one week. The work presented here demonstrates the use of this approach through the conjugation of paclitaxel, an anti-cancer drug, to vitamin E succinate followed by formulation into controlled size nanoparticles via Flash NanoPrecipitation using methoxy poly (ethylene glycol)-*b*-poly (ε-caprolactone) block copolymer with molecular weight of 5,000-*b*-7,000 g/mole, respectively.

## EXPERIMENTAL

### *Flash NanoPrecipitation using Confined Impinging Jets and tangential flow mixers*

In the Flash NanoPrecipitation process, Confined Impinging Jets (CIJ) are used to provide micromixing of the copolymer and drug. 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. 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. A schematic of the mixer is depicted in Figure 1.

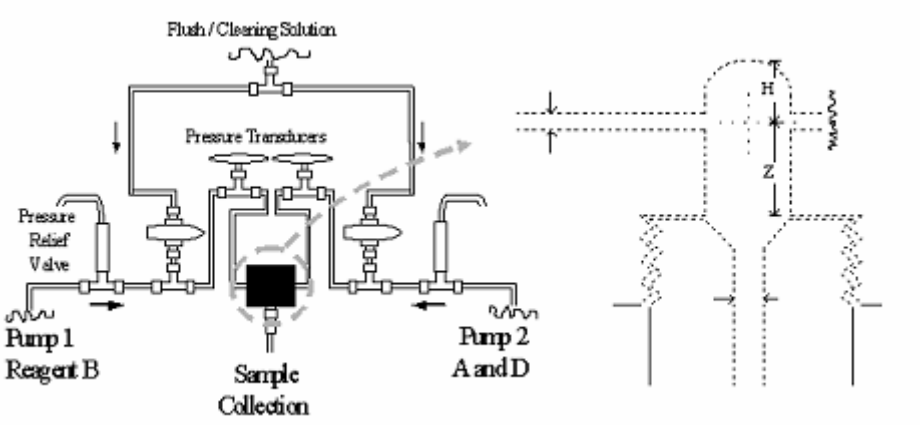


*Figure 1: Schematic diagram of the CIJ mixer.*

In the CIJ mixer, the amphiphilic diblock copolymer, drug, and any other hydrophobic component are dissolved in a water-miscible solvent such as Tetrahydrofuran, and sent in a stream through the CIJ mixer chamber, where it collides at equal momentum with an opposing water stream, leading to the formation of nanoparticles, collected at the mixer outlet tube. When producing nanoparticles via impinging jets, precipitation occurs under conditions of high supersaturation, which favors nucleation over growth processes, yielding smaller size particles. CIJ mixers with various geometries have been characterized, and the scale up relation determined.[1]

The CIJ mixer geometry, however, fixes the ratio of solvent to non-solvent that can be used in the mixing process, since the incoming jets have to collide at equal momentum. This restricts the modification of supersaturation by changing the ratio of solvent to non-solvent. In order to achieve higher supersaturation levels, a tangential flow mixing cell was used, allowing for mixing at ratios of solvent to non-solvent ranging from 1:1 to 1:20, yielding higher supersaturation levels. A schematic of the tangential flow mixing cell is shown in *Figure 2*.

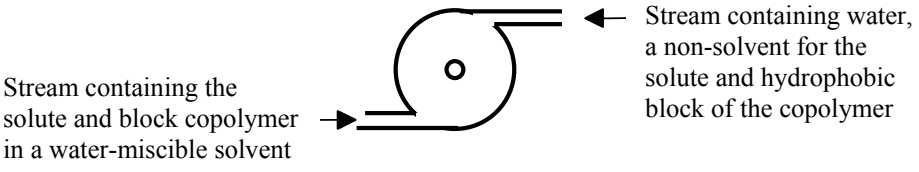


*Figure 2: Schematic diagram for a tangential flow mixing cell which permits unequal stream velocity mixing. The mixer effluent is collected through the center outlet stream*

***Conjugation of paclitaxel to vitamin E succinate***

While most approaches to prodrug formation focused on enhancing water solubility of hydrophobic drugs by conjugation to a hydrophilic anchor, such as poly (ethylene glycol), the strategy outlined here aims at further reducing water solubility of

the solute. This will (1) limit recrystallization of the solute and Ostwald ripening following nanoparticle formation, and (2) retain the solute in the nanoparticle core, where water and enzymatic activities are limited. The nanoparticle formulations show improved stability, and are expected to prolong the drug half-life in vivo, since cleavage of the drug is now determined by the linker chemistry used to conjugate the drug to the hydrophobic anchor, and not by enzymatic activity.

## RESULTS & DISCUSSION

In order to produce paclitaxel nanoparticles, the drug was first conjugated to vitamin E succinate, based on the procedure of Greenwald et al.[3], which used methoxy poly (ethylene glycol) (mPEG) with terminal carboxylic acid to form an mPEG-paclitaxel conjugate. The same chemistry is applied here, using the acid functionality on vitamin E succinate instead of the mPEG acid used in Greenwald's study.

Using Flash NanoPrecipitation and methoxy poly (ethylene glycol)-*b*-poly (ε-caprolactone) block copolymer with molecular weight of 5,000-*b*-7,000 g/mole, respectively, paclitaxel-vitamin E succinate and vitamin E succinate were formulated into nanoparticles via the tangential flow mixer shown in *Figure 2*. The nanoparticle size was determined by dynamic light scattering (DLS), shown in *Figure 3*.

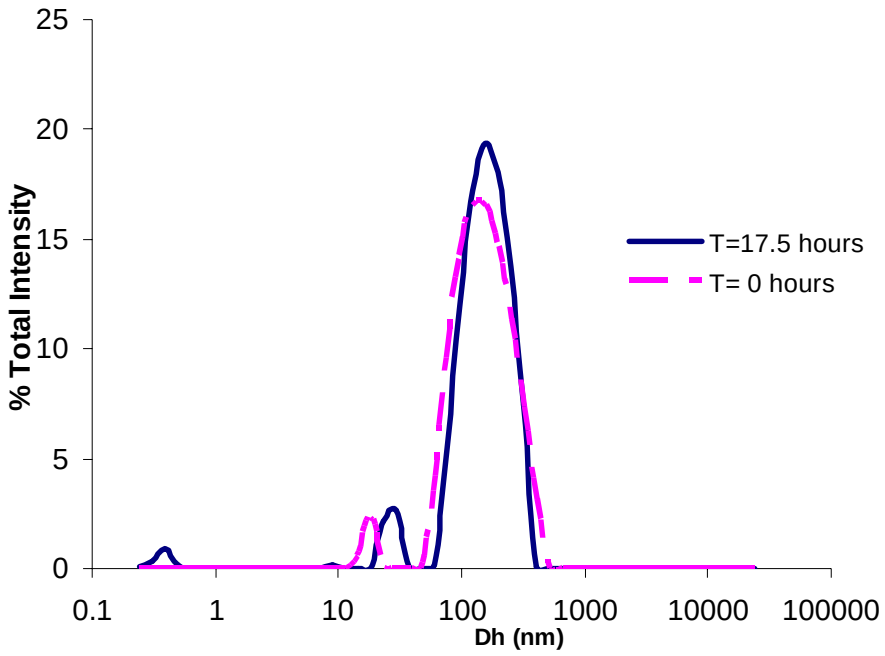


*Figure 3: Size distribution for nanoparticles composed of paclitaxel-vitamin E succinate conjugate with vitamin E succinate prepared via Flash NanoPrecipitation and methoxy poly (ethylene glycol)-b-poly (ε-caprolactone) block copolymer with molecular weight of 5,000-b-7,000 g/mole, respectively. The ratio of conjugate: vitamin E succinate: block copolymer is 1.12: 0.88: 1 (w: w: w), respectively. Distributions shown for 0 and 17.5 hours after mixing.*

The nanoparticle size can easily be tuned by changing the initial solute concentrations. Changing the total initial concentrations of paclitaxel-vitamin E conjugate and vitamin E succinate results in nanoparticles with different sizes. The results are shown in *Figure 4*.

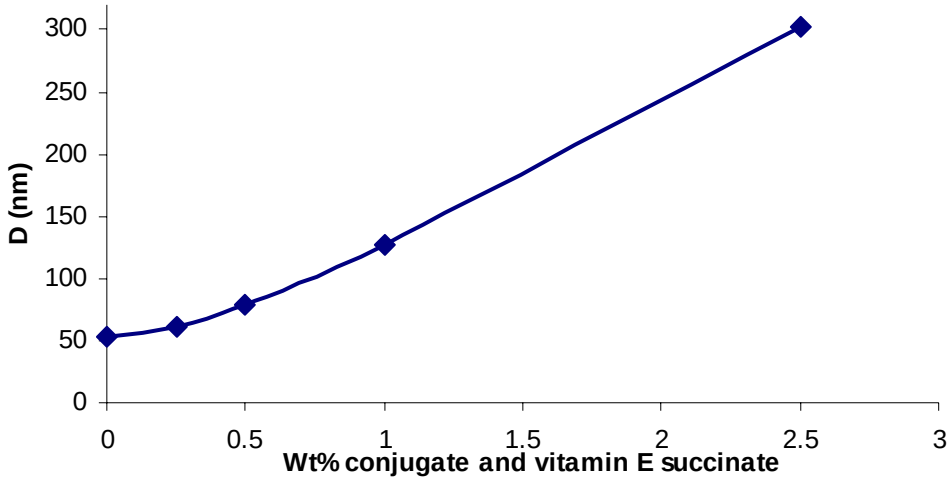


*Figure 4: Nanoparticle size can be tuned by changing the concentration of drug conjugate and vitamin E succinate. Nanoparticle size determined by DLS.*

## CONCLUSIONS AND FUTURE WORK

Flash NanoPrecipitation is an easily scalable technique to produce nanoparticles with controlled size and narrow polydispersity. For solutes with moderately low water solubility which do not show stability when formulated in nanoparticles using this technique, a solute-hydrophobic anchor conjugate was synthesized, prior to mixing through a tangential flow mixing cell. This approach provides both stability and control of release of the solute from the nanoparticles.

Current focus is on determining the release behavior of paclitaxel from paclitaxel-vitamin E succinate conjugate formulated into nanoparticles using Flash NanoPrecipitation and methoxy poly (ethylene glycol)-*b*-poly (ε-caprolactone) block copolymer with various molecular weights.

## REFERENCES

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