Liquid core nanocapsules synthesized using flash nanoprecipitation

Edward Van Keuren, Sophia Taylor, Yuri Chung, Leah Chen, Ugomma Ugwu-Uche, Vereni Amaya Aparicio, Ryan Meehan, Eleni Hughes

Georgetown University, Department of Physics and Institute for Soft Matter Synthesis and Metrology, Washington, DC, USA, erv@georgetown.edu

ABSTRACT

The synthesis and application of multicomponent and/or multifunctional nanoparticles is an area that has seen significant growth over the past decade. Nanocapsules, nanoparticles with a liquid core and hard shell, are one example. They have found use in numerous applications, for example, nanodrug formulations, nanoreactors, paints and inks, etc. Here we show that one method for creating nanoparticles, flash nanoprecipitation, can be used to create a variety of nanocapsules. Flash nanoprecipitation is a simple, scalable method that consists of rapidly mixing a solution with a miscible non-solvent, which induces aggregation/self-assembly of the solute into nanoparticles. We will present results on the synthesis of a number of different nanocapsules, in particular those developed for medical diagnostics and therapeutics.

Keywords nanocapsules, drug delivery, flash nanoprecipitation

1 INTRODUCTION

There has been significant development over the past few decades on creating multicomponent, multifunctional nanomaterials. Solutions based methods are of particular interest due to their generally low-cost, mild synthetic conditions, and scalability. A simple method for inducing nanoparticle formation in organic materials, known as flash nanoprecipitation, consists of rapidly mixing a solution and a miscible nonsolvent [1]. This method produces stable dispersions of nanoparticles with sizes in the 10's to 100's of nm, and has been used to create nanoparticles of materials such as various chromophores [2], polymers[3], and drug formulations [4].

While the method has primarily been used with single components, it can also be used to synthesize multicomponent nanoparticles. For example, we have shown that cocrystals of charge transfer compounds can be synthesized from a variety of different combinations of electron donors and acceptors [5-7]. Recently, Wu et al. showed that a similar method could be used to create liquid core nanocapsules by coprecipitating a polymer and an oily material in a method similar to flash nanoprecipitation [8].

Liquid-core/polymer -shell nanocapsules are interesting materials for a number of applications [9], including as corrosion inhibitors [10], nanoreactors [11], and in biomedical applications such as drug delivery [12]. There are a number of different methods for synthesizing nanocapsules, including in-situ polymerization [13], phase separation followed by photopolymerization, nanoprecipitation [14], and chemically induced nucleation and growth followed by surface passivation [15].

Here we present studies of the use of flash nanoprecipitation to create nanocapsules consisting of a polystyrene shell surrounding a liquid core of n-hexadecane. The formation of the core-shell morphology can be understood using a droplet model, in which regions of the injected fluid that are formed by the turbulent mixing form the precursors of the final particles [16].

2 MATERIALS AND METHODS

2.1 Sample preparation

Atactic polystyrene with a molecular weight of 260 kDa (Scientific Polymer Products) was dissolved in tetrahydrofuran (THF) at concentrations ranging from 0.2 to 2.0 mg/mL. These values are all below the overlap concentration for the polymer. A given volume of n-hexadecane was added to these solutions at ratios of PS:hexadecane ranging from 1:0 to 1:2. The solutions were injected through an 18 gauge pipet needle (diameter = 0.838 mm) into distilled water at a rate of 1.0 mL/s using an automated syringe pump (Hamilton Microlab 500). The volume ratio of polymer solution:water was 1:9.The water was vortexed at a rate of 1000 rpm during and after the injection.

2.2 Characterization

The radii of the nanoparticles were measured using a dynamic light scattering (DLS) apparatus based on an ALV-5000 hardware autocorrelator (ALV GmbH) and discrete optical components. Details of the apparatus and data analysis can be found in reference [17]. Atomic force microscopy (AFM) images were acquired using an NTEGRA Prima AFM (NT-MDT Spectrum Instruments). Scanning electron microscopy (SEM) was done using a Zeiss Supra 55VP. All the samples were measured using the secondary electron detector at 0.5 kV to 2 kV beam energy. Samples for AFM and SEM were prepared by several methods, including spin-coating, blade coating and drop-casting. All substrates were Si wafers washed with acetone followed by cleaning with an air plasma.

3 RESULTS AND DISCUSSION

Figure 1 shows SEM images of nanoparticles of polystyrene with and without hexadecane. When hexadecane was included, we observe many instances of what appear to be collapsed shells, suggesting that liquid filled nanocapsules are formed, with the hexadecane escaping during sample preparation. We believe these images can be understood within the context of the droplet model that we developed for single polymer component nanoparticles made with flash nanoprecipitation. According to this model, the injected solution rapidly breaks into droplets due to the turbulent mixing [16]. The size of the droplets is determined by the fluid dynamics: the mixing conditions and fluid properties. While these droplets form, the solvent and non-solvent interdiffuse, leading to the hydrophobic components (e.g. polystyrene and n-hexadecane) that are initially dissolved in the solution to become highly supersaturated. This interdiffusion is partially hindered by interactions with the polymer, which is preferentially solvated by the good solvent. The free energy gradient at the droplet surface will result in t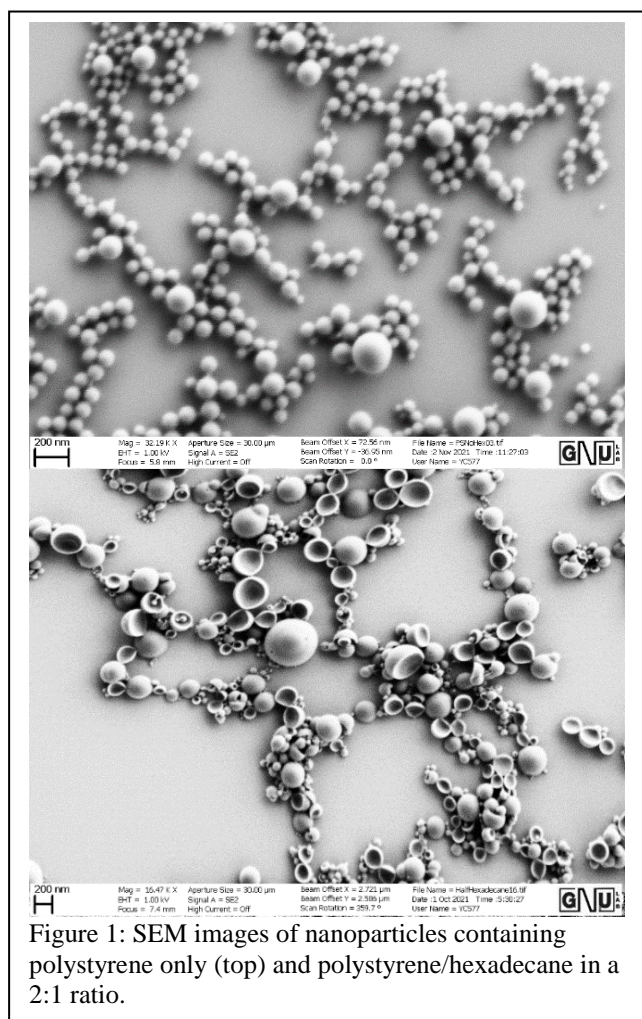he diffusion of the hydrophobic components away from the interface. At some point during this process, the polymer may undergo a glass transition, if the bulk glass transition temperature is above the temperature at which the nanoprecipitation is performed, locking in the morphology of the polymer at that point.

When there are two components dissolved in the good solvent, e.g. polystyrene and hexadecane, they will initially be distributed homogeneously in the droplets. The interdiffusion of the THF and water will lead to free energy gradients causing both the polystyrene and hexadecane to diffuse away from the droplet surface. The larger diffusivity of the hexadecane will lead to it reaching the particle center first, while the slower diffusing polystyrene will be more concentrated at the surface. As in single component polystyrene nanoparticles formed with this method, it will reach a glass transition at some point, locking in its shell structure with the liquid hexadecane as the core.

This hypothesis is further supported by images of samples with a higher ratio of hexadecane to polystyrene as shown in Figure 2. These showed somewhat larger, thinner shells. In this case, the added hexadecane increases the volume of material in the droplets, leading to larger particles. However, the higher ratio also leads to less polystyrene available to form the shell, hence making them thinner.

Figure 1: SEM images of nanoparticles containing polystyrene only (top) and polystyrene/hexadecane in a 2:1 ratio.
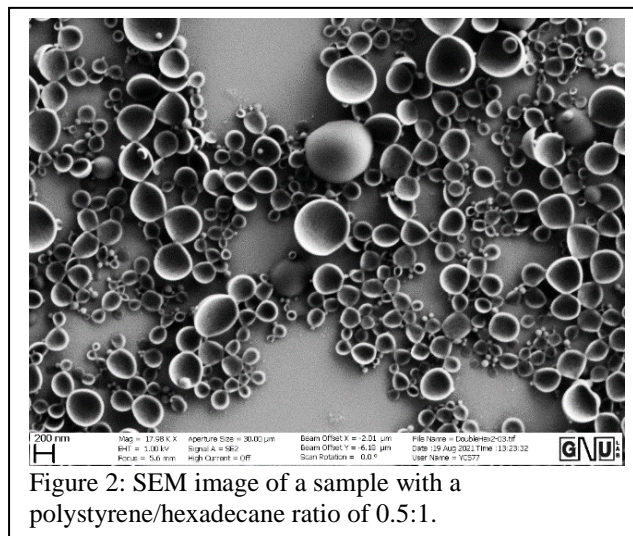

Figure 2: SEM image of a sample with a polystyrene/hexadecane ratio of 0.5:1.

These images were corroborated by similar measurements using AFM, as shown in Figure 3, which shows a sample which had equals amounts of polystyrene and hexadecane.

Our model was further supported by measurements of the particle size as a function of the concentration of the initial polymer solution and the ratio of hexadecane to polystyrene. Figure 4 shows the particle volume calculated from the radii measured by DLS, as a function of the initial concentrations of the polystyrene in THF and for different ratios of hexadecane to polystyrene.
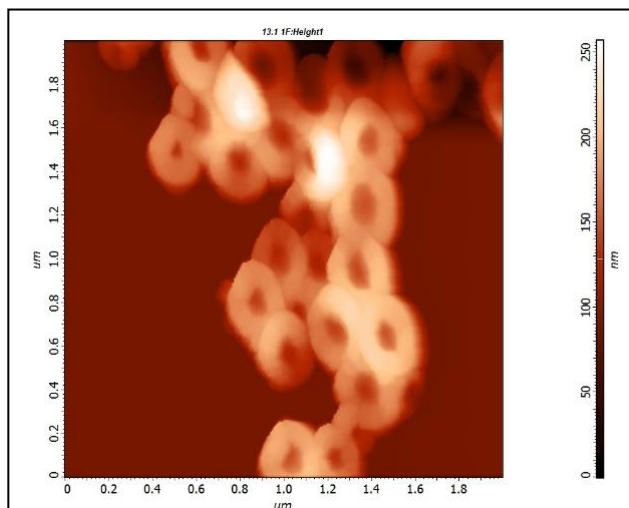
Figure 3: AFM image of a sample with a polystyrene/hexadecane ratio of 1:1.

In single component polystyrene nanoparticles formed using flash nanoprecipitation, we observed a linear relationship between volume and the concentration of the initial polymer solution. This behavior is consistent with a droplet model, in which the mixing process alone sets the size of the droplets of high polymer concentration, after which the polymers collapse as the solvents interdiffuse [16]. However, for the hexadecane/polystyrene nanocapsules, we initially observed a nonlinear dependence, as well as much larger particle volumes than would be expected from simply adding the hexadecane volume to that of the polystyrene. There are several possible explanations for this size dependence, such as the influence of the hexadecane on the fluid dynamics of the initial droplet formation, the possibility that it is plasticizing the polymer, making particles more likely to coalesce into larger particles upon making contact, or some amount of THF being incorporated into the particle due to the strong
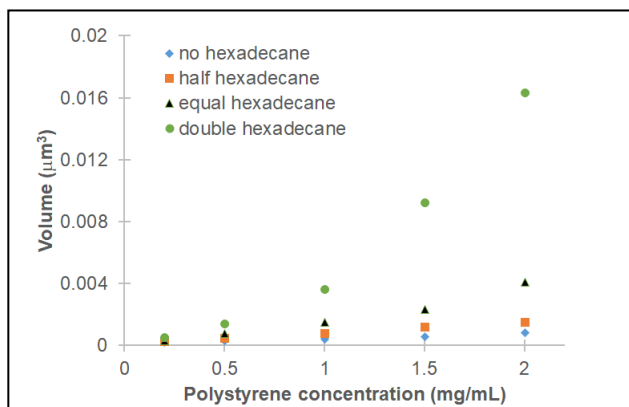

Figure 4: Particle volume vs. initial polymer concentration for particles with and without hexadecane. Volumes were calculated using the particle radius measured using DLS, assuming spherical particles.

hydrophobicity of the hexadecane. We checked this latter possibility by leaving samples uncovered for several days in order to allow THF in the solvent to evaporate, which should in turn reduce the amount trapped in the particles as the solvents in and outside of the particles equilibrate. The resulting particle sizes were much smaller, with a larger drop for the particles with higher ratios of n-hexadecane to polystyrene. In addition, the dependence of the particle size on the initial polymer concentration became roughly linear, as shown in Figure 5, similar to what we found for single component polymer nanoparticles.
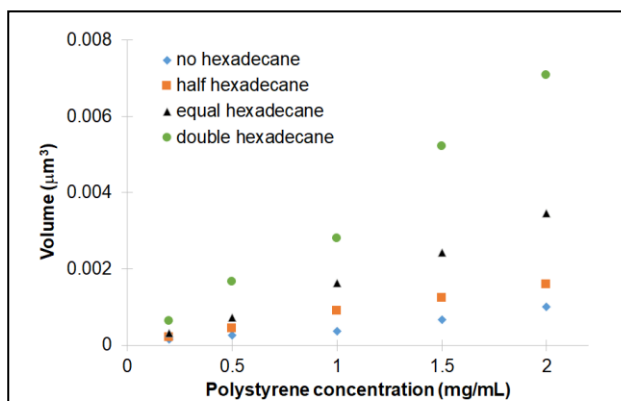

Figure 5: Particle volume vs. initial polymer concentration for particles with and without hexadecane. The samples were left out 4 days in order to remove any THF that was encapsulated in the particles. Volumes were calculated using the particle radius measured using DLS, assuming spherical particles.

4   CONCLUSIONS

We have shown that flash nanoprecipitation, a simple and scalable method for solution synthesis of nanoparticles, can be used to create liquid-core nanocapsules. Nanocapsules consisting of a hexadecane core and polystyrene shell were synthesized. The size and ratio of core to shell was controlled by varying the concentrations of the initial polymer/hexadecane. We propose the extension of the droplet model to explain the formation and dependence of the properties on the synthesis conditions.

REFERENCES

[1]   Horn, D. "Preparation and Characterization of Microdisperse Bioavailable Carotenoid Hydrosols" Angew. Makromol. Chem. 1989, 166, 139-153.

[2]   Kasai, H.; Nalwa, H. S.; Oikawa, H.; Okada, S.; Matsuda, H.; Minami, N.; Kakuta, A.; Ono, K.; Mukoh, A.; Nakanishi, H. "Novel Preparation Method of Organic Microcrystals" Jpn. J. Appl. Phys. , Part 2: 1992, 31, L1132-L1134.

[3]   Zhang, C.; Pansare, V. J.; Prud'homme, R. K.; Priestley, R. D. "Flash Nanoprecipitation of

Polystyrene Nanoparticles" Soft Matter 2012, 8, 86-93.

[4] D'Addio, S. M.; Prud'homme, R. K. Controlling Drug "Nanoparticle Formation by Rapid Precipitation" Adv. Drug Deliv. Rev. 2011, 63, 417-426.

[5] Van Keuren, E.; Nishida, M. "Synthesis of Nanocomposite Materials using the Reprecipitation Method" CMC-Comput. Mater. Con. 2010, 409, 61-77.

[6] Li, T.; Melis, S.; Bagade, C.; Khatib, A.; Kosarzycki, R.; Maglieri, G.; Zhang, X.; Van Keuren, E. "Mechanisms of Nucleation and Growth in the Formation of Charge Transfer Nanocrystals" J. Nanopart. Res. 2019, 21, 147.

[7] Van Keuren, E.; Melis, S. "The formation of charge transfer cocrystals for optical and electronic applications" in "Charge transfer nanocrystals for optical and electronic applications; in Nanocomposites for Photonic and Electronic Applications" Kassab, L. R. P., Ribiero, S. J. L. and Rangel-Rojo, R., Eds.; Elsevier: 2020; pp 139-165.

[8] Wu, B. H.; Yang, C. J.; Weitz, D. A.; Wu, B.; Yang, C.; Li, B.; Feng, L.; Hai, M.; Zhao, C.; Chen, D.; Liu, K.; Weitz, D. A. "Active Encapsulation in Biocompatible Nanocapsules" SMALL 2020, 16, 2002716.

[9] Yow, H. N.; Routh, A. F.; Yow, H. N.; Routh, A. F. "Formation of Liquid Core–polymer Shell Microcapsules" Soft Matter 2006, 2, 940-949.

[10] Golovin, V. A.; Tyurina, S. A. "Microencapsulation of Corrosion Inhibitors and Active Additives for Anticorrosive Protective Polymer Coatings" International Journal of Corrosion and Scale Inhibition 2019, 8, 179-198.

[11] Crespy, D.; Stark, M.; Hoffmann-Richter, C.; Ziener, U.; Landfester, K. "Polymeric Nanoreactors for Hydrophilic Reagents Synthesized by Interfacial Polycondensation on Miniemulsion Droplets" Macromolecules 2007, 40, 3122-3135.

[12] Mora-Huertas, C. E.; Fessi, H.; Elaissari, A. "Polymer-Based Nanocapsules for Drug Delivery" Int. J. Pharm. 2010, 385, 113-142.

[13] Sottos, N. R.; Geubelle, P. H.; Moore, J. S.; Kessler, M. R.; White, S. R.; Sottos, N. R.; Geubelle, P. H.; Moore, J. S.; Kessler, M. R.; Sriram, S. R.; Brown, E. N.; Viswanathan, S. "Autonomic Healing of Polymer Composites" Nature 2001, 409, 794-797.

[14] Echeverri, J. D.; Guerrero-Escalante, S.; Salamanca, C. H. "Relationship between the Process Variables and Physicochemical Features of Liquid-Core Nanocapsules Produced Via Nanoprecipitation" Biointerface Research in Applied Chemistry 2019, 9, 4037-4043.

[15] Wang, R.; Han, F.; Chen, B.; Liu, L.; Wang, S.; Zhang, H.; Han, Y.; Chen, H. "Liquid Nanoparticles: Manipulating the Nucleation and Growth of Nanoscale Droplets" Angew. Chem. Int. Ed. 2021, 60, 3047-3054.

[16] Zhao, C.; Melis, S.; Hughes, E. P.; Li, T.; Zhang, X.; Olmsted, P. D.; Van Keuren, E. "Particle Formation Mechanisms in the Nanoprecipitation of Polystyrene" Langmuir 2020, 36, 13210-13217.

[17] Van Keuren, E.; Bone, A.; Ma, C. "Phthalocyanine Nanoparticle Formation in Supersaturated Solutions" Langmuir 2008, 24, 6079-6084.