Microfluidic Manufacture of PLGA Nano- and Microparticle Drug Delivery Vehicles.

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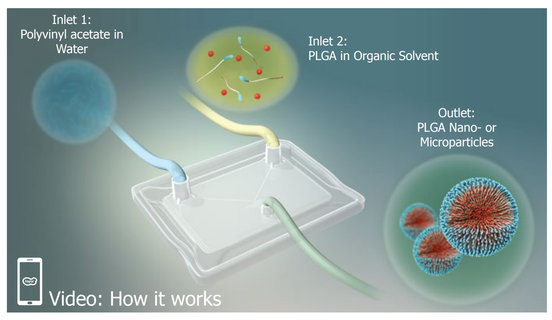
Introduction

Purpose

- Polymer nano- and microparticles are desirable drug delivery vehicles for numerous indications
- With conventional methods of making particles it is challenging to achieve population uniformity, batch-to-batch reproducibility, and to scale manufacturing
- Demonstrated is a scalable microfluidic process for developing and optimizing both nano- and microparticles composed of biodegradable polymers
- Nanoparticle size was tuned between 70- 200 nm
- Microparticles were tuned between 1 - 5 µm
- Total Flow Rate, Flow Rate Ratio, and concentration of polymers were systematically explored

General Method

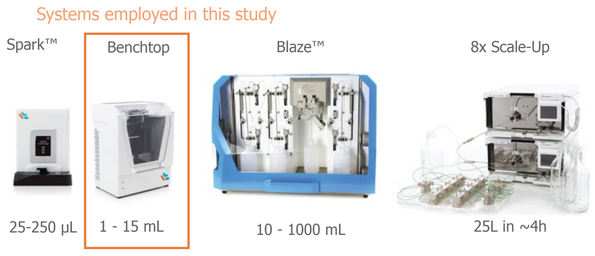
Microfluidic Mixing: Homogeneous Solvent/Antisolvent Precipitation



NanoAssemblr™ Systems

Scalable Platform for Manufacturing Nanoparticles

Systems employed in this study

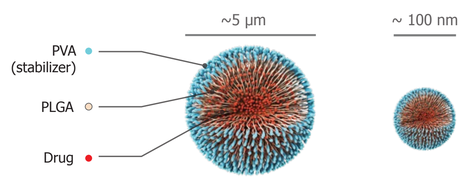


Video: NanoAssemblr Benchtop Demo
Info: Detailed Materials & Methods

Nano- or Microparticles

Nano- or microparticles were obtained when using different organic solvents and different concentrations of the stabilizer PVA.

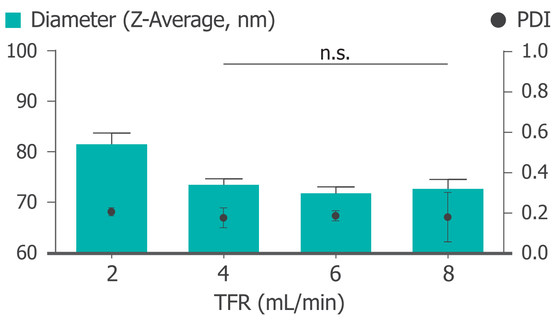
	Microparticles	Nanoparticles
Solvent	Ethy Acetate (semi-miscible)	Acetonitrile (miscible)
PVA Conc.	0.1%	2%



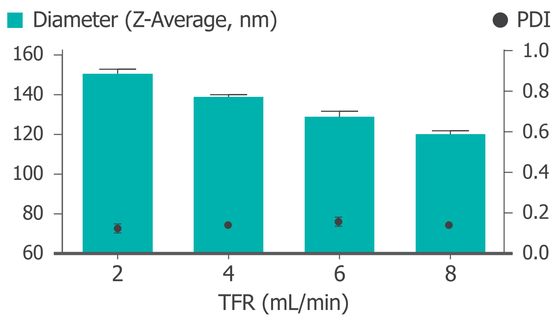
Optimizing Nanoparticle Size

Increasing the total flow rate decreases nanoparticle size

A 5 mg/mL PLGA



B 20 mg/mL PLGA

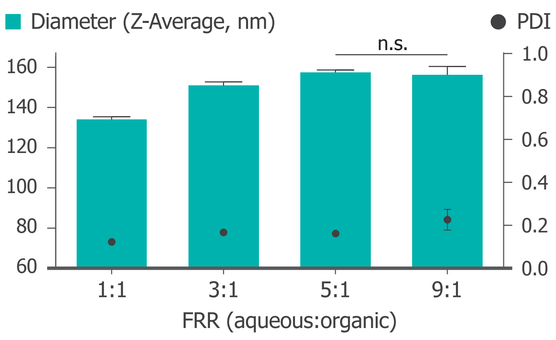


Higher polymer concentrations led to larger particles.

Data points are the mean ± SD for three independent size/PDI measurements by dynamic light scattering on three independent samples (n = 3). Horizontal bar indicates diameters were not significantly different (P>0.05) by one-way ANOVA followed by Tukey's post-hoc test.

Polymer	PLGA (50:50) ester-term. 45-55 kDa
Aqueous Phase	2% w/v PVA in deionized water
Organic Phase	A) 5 mg/mL in acetonitrile B) 20 mg/mL in acetonitrile
Total Flow Rate	As labeled
Flow Rate Ratio	1:1 (Aq:Or)

Increasing the aqueous:organic flow rate ratio leads to an increase in nanoparticle size



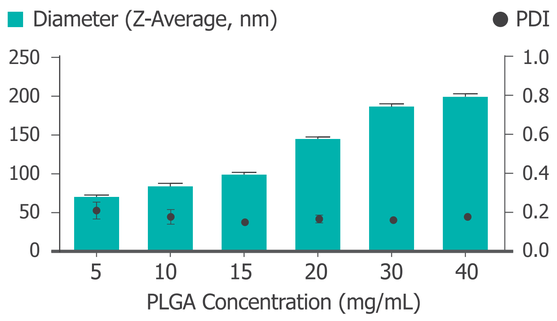
Data points are the mean ± SD (n = 3). Horizontal bar indicates diameters were not significantly different (P>0.05) by one-way ANOVA followed by Tukey's post-hoc test.

Polymer Mol. Wt.	PLGA (50:50) ester-term. 45-55 kDa
Aqueous Phase	2% w/v PVA in deionized water
Organic Phase	20 mg/mL Polymer in acetonitrile
Total Flow Rate	8 mL/min
Flow Rate Ratio	As labeled (Aq:Or)

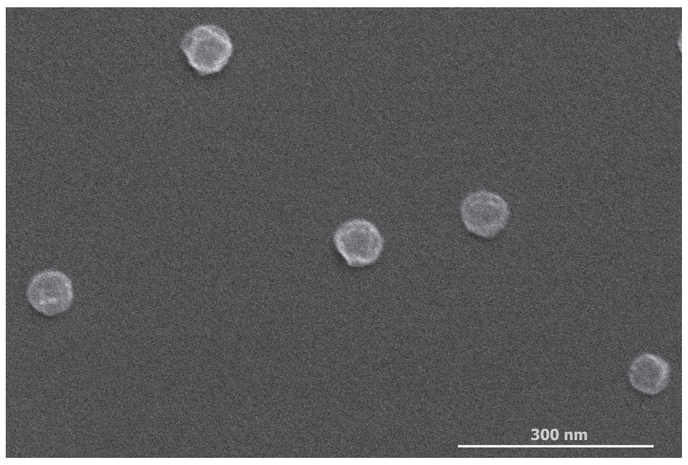
Increasing the PLGA concentration leads to an increase in nanoparticle size

Data points are the mean ± SD (n = 3). Horizontal bar indicates diameters were not significantly different (P>0.05) by one-way ANOVA followed by Tukey's post-hoc test.

Polymer Mol. Wt.	PLGA (50:50) ester-term. 45-55 kDa
Aqueous Phase	2% w/v PVA in deionized water
Organic Phase	Polymer in acetonitrile
Total Flow Rate	8 mL/min
Flow Rate Ratio	1:1 (Aq:Or)



PLGA microparticles show a spherical morphology with sizes between 60-100 nm



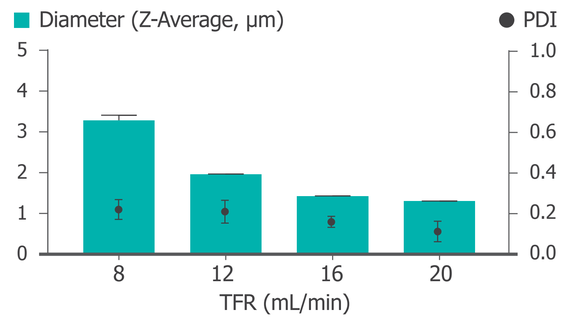
Scanning electron micrographs of PLGA nanoparticles prepared using the NanoAssemblr Benchtop. For SEM, samples were washed 3x by centrifugation and resuspention in DI water, dispersed on a Si chip, allowed to dry, and sputter coated with 5 nm Iridium. Scale bar = 300 nm

Polymer Mol. Wt.	PLGA (50:50) ester-term. 45-55 kDa
Aqueous Phase	2% w/v PVA in deionized water
Organic Phase	Polymer in acetonitrile
Total Flow Rate	8 mL/min
Flow Rate Ratio	1:1

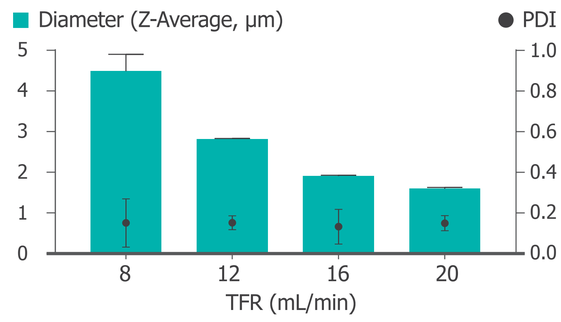
Optimizing Microparticle Size

Increasing the total flow rate decreases microparticle size

A 20 mg/mL PLGA



B 50 mg/mL PLGA

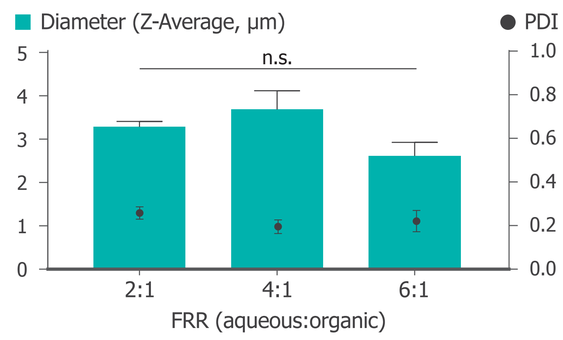


Using semi-miscible ethyl acetate instead of acetonitrile plays a large role in microparticle formation.

Data points are the mean ± SD for three independent size/PDI measurements by dynamic light scattering on three independent samples (n = 3). Horizontal bar indicates diameters were not significantly different (P>0.05) by one-way ANOVA followed by Tukey's post-hoc test.

Polymer	PLGA (50:50) ester-term. 70-100 kDa
Aqueous Phase	0.1% w/v PVA in deionized water
Organic Phase	A) 20 mg/mL in ethyl acetate B) 50 mg/mL in ethyl acetate
Total Flow Rate	As labeled
Flow Rate Ratio	2:1 (Aq:Or)

Increasing the aqueous:organic flow rate ratio does not affect microparticle size



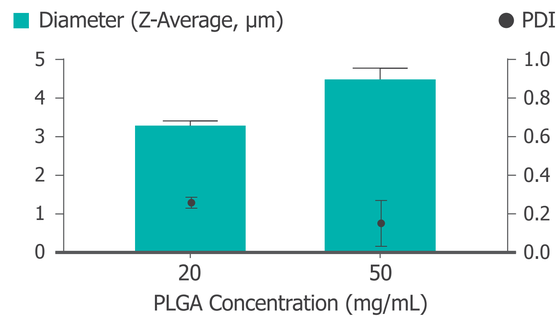
Data points are the mean ± SD (n = 3). Horizontal bar indicates diameters were not significantly different (P>0.05) by one-way ANOVA followed by Tukey's post-hoc test.

Polymer Mol. Wt.	PLGA (50:50) ester-term. 70-100 kDa
Aqueous Phase	0.1% w/v PVA in deionized water
Organic Phase	20 mg/mL Polymer in ethyl acetate
Total Flow Rate	8 mL/min
Flow Rate Ratio	As labeled (Aq:Or)

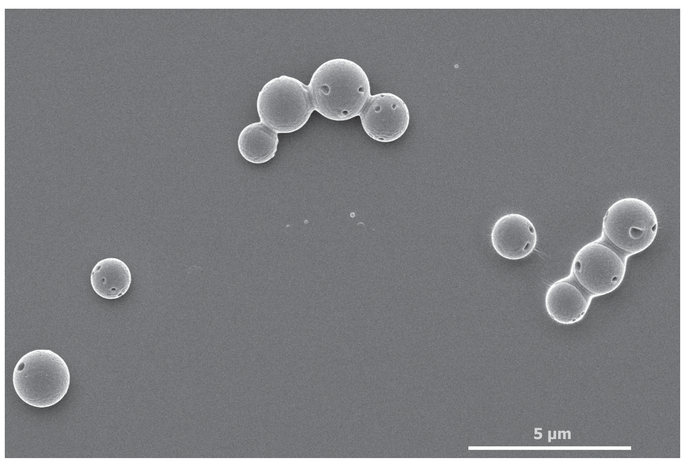
Increasing the PLGA concentration leads to an increase in microparticle size

Data points are the mean ± SD (n = 3). Horizontal bar indicates diameters were not significantly different (P>0.05) by unparied Student's T-test.

Polymer Mol. Wt.	PLGA (50:50) ester-term. 70-100 kDa
Aqueous Phase	0.1% w/v PVA in deionized water
Organic Phase	Polymer in ethyl acetate
Total Flow Rate	8 mL/min
Flow Rate Ratio	2:1 (Aq:Or)



PLGA microparticles show a spherical morphology with sizes between 1.2 - 1.9 µm



Scanning electron micrographs of PLGA microparticles prepared using the NanoAssemblr Benchtop. For SEM, samples were washed 3x by centrifugation and resuspention in DI water, dispersed on a Si chip, allowed to dry, and sputter coated with 5 nm Iridium. Scale bar = 5 µm

Polymer Mol. Wt.	PLGA (50:50) ester-term. 70-100 kDa
Aqueous Phase	0.1% w/v PVA in DI water
Organic Phase	50mg/mL PLGA in ethyl acetate
Total Flow Rate	20 mL/min
Flow Rate Ratio	2:1

Conclusions

- Microfluidics offers a reproducible, tunable, and scalable method for developing and manufacturing both nano- and microparticle drug delivery systems
- Choice of solvent and stabilizer concentration influence whether nano- or microparticles form
- Generally, using a semi-miscible solvent slowed kinetics of particle precipitation, allowing larger particles to be formed
- Higher polymer concentrations led to larger particles
- Higher concentrations of stabilizer allows formation of particles with larger surface area-to-volume ratios (ie smaller particles)

Links: Webinars, Application Notes, and more resources