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Spray stability of self-assembled filaments for delivery

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ABSTRACT

Filamentous viruses are common in nature and efficiently deliver – sometimes via aerosol – genetic material, viral proteins, and other factors to animals and plants. Aerosolization can be a severe physicochemical test of the stability of any filamentous assembly whether it is made from natural polymers such as viral proteins or synthetic polymers. Here, worm-like "filomicelles" that self-assemble in water from amphiphilic block copolymers were investigated as aerosolized delivery vehicles. After spraying and drying, fluorophore-loaded filomicelles that were originally ~10–20 μm long could be imaged as 2–5 μm long fragments that survived rehydration on natural and artificial surfaces (i.e. plant leaves and glass). As a functional test of delivery, the hydrophobic pesticide bifenthrin was loaded into filomicelles (up to 25% w/w) and sprayed onto plants infested with two agricultural pests, beet army worm or two-spotted spider mites; pesticidal efficacy exceeded that of commercial formulations. Persistent delivery by the filomicelle formulation was especially notable and broadly consistent with previous intravenous delivery of other drugs and dyes with the highly elongated filomicelles.

1. Introduction

Viruses are nature's self-assembled nanoparticles and exist in various shapes including micron-long filamentous forms. Such viruses include ebola that infects humans and tobacco mosaic virus that infects plants. A current fear is that ebola, with ~50% mortality, could evolve to become more transmissible via vomit or cough-generated aerosols of small droplets (~1–5 μm) or large droplets (5–100 μm) – based on findings that the virus can remain infectious in aerosols for almost 2 h (at ~50% relative humidity and 22 ± 3 °C) [1]. In general, whether self-assemblies bend and break within confining droplets or deactivate (e.g. denature) at the extensive air-water interface of a droplet is unclear, and this poor understanding of the physicochemical stability of filamentous assemblies broadly motivates studies of structure and function using highly controlled chemistries.

Amphiphilic block copolymers are roughly similar in size to proteins that assemble into virus coats but are otherwise chemically more analogous to much smaller and simpler surfactants or lipids (≤ 1000 g/mol) that can also self-assemble in water into a variety of shapes including filaments [2,3]. With the proper ratio of block sizes, worm micelles many microns in length can indeed be made and are sometimes referred to as "filomicelles" when the intent – as here – is to mimic filamentous viruses. On the scale of supramolecular assembly, filomicelles are poised between the molecular level assembly of spherical micelles and so-called giant vesicles of lamellar structure, all of which result – in equilibrium with water – from suitable block ratios of hydrophilic to hydrophobic [3,4]. Non-equilibrium stresses can, however, disrupt micron-size morphologies, and stresses of relevance to various applications generally range from fluid shear to dehydration.

The large molecular weights of block copolymers can impart high thermodynamic stability [5–6] while still permitting degradability and compatibility for drug delivery [7–8]. Poly(ethylene oxide)-*block*-poly (ε-caprolactone) (designated OCL) is an example of interest for biomedical applications: its hydrophobic polyester block is biodegradable and approved by FDA for human application, while the hydrophilic brush of poly(ethylene oxide) (PEO, or PEG) is biocompatible and already in clinical use in parenteral formulations. OCL filomicelles can be sufficiently stable to be injected intravenously and subsequently withstand the fluid shears of blood circulation for days, ultimately enhancing tumor delivery of the hydrophobic drug paclitaxel when compared to spherical micelles [9–10].

Spraying of filomicelles is described here and can also be a major challenge to the stability of these large, soft assemblies. While biomedical applications of sprays are many, we sought to illustrate some broader possibilities through delivery of hydrophobic pesticides

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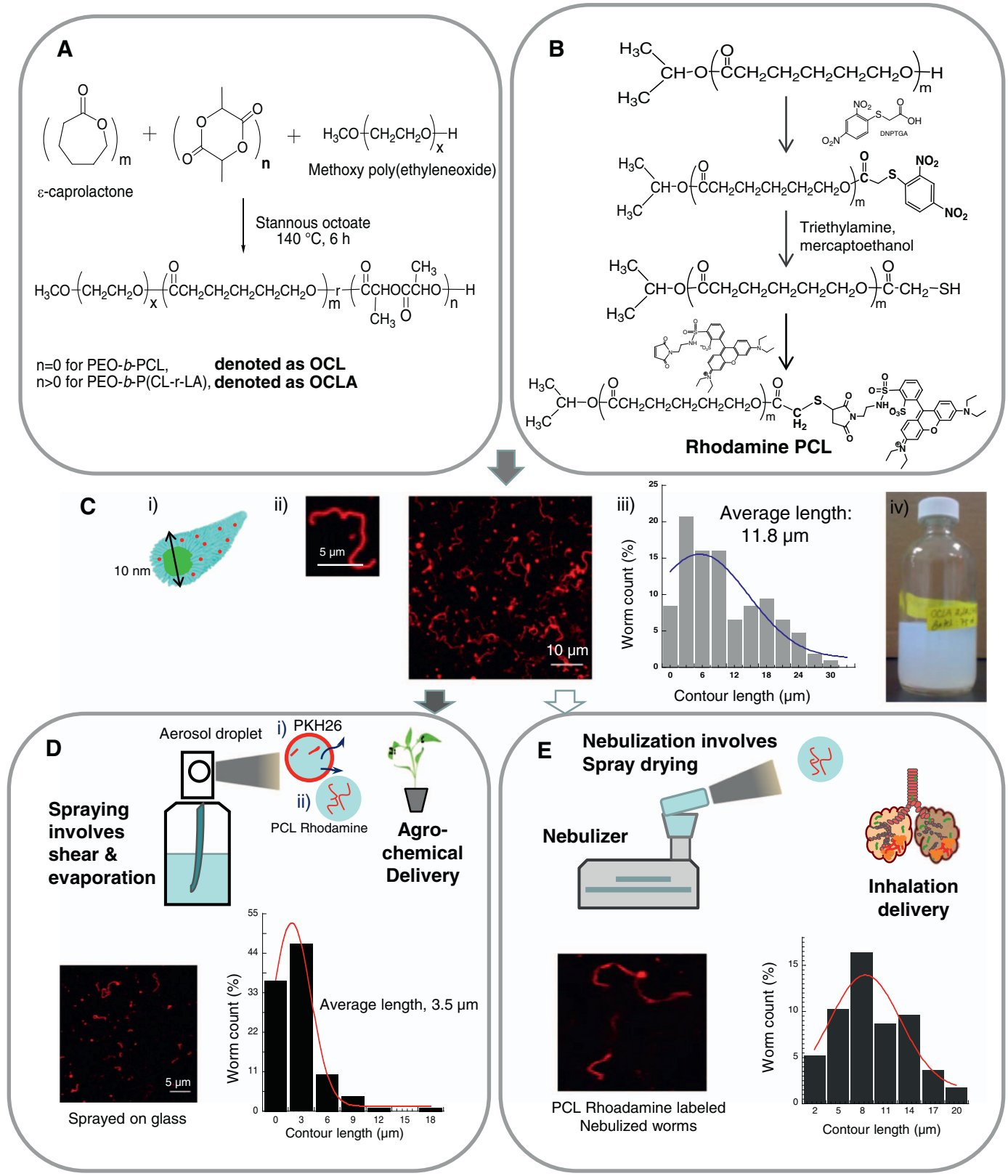

Fig. 1. Spray survival of worm like filo-micelles- A) Synthesis scheme of OCL or OCLA polymer. B) Preparation of Fluorescent dye conjugated PCL (Rhodamine PCL), C) i) Cartoon of a single worm micelle where red spots indicate the integration of Rhodamine PCL. ii) Fluorescent microscopy image of Rhodamine PCL worm micelles confined within a microscope glass slide and cover slip. iii) Contour length distribution of OCLA worm micelles which was measured from several hundreds of worms. Contour length of the worm micelles was measured by straightening and attaching the worms to the positively charged glass slide with the addition of 0.5 mM of NaCl and imaged under fluorescent microscope. iv) The 50 mL bottle is half-filled with an aqueous solution of worm micelles that scatter light, which gives an opaque appearance. D) Spray application of fluorescent dye loaded worm like micelles for the delivery of agrochemicals to the plant: i) Spray droplet redistribution loss of low MW dye PKH 26. ii) Spray droplet with high MW dye PCL-Rhodamine where dye is covalently bound to the worm micelle. Rhodamine PCL labeled OCLA (2, 12) worm micelles sprayed on glass slide with contour length distribution after spray test. E) Nebulization of fluorescent dye loaded worm micelles for the delivery of drugs to the lungs via inhalation: Rhodamine PCL labeled OCLA (2, 12) worm micelles nebulized on glass slide with contour length distribution after nebulization. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)