

Shaken or stirred? It matters when addressing the dynamics and stability of macromolecular nanocarriers in aqueous solution

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The solution self-assembly of macromolecular amphiphiles, such as block copolymers, offers an efficient strategy for producing well-defined nanocarriers, with applications ranging from drug delivery and diagnostics to nanoreactors and reagent recovery. Typically, the formation of nanocarrier architectures is dictated by processing methods that employ cosolvent mixtures. These fabrication strategies rely on the assumption that polymeric solution nanostructures are kinetically stable following transfer from an organic/aqueous solution into an aqueous medium. We recently demonstrated that step-changes in polymer micelle populations could occur over days to weeks following transfer into a highly selective solvent, such as water [1]. This unexpected micelle growth was critically dependent on the method and rate of solution agitation (Fig. 1) and has a major impact on the assumed stability of polymer assemblies for therapeutic applications.

Amphiphilic macromolecules, such as block copolymers, are promising for many applications as molecular design offers enormous chemical versatility and exquisite control over the size and shape of solution assemblies. Of particular interest are the unique material properties conferred by the macromolecular nature of the hydrophobic block, such as exceptionally slow inter-aggregate chain exchange in highly selective solvents. These characteristics overcome key limitations of small molecule aggregates by improving the retention of encapsulated cargo for delivery and nanoreactor applications [2].

Many common preparation methods employ cosolvent mixtures to enable the loading of self-assembled morphologies with various hydrophobic cargoes such as dyes and therapeutic agents for diagnostics and drug delivery applications [2]. Cosolvent methods are essential to solubilize both the hydrophobic cargo and amphiphilic copolymer to facilitate efficient encapsulation. As nanocarriers are routinely used in aqueous solution, these preparation methods also hinge on the assumption that the assemblies are kinetically trapped (and nanostructure is preserved) following transfer from an organic/aqueous solution into water.

Although the effects of cosolvent introduction on the generation of block copolymer assemblies are well researched, the consequences of cosolvent removal on self-assembled structures typically are overlooked [1]. While some macromolecular assemblies are known to be kinetically trapped over time scales of days

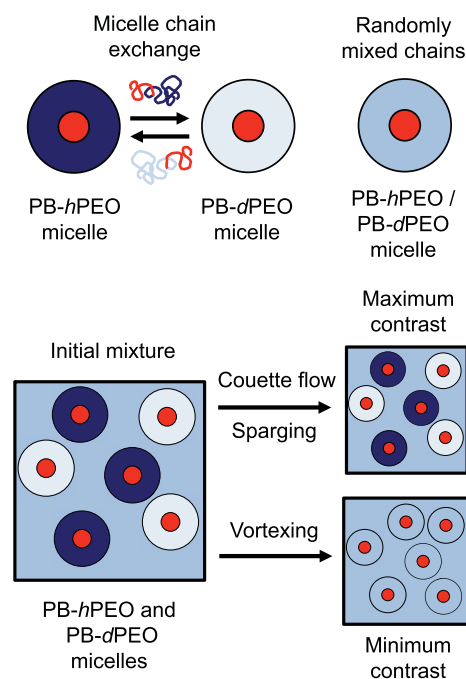


FIGURE 1: Schematic representation of contrast conditions used to study chain exchange as a result of solution agitation. Micelles containing protonated PB chains in the core and either non-deuterated or deuterated PEO chains in the corona (lower left panel) were agitated using rapid vortex mixing, Couette flow, or nitrogen gas sparging. SANS was used to measure the scattering intensity as a function of mix time and hence to quantify the extent of chain exchange (lower right panels). Chain exchange between micelles decreases the solvent-corona contrast and the scattered intensity, and under certain agitation conditions, the scattered intensity gradually approaches that of micelles with randomly mixed hPEO/dPEO corona chains.

or even months, a cohesive understanding of polymeric micelle dynamics is still lacking [1]. In the present work, it is shown that significant dynamic processes occur in block copolymer micelles following cosolvent removal, even in highly selective solvents. In the absence of agitation, the micelles are stable, consistent with scaling theories. However, gentle agitation, which is not considered in many scaling theories, leads to a marked increase in the micelle size. The micelle sizes evolve through a bimodal distribution, in which well-defined step-changes in size lead to a monodisperse final nanostructure population with an aggregation number much larger than that of the starting population.