Janus-dendrimer supramolecular structures as delivery agents for small molecules, peptides and proteins

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Introduction: Janus-dendrimers are synthetic amphiphiles formed by linking two chemically distinct hydrophilic and hydrophobic dendrons by their core, which can self-assemble as vesicles (dendrimersomes) or fibres in aqueous solutions, as well as in biological media. This research shows that the dendrimersomes can differentially encapsulate drug compounds, are stable for long periods of time, and can be annealed from 22 °C to 70 °C with minimal change (2-5 nm) in their hydrodynamic radius [1]. Also, by modulating the hydrophilic branch generation we found that Janus-dendrimers were also able to self-assemble into a variety of other architectures such as fibres, giving rise to supramolecular hydrogels capable of encapsulating and releasing small molecules, peptides, and proteins [2], or even function as colloidal suspensions' stabilizers [3]. Thus, the small library of Janus-dendrimers reported herein expand the scope of dendrimer-based supramolecular drug delivery systems and suggest that these materials can be further used in biomedical sol–gel applications.

Methods: Amphiphilic Janus dendrimers were obtained via a copper-catalyzed click-chemistry reaction combining propargyl-modified bis-MPA dendrons and Percec-type hydrophobic azide dendrons into a single molecule. The resulting molecules were characterized using NMR, MALDI-TOF and DSC. The structures were then diluted into ethanolic solutions and directly injected into water or other biologically relevant media to obtain either vesicles or hydrogels. Both molecular arrangements were then imaged by electron microscopy. Characterization of the vesicles included measuring size and stability by DLS as a function of time and temperature, whereas the hydrogels were characterized by conducting rheological and SAXS measurements. The compound encapsulation in the vesicles was examined by confocal microscopy and the release was monitored by UV spectroscopy. The small molecule, peptide, and protein release from the hydrogels was monitored by HPLC (small molecule and peptide) or spectrometry (protein).

Results: The vesicles obtained through ethanol injection were remarkably uniform (PDI <0.02) and ranged from 77 to 240 nm depending on the arrangement of hydrophobic dendron, the generation of the hydrophilic dendron and the solvent from which they were injected from (Fig. 1A). When prepared by film hydration, the dendrimersomes were *ca.* 10 µm in diameter (Fig. 1B). The hydrogel-constituting

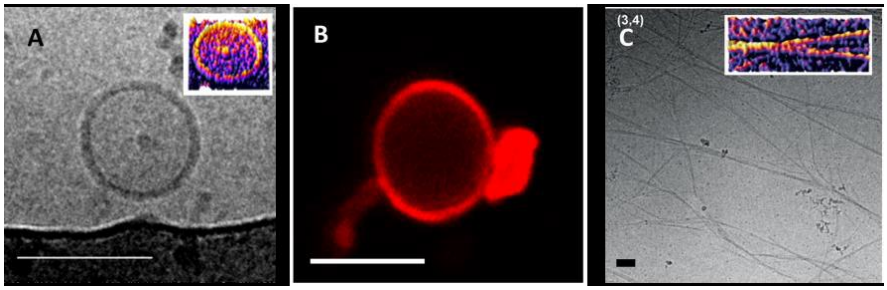

Fig. 1 (**A**) Cryo-TEM of ethanol-injected dendrimersomes, (**B**) Confocal microscope imaging of film-hydrated dendrimersomes, and (**C**) Cryo-TEM of ethanol-injected supramolecular fibres. Scale bars are 100 nm in (**A**) and (**C**), and 10 µm in (**B**).

supramolecular fibres were between 4.8 and 5.6 nm assessed by electron microscopy (Fig. 1C) and SAXS. The dendrimersomes could encapsulate and release the drug propranolol upon stimulus (Fig. 2A), whereas the release of the drugs from the hydrogels followed a first-order kinetics (Fig. 2B).

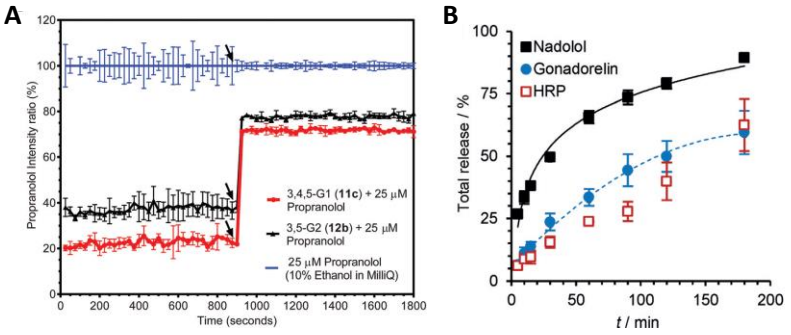

Fig. 2 (**A**), propranolol loaded into dendrimersomes (red and black, respectively) measured by relative fluorescence. Arrows denote the time when 50 μL 3% Triton X-100 solution was added in order to disrupt the samples and the control. Error bars represent ± SD (n = 3). (**B**) Release of nadolol (small-molecule drug), gonadorelin (decapeptide), and HRP (protein) from 0.2 wt% Janus-dendrimer hydrogel.

Conclusion: This report highlights, for the first time, the chemical versatility and robustness offered by Janus-dendrimers supramolecular architectures for drug delivery applications and the translation potential of these structures into the clinical setting.

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[3] Selin M., et al. Biomacromolecules. 2018, 19(10): 3983-3993

Learning Objectives

Identify the impact of the hydrophilic/hydrophobic dendron balance in Janus-dendrimers self-assembly
Differentiate between the different approaches for dendrimersomes self-assembly
Explain the advantages of dendrimersomes as colloidal drug delivery systems
Evaluate the factors affecting the differential drug release profiles from the Janus-dendrimer hydrogels