Microfluidics-based Manufacture of PEG-b-PLGA Block Copolymer Nanoparticles for the Delivery of Small Molecule Therapeutics

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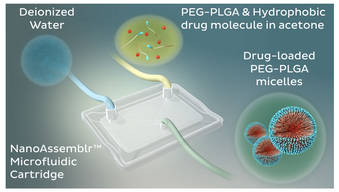
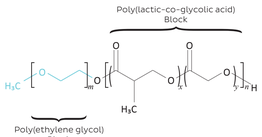
Purpose and Objectives

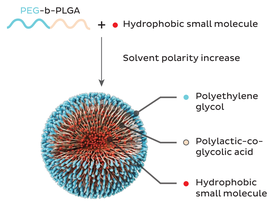
- Methods of production for block copolymer nanoparticle as drug delivery vehicles pose numerous challenges:
  - Maintaining consistent nanoparticle quality
  - Tuning size depending on the application
  - Optimization for scale-up
  - Reproducibility
- Automated microfluidics-based production eliminates user variability and is capable of reproducible, and scalable manufacture of nanoparticles
- We describe manufacture of PEG-b-PLGA nanoparticles using the NanoAssemblr™ Benchtop microfluidic instrument for optimization of size and physical encapsulation of a hydrophobic model drug coumarin-6.

Methods



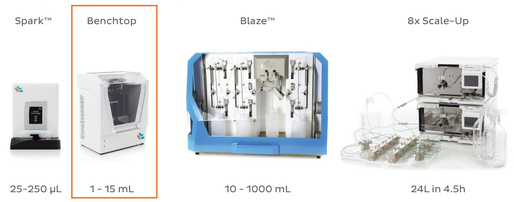
PEG-b-PLGA Structural formula





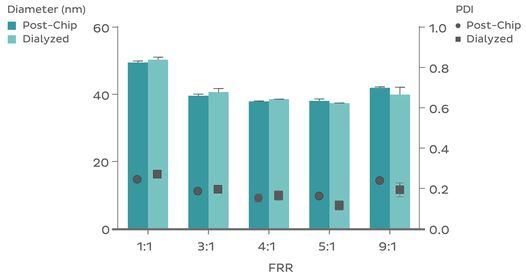
NanoAssemblr™ Systems

Systems employed in this study

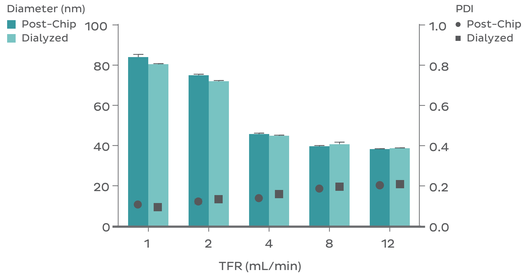


Tuning Size by NanoAssemblr Parameters

A Flow Rate Ratio (FRR) has subtle effect on size, mostly at low FRR.



B Micelle size decreased asymptotically with increasing Total Flow Rate (TFR)



- FRR controls the magnitude of solvent polarity shift upon mixing and TFR is proportional to mixing speed

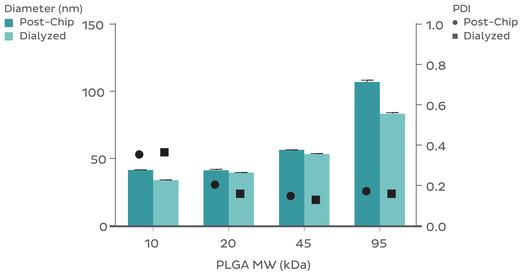
Detailed information

Polymer	PEG_{5k}-$PLGA_{20k}$
Aqueous Phase	Deionized water
Organic Phase	20 mg/mL polymer in acetone
TFR	A) 8 mL/min B) As indicated
FRR (aqueous:organic)	A) As indicated B) 3:1
Solvent Removal	Dialysis

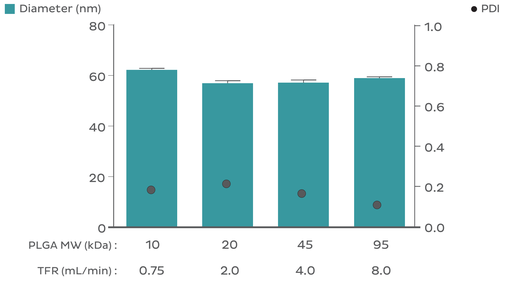
Dialysis did not affect particle size. Hydrodynamic size and particle size distribution (expressed as polydispersity index, PDI) were determined by dynamic light scattering. PEG-PLGA particles were formulated at different FRR as indicated and dialyzed against water for 12h. Samples were formulated in triplicate and measurements represent the mean and error bars are SEM

Tuning Size by Polymer Properties

A PEG-PLGA micelle size increases with increasing MW of hydrophobic PLGA block (PEG MW held constant)



B Particle size can be equalized despite differnt PLGA MWs by tuning TFR



- Size is affects biodistribution and drug release. Hence to compare polymer micelles of different composition, it's important their sizes be comparable.

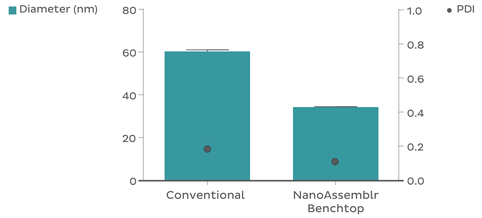
Detailed information

Polymer	PEG_{5k}-$PLGA_x$; x = 10 - 95 kDa
Aqueous Phase	Deionized water
Organic Phase	20 mg/mL polymer in acetone
TFR	A) 8 mL/min B) As indicated
FRR (aqueous:organic)	3:1
Solvent Removal	Dialysis

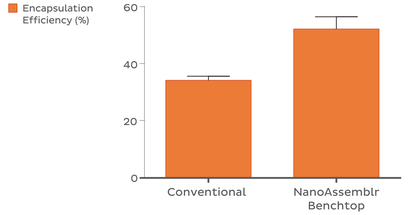
Hydrodynamic size and particle size distribution (expressed as polydispersity index, PDI) were determined by dynamic light scattering. PEG-PLGA particles were formulated n triplicate and measurements represent the mean and error bars are SEM. Where indicated, samples were dialyzed against water for 12h

Hydrophobic Small Molecule Drug Loading

A Coumarin 6 loaded PEG-PLGA micelle size: NanoAssemblr technology < beaker precipitation



B Encapsulation efficiency: NanoAssemblr technology > beaker precipitation



Detailed information

Hydrodynamic size and particle size distribution (expressed as polydispersity index, PDI) were determined by dynamic light scattering. All samples were formulated in triplicate and dialyzed against water for 12h. Measurements represent the mean and error bars are SEM. Encapsulation Efficiency was measured by centrifuging the particles and measuring coumarin 6 in the supernatant by fluorescence spectroscopy against a standard curve.

Polymer	PEG_{5k}-$PLGA_{20k}$
Polymer:Coumarin 6	1:400
Organic Phase	20 mg/mL polymer in acetone
Aqueous Phase	Deionized water
TFR	Benchtop: 8 mL/min Beaker: Dropwise
FRR (aqueous:organic)	3:1
Solvent Removal	Dialysis

Conclusions

Polymer composition affects nanoparticle size, but instrument parameters can be used to make micelles of different composition the same size, which is essential to compare performance of different formulations.

NanoAssemblr formulations were smaller and had greater encapsulation efficiency than conventional beaker precipitation.