Control of PLGA Nanoparticle Size in Flash Nanoprecipitation: Understanding the Roles of Solvent, Concentration, Flow Rate, and Mixing Kinetics

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The success of Lipid nanoparticles (LNPs) in COVID-19 mRNA vaccines, have highlighted the potential of nucleic acid therapeutics. (1) However, their high cost and reliance on specialized lipids limit broader application. This motivates the development of scalable manufacturing approaches and delivery systems based on inexpensive, readily available materials. In this work, flash nanoprecipitation is explored as a scalable process, and poly (lactic-co-glycolic acid) as a cost-effective alternative material. (2)

To achieve predictive control over particle size, the effects of polymer concentration, solvent selection, and flow rate on PLGA nanoparticle formation are systematically studied under well-mixed FNP conditions. A strong solvent-dependent size trend is observed (DMSO < acetone < acetonitrile < THF), with particle diameters varying by more than a factor of three. This trend is independent of macroscopic mixing, indicating that nanoparticle size is governed by molecular-level solvent–antisolvent interactions.

An empirical scaling law is developed to quantitatively describe nanoparticle size as a function of polymer concentration and flow rate, yielding power-law exponents of 0.43 and 0.10, respectively, with excellent predictive accuracy (R^2 = 0.99). Solvent effects are captured through a dimensionless factor, which is subsequently reformulated using principal component analysis of solvent physicochemical descriptors, including dielectric constant and interaction parameters.

Keywords:
Flash nanoprecipitation,
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Solvent effects
Phase separation
Flory–Huggins interaction parameter
Solvent–water

a) FNP setup. (b) Particle size vs solvent and concentration (5–30 mg/mL). (c–f) Particle number vs f (PLGA) for DMSO, acetone, acetonitrile, and THF..

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