The development of hybrid lipid-polymer nanoparticle architectures for the sustained-release of small hydrophilic molecules

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Abstract

Introduction: Polymeric nanoparticles (NPs) have been utilized as drug delivery vehicles for a variety of applications. However, achieving sustained-release of small hydrophilic agents is a primary challenge for their use in prolonged delivery applications.

Objective: This study investigates how novel lipid-polymer hybrid particle architectures can be used to improve the release profile of small hydrophilic encapsulants. Here, PLGA NPs were produced via electrospraying and emulsions. Particles with a core-shell architecture were produced via coaxial electrospraying and the ability of this architecture to sustain release was examined. In addition, we combined polymeric core-shell NPs with a lipid coating to improve biocompatibility, biofunctionalization, and particle release kinetics. We ***hypothesized*** that coaxial spun formulations would provide prolonged release of hydrophilic agents due to their complex architecture.

Methods: PLGA NPs incorporating rhodamine B (RhB) as a model small molecule hydrophilic agent, were produced using electrospraying and double emulsion techniques. The PLGA NPs were coated with a lipid layer using either gentle hydration (post-synthesis, two-step), or self-assembly through emulsion (*in situ*, one-step). The total amount of RhB encapsulated in the NPs and the release profiles were determined via fluorescence spectroscopy, while physiochemical characteristics were investigated via scanning electron microscopy (SEM). Future work will evaluate NP morphology using scanning transmission electron microscopy (STEM), energy dispersive x-ray spectroscopy (EDS), and dynamic light scattering (DLS).

Results: Polymeric and lipid-polymer hybrid particles formed via emulsion were relatively monodisperse with diameters ranging from 100-400 nm, while particles formed via electrospraying were larger and more polydisperse with diameters ranging from 100-1000 nm. Electrosprayed coaxial and lipid-coated architectures were shown to sustain the release of RhB, and moreover demonstrated high encapsulation efficiency (EE) (~90%). In contrast, emulsion particles had a lower EE of ~70%, with the two-step lipid-coated particles exhibiting RhB leaching and a significantly lower EE of ~25%.

Conclusions: Our data suggests that this novel architecture shows promise to sustain the release of small molecule hydrophilic agents, and we look forward to conducting functionality experiments with chemotherapeutic agents.

Polymeric Particle Synthesis

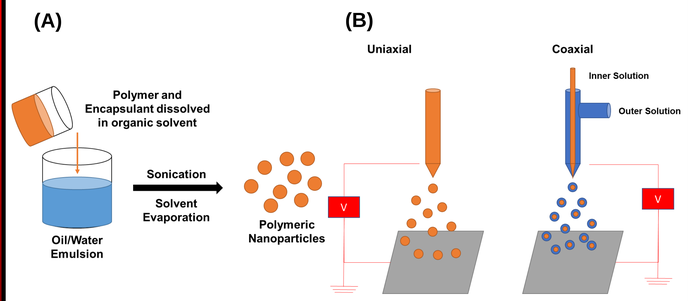

Figure 1. Schematics of the two particle synthesis methods utilized: **(A)** Nanometric-scale emulsions, and **(B)** uniaxial and coaxial electrospraying.

Synthesis of Polymer-Lipid Hybrids

Two-Step Lipid Coating

- Historically is the initial methodology developed to coat polymeric particles with a lipid layer.
- Two-step methods generally rely on hydration of a lipid film in the presence of polymeric particles.
- Due to hydrophobic and surface charge interactions, the lipids form a protective coating around the polymeric particles.

One-Step Lipid Coating

- Once developed, the one-step lipid coating processes quickly became the preferred method.
- This is due to its streamlined procedure and improving scalability, as well as avoiding encapsulant leaching that can occur during the incubation period of two-step methods.
- In one-step methods, both the polymeric core and the lipid coating self-assemble at the same time.

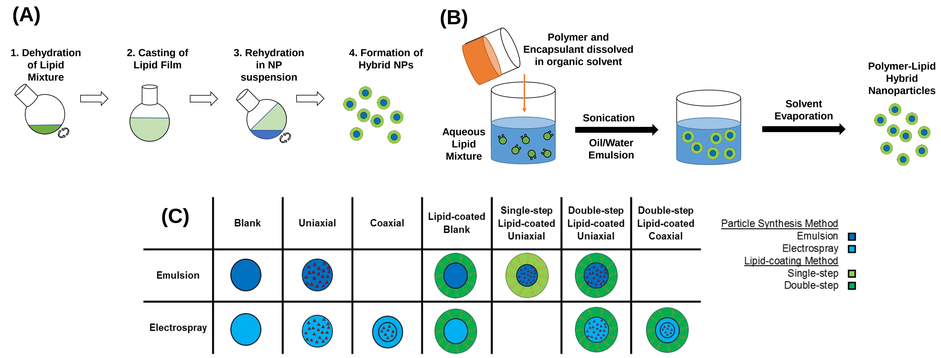

Figure 2. Schematics of the **(A)** two-step and **(B)** one-step lipid coating processes. **(C)** Table of experimental groups.

Particle Morphology

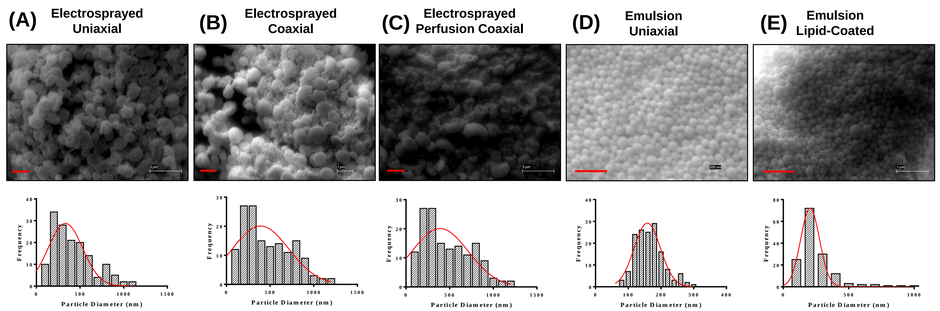

Figure 3. Scanning electron microscopy images (Zeiss EVO40 SEM, EHT 10 kV) and the corresponding size distribution graphs (n=150) of the **(A)** uniaxial, **(B)** coaxial, and **(C)** perfusion coaxial PLGA particles produced via electrospraying; **(D)** uniaxial PLGA nanoparticles produced through double emulsion, and **(E)** lipid-polymer hybrid particles produced via emulsion followed by a two-step lipid coating procedure. Red scale bar = 1µm.

Release Data

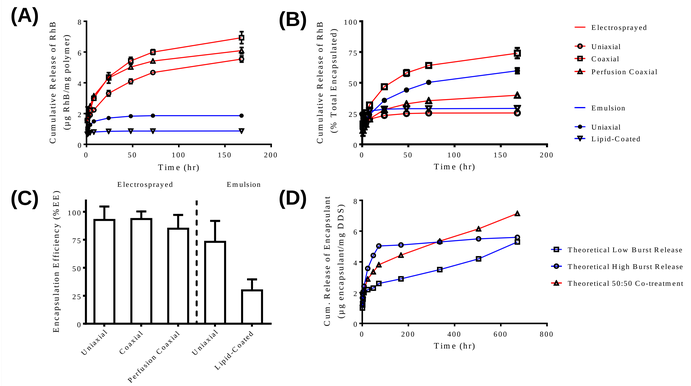

Figure 4. Cumulative release of RhB from various particle architectures incubated in PBS (37˚C, pH 7.4) in terms of **(A)** µg RhB/mg NP and **(B)** percent total encapsulated RhB. **(C)** Encapsulation efficiency based on a theoretical loading of 10 µg RhB/mg NP. **(D)** Release plot depicting the proposed benefit of modulating sustained-release kinetics. Data shown represent mean values ± SD (n=3).

Conclusions and Future Work

- Our data suggest that this novel architecture shows promise to sustain the release of a challenging “model” small molecule hydrophilic agent.
- Further investigate the morphology of the different particle architectures via STEM and EDS.
- Fabricate electrosprayed polymer-lipid hybrid NPs (as opposed to the double emulsion technique).
- Functionalize polymer-lipid hybrids via one-step lipid coating.
- Further optimize electrospraying process to produce smaller particles.
- Compare the release of polymer-lipid hybrid NPs produced via one-step or two-step lipid coating techniques.
- Explore the release profile of a novel electrosprayed lipid-coated polymeric core-shell particle architectures.
- Leverage this platform in functional cell culture assays and as a potential co-treatment modality to reduce administration frequency.

Acknowledgments

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