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REVIEW

Principles of nanoparticle formation by flash nanoprecipitation

Walid S. Saad[a], Robert K. Prud'homme[b,*]

[a] *Department of Chemical and Petroleum Engineering, American University of Beirut, Beirut 1107 2020, Lebanon*
[b] *Chemical and Biological Engineering, Princeton University, Princeton, NJ 08544, USA*

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Summary Rapid precipitation is an efficient approach for engineering materials at the nanoscale. By controlling solute nucleation and growth rates in solvent precipitation processes, the size of the resulting nanoparticles (NP) can be controlled. This review discusses Flash Nanoprecipitation (FNP), a technique developed for NP formation using copolymer stabilization. FNP has been explored for various applications, including NP formulation for drugs and imaging agents. The review highlights mixing considerations, supersaturation requirements, and stabilizer selection to provide controlled size NP *via* FNP, and includes a summary of current understanding of the FNP process, as well as relevant examples and applications.
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The utility of nanoparticles from hydrophobic constructs

The recently acquired ability to engineer materials at the nano-scale in order to achieve desired properties at the macro-scale has made nanotechnology of interest in several fields. In particular, nanoparticles (NP) are being explored as novel tools for applications including solar energy conversion and photovoltaics [1], pigments and catalysts [2], and perhaps most actively, medicine [3,4]. In nanomedicine, formulating therapeutic components that are often hydrophobic in nature into the nanoparticle size range of a few nm to about 100 nm provides several advantages, including: (1) solubilize hydrophobic drugs, (2) increase bioavailability and total absorption of orally administered drugs [5], (3) concentrate cancer drugs at the tumor site by passive targeting through the Enhanced Permeability and Retention (EPR) effect, and active targeting through ligand—receptor interactions [6], (4) deliver drugs to the lungs [7], and (5) modify the drug activity through NP surface modification, for instance using polyethylene glycol (PEG), which reduces complement binding and decreases the drug clearance rates during *in vivo* circulation [8]. Research efforts in that area lead several nanomedicine-based therapies to reach the market [9].

* Corresponding author at: Department of Chemical Engineering, Princeton University, Princeton, NJ 08544, USA.
Tel.: +1 609 258 4577; fax: +1 609 258 0211.
E-mail address: prudhomm@princeton.edu (R.K. Prud'homme).

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NP formation by rapid precipitation affords high drug loading contents through the coating of NP surface using protecting agents. The coating materials are of amphiphilic nature, and include block copolymers and lipids. These provide steric stabilization and limit instabilities due to aggregation and Ostwald ripening [10]. In contrast, polymeric drug micelles formed by imbibing drugs into the hydrophobic core of a micelle are fundamentally different and are thermodynamically bound to lower drug loading contents than NP [11].

The synthesis route used for NP formation determines the resulting NP properties. Several factors require consideration to afford stable, controlled-size distribution of high loading NP of hydrophobic constructs. This can be achieved through imposing rapid processing conditions that yield short length scales where nucleation, growth, and the subsequent equilibration of NP are controlled [12]. In rapid precipitation, the nucleation and growth time of a hydrophobic molecule under supersaturated conditions is matched with the aggregation time of the stabilizing amphiphilic molecule, resulting in narrow, controlled size distribution of NP.

This review summarizes factors controlling NP formation by block copolymer directed, rapid precipitations.

Overview of particle size from rapid precipitations

Precipitation is a commonly used technique in the pharmaceutical industry. Active pharmaceutical ingredients (API) are often precipitated from solution through the addition of a non-solvent, or through temperature quenching. Controlled precipitation conditions are used to optimize the API particle size, which affects drug product performance requirements such as dissolution properties and bioavailability [13]. NP formation by temperature quenching remains challenging due to low supersaturation levels and non-uniform spatial temperature distribution in the precipitation vessel, resulting in wide particle size distributions.

In rapid precipitation, mixing conditions control the final particle size distribution. Mixing characteristic time can be categorized as macromixing (decimeter scale, *e.g.* on the order of the vessel), mesomixing (millimeters, on the order of the turbulent eddies that form when viscous forces dominate over inertial ones), or micromixing (micrometer scale, on the order of molecular diffusion in fluid lamellae) [14,15]. Micromixing conditions are required to afford characteristic times on the order of nucleation and growth times needed for the formation of NP with controlled size distributions.

Nucleation is a strong function of supersaturation

Starting from a single phase of molecularly dissolved molecular species in solution, rapid precipitation is achieved through imposing a condition of high supersaturation. This leads to nucleation and growth of particles at a nucleation rate J given by [16]

$$J = A \exp\left(\frac{-16\pi\gamma^3 v^2}{3k^3T^3(\ln(S))^2}\right) \quad (1)$$

Where A is a constant, γ is the surface tension, ν is the molar volume, k is Boltzmann's constant, T absolute temperature, and S the supersaturation. The relationship reveals the strong dependence of nucleation on both supersaturation and temperature.

Starting from the supersaturated state, nuclei start to form once the critical nucleation concentration is reached. As a result, the bulk solute concentration decreases. The concentration drop freezes any additional nuclei formation and leads to the growth of the already formed nuclei by aggregation and association with solute molecules in the bulk. The growth continues until the solute concentration reaches the equilibrium saturation concentration.

From the processing aspect, creating homogenous nucleation conditions are challenging, particularly because achieving high local supersaturation levels is technically difficult. For instance, particle creation by solvent/anti-solvent mixing in a batch vessel does not provide the micromixing conditions needed for high local supersaturations. This results in wide particle size distributions and subsequent solute precipitation. Mahajan and Kirwan [17] overcame the mixing limitation by using a grid mixer device with a characteristic mixing time of <3 ms to study the nucleation and growth kinetics of pharmaceuticals. The short micromixing time provides rapid and uniform solute mixing, which allows for the nucleation rates to be controlled. The authors investigated the precipitation of lovastatin and asparagine monohydrate over low to moderate supersaturation ranges. Their results reveal an increase in supersaturation levels for both drugs is accompanied by an increase in the nucleation rates as predicted by Eq. (1), and a decrease in the growth rates [16,17]. Therefore, in order to afford NP smaller than a few hundred nanometers, nucleation should be favored over growth. High nucleation rates provide high nuclei density resulting in high nanoparticle yield. When growth is favored over nucleation, few nuclei form and will likely grow to micron-size particles.

Particle formation can also occur through a spinodal decomposition mechanism. Starting with an unstable state under very high supersaturation conditions, phase separation occurs spontaneously to produce a solute-rich phase. [14]

Controlling growth rates

Key diffusion limited processes for mass transport involved in particle growth include [12]:

a. Diffusion-limited stepwise molecular growth of solute on the particle surface
b. Particle aggregation determined by the Smoluchowski kinetics with no barrier to aggregation
c. Ostwald ripening by diffusion mass transfer

Calculated maximum growth rates and the corresponding dependence on particle diameter for β-carotene obtained for each process [12] are illustrated in Fig. 1. These processes affect NP due to their small size and the strong dependence of growth rate G (nm/min) on particle diameter, d (nm), represented as n ($G \sim 1/d^n$), on the secondary axis of the graph. The fast rates shown in the

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