RAFT dispersion polymerization induced block copolymer self-assembly

Tiarnui Xue Literature Seminar Nov. 15th. 2018

Since the successful synthesis of polymersomes by well-defined block copolymers,[1] amphiphilic block polymer that could self-assemble into various morphologies have been widely utilized.[2] Theoretically, their morphology can be rationally designed in terms of the packing parameter, *p* which is calculated by the physical behavior of the block copolymer in a specific solvent.[3] However, for common copolymer self-assembly, a pre-polymerization step to synthesize and purify block copolymers and a post processing step to make the polymers aggregate by tuning the solubility of the copolymer in a solution, usually less than 1 wt%, were demanded which extremely limited the yield as well as the efficiency for nanoparticle preparation.[4]

Recently, there has been dramatic development in synthetic controlled polymerization methods at high monomer concentration which result in *in situ* nanoparticle formation thus producing nanoparticles in high yield while avoiding the processing step.[5] This strategy to produce nanoparticles *in situ* with different morphologies is called polymerization induced self-assembly (PISA). Controlled radical polymerization (CRP) is widely used for PISA due to their convenience in affording controllable molecular weight and narrow polydispersity amphiphilic block copolymers.[4] Among all common CRP methods, reversible addition-fragment chain transfer (RAFT) polymerization, mainly due to its metal free deactivation mechanism, was a desirable polymerization method to avoid the biotoxicity concern.[6]

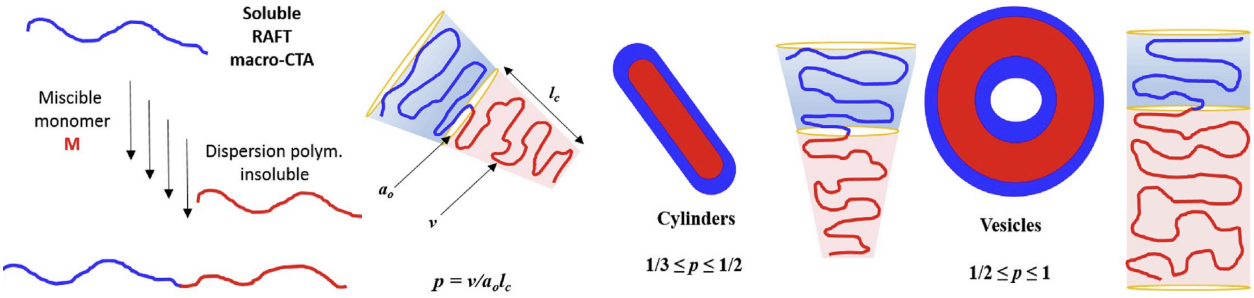

Figure 1. In RAFT dispersion PISA, miscible monomer grow along a soluble macro CTA and form an insoluble segment. Tuning *p*, different morphologies could be observed.[5]

The first two RAFT polymerization induced block copolymer self-assembly were observed by Caiyuan Pan and coworkers in 2009.[7] They designed a macro chain transfer agent (CTA) which is trithiocarbonate-terminated poly(4-vinylpyridine) and polymerize styrene in methanol at 80℃. The macro CTA as well as the styrene monomer could dissolve well while the solubility for polystyrene in methanol is relatively poor. As the polystyrene chain grows, there is a transition from homogenous to heterogeneous polymerization, which is called dispersion polymerization (Fig 1).[5] Soon after reaching the critical chain length, the polystyrene blocks aggregate to form the core, and the copolymer automatically forms a micelle structure. By tuning the packing parameter

for this diblock copolymer, they found that their copolymer could eventually form various vesicle structures with a maximum styrene concentration up to 500mg/ml.

These two examples proved the possibility of using RAFT polymerization in dispersion condition to directly form nanoparticle with selected morphologies. However, for further biological application, methanol, as well as the reaction temperature, was not ideal since most biological cargo such as protein, DNA, or drugs are not stable in these conditions.[8] Moreover, the controlling over the morphologies of copolymer and their mutation process kept unclear which limited the repeatability for this method.

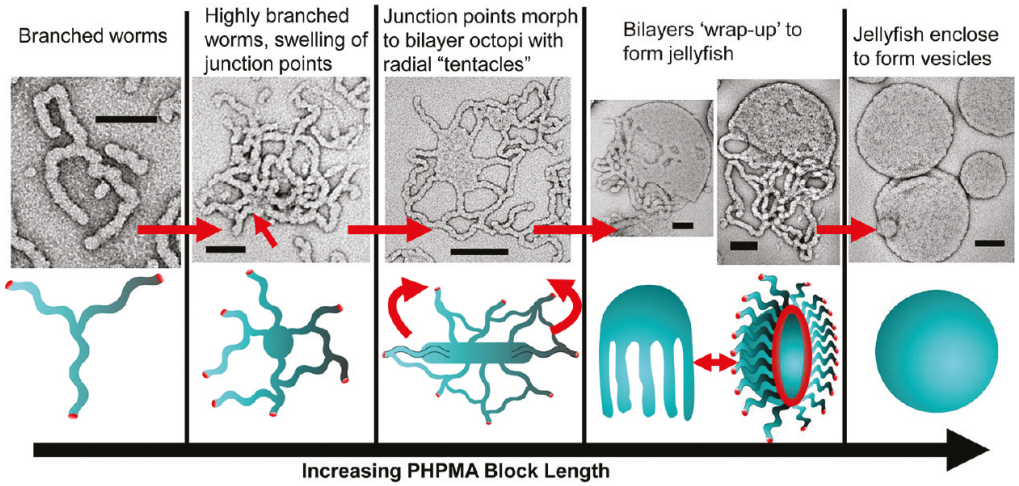

Figure 2. Morphologies mutation as insoluble segment growing. Scale bar = 200 nm.[12]

To undergo RAFT dispersion PISA in aqueous condition for further use in biological application, water soluble monomers which later form hydrophobic polymers were highly demanded. Even though aqueous RAFT dispersion polymerization had been reported for years,[9] it was not until 2010 that Steven P. Armes and coworkers used one such monomer 2-hydroxypropyl methacrylate (HPMA) with a maximum weight concentration of 50% to proceed PISA via RAFT in aqueous dispersion condition.[10] In their design, they introduced a water soluble macro CTA Poly(glycidyl methacrylate) (PGMA) and the polymerization underwent at 70℃. In 2011, the Sugihara group used poly(2-(methacryloyloxy) ethylphosphorylcholine) as the macro CTA and polymerized HPMA monomer at different weight concentration and designed degree of polymerization.[11] They semi empirically illustrated the control over nanoparticle morphologies by attaining various morphologies at different feeding conditions with great repeatability. At the same time, Armes group reported the TEM data which illustrated the mutation of morphologies during the growing of PHPMA triggered by PGMA.[12] Intriguingly, they found that the block polymer would initially form a micelle and then a worm like structure which later would be reorganized into a vesicular structure (Fig2). In 2014 they used a polyethylene glycol (PEG) segment as the macro CTA and attained different morphologies of PEG-block-PHPMA at 50℃ which was a relatively mild temperature for most biomolecules.[13]

In recent years, RAFT dispersion PISA were utilized for drug[14] and protein[15] delivery. For now, polymerization induced self-assembly via RAFT dispersion polymerization is a novel and efficient method to prepare functional nanoparticles with different morphologies. The morphologies of PISA in aqueous solution can be controlled by tuning feeding at relatively mild condition. However, as for synthesis, HPMA seems to be the only particle monomer and thus the library of RAFT dispersion PISA with versatile monomers needed to be explored. Besides, a more precise mathematic model is needed since packing parameter is used for equilibrium states while the morphologies mutation for PISA is a thermodynamic result.

References

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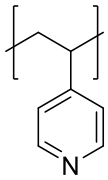
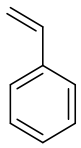
Chemical structure for all compounds above.

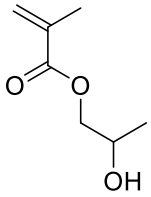
poly(4-vinylpyridine)



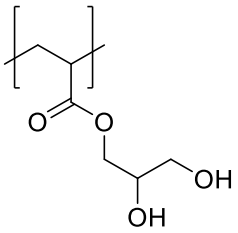
styrene



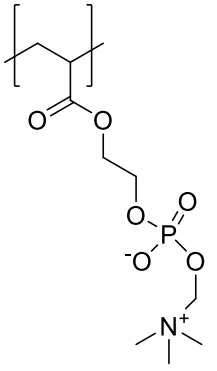
2-hydroxypropyl methacrylate



poly(glycidyl methacrylate)



poly(2-(methacryloyloxy) ethylphosphorylcholine)



polyethylene glycol