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Polymerization-Induced Self-Assembly of Block Copolymer Nanoparticles via RAFT Non-Aqueous Dispersion Polymerization

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Abstract

There is considerable current interest in polymerization-induced self-assembly (PISA) via reversible addition-fragmentation chain transfer (RAFT) polymerization as a versatile and efficient route to various types of block copolymer nano-objects. Many successful PISA syntheses have been conducted in water using either RAFT aqueous dispersion polymerization or RAFT aqueous emulsion polymerization. In contrast, this review article is focused on the growing number of RAFT PISA formulations developed for non-aqueous media. A wide range of monomers have been utilized for both the stabilizer and core-forming blocks to produce diblock copolymer nanoparticles in either polar or non-polar solvents via RAFT dispersion polymerization. Such nanoparticles can exhibit spherical, worm-like or vesicular morphologies, often with controllable size and functionality. Detailed characterization of such sterically-stabilized diblock copolymer dispersions provide important insights into the various morphological transformations that can occur both during the PISA synthesis and also subsequently on exposure to a suitable external stimulus (e.g. temperature).

Keywords (max. 6): Polymerization-induced self-assembly; Block copolymers; Nanoparticles; RAFT; Non-aqueous; Dispersion polymerization

Abbreviations: PISA, polymerization-induced self-assembly; RAFT, reversible addition-fragmentation chain transfer; CTA, chain transfer agent; macro-CTA, macromolecular chain transfer agent; T_g, glass transition temperature; TEM, transmission electron microscopy; DLS, dynamic light scattering; SAXS, small-angle X-ray scattering; LCST, lower critical solution temperature; UCST, upper critical solution temperature; M_w, weight-average molecular weight; M_n, number-average molecular weight; G', storage modulus; CGT, critical gelation temperature; CGC, critical gelation concentration; o/w, oil-in-water; w/o, water-in-oil.

1. Introduction

It is well known that amphiphilic AB diblock copolymers undergo self-assembly in a selective solvent for one of the two blocks [1]. In principle, the morphology of the resulting diblock copolymer nanoparticles [2-5] is dictated by the relative block volume fractions, as defined by the so-called packing parameter (Figure 1) [6-8]. In practice, the copolymer concentration can also influence the morphology in some cases [9-12].

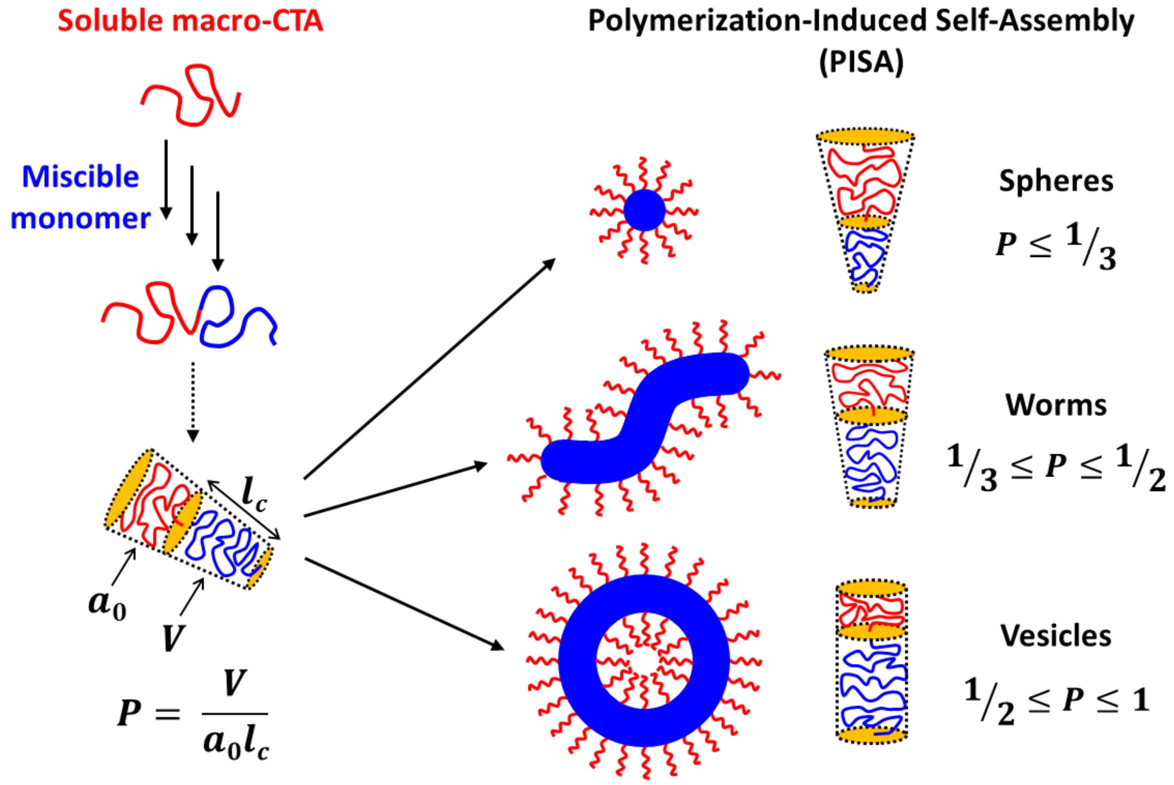
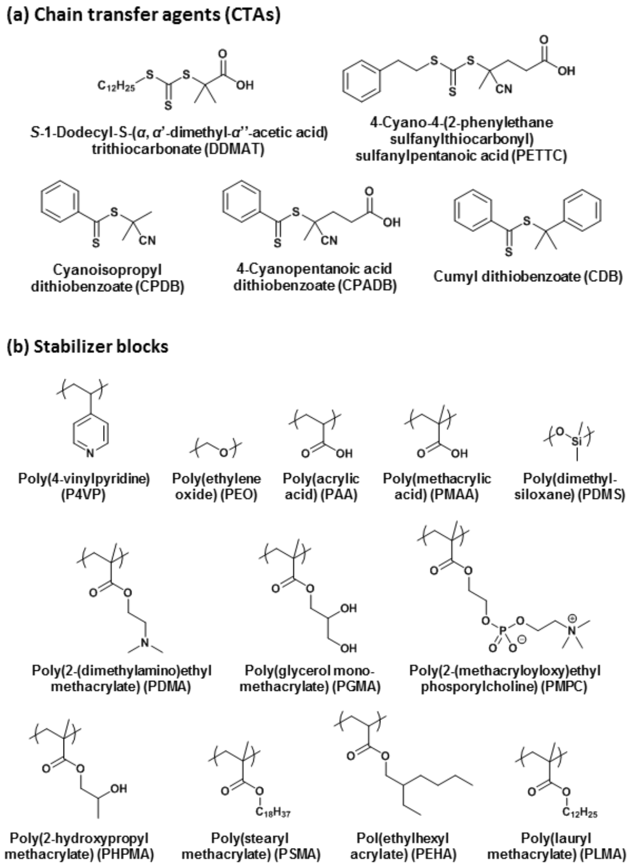


Figure 1. Schematic representation of RAFT dispersion polymerization, whereby a soluble macromolecular chain transfer agent (macro-CTA, red) is chain-extended by an initially miscible monomer to yield an insoluble polymer block (depicted in blue). The packing parameter, *P*, for the resulting individual block copolymer chains in a selective solvent is defined in terms of the volume of

the core-forming blue chain, V, the optimal area of the stabilizing red chain, a_0, and the length of the core-forming blue chain, l_c. The corresponding nanoparticle morphology is normally dictated by the value of P.

Recently, many academic groups have examined the use of controlled radical polymerisation techniques, particularly reversible addition-fragmentation chain transfer (RAFT) [13, 14] polymerization, for the synthesis of amphiphilic diblock copolymer nanoparticles via polymerization-induced self-assembly (PISA) [15-36]. Initial research focused on RAFT aqueous emulsion polymerization using water-immiscible monomers such as methyl methacrylate, *n*-butyl acrylate or styrene [15-20]. Such formulations can be very efficient [15-17], but in many cases this approach leads to the formation of kinetically-trapped spheres, rather than the full range of copolymer morphologies [15-21]. In contrast, there are many examples of RAFT dispersion polymerization formulations that yield spheres, worms and vesicles [17, 22-29]. In this approach, a soluble macromolecular chain transfer agent (macro-CTA) is utilized to polymerize a soluble monomer to form an insoluble polymer block, thus forming amphiphilic diblock copolymers that undergo spontaneous in situ self-assembly during chain growth (see Figure 1). Considerable research has been devoted to PISA syntheses via RAFT *aqueous* dispersion polymerization using water-miscible monomers such as 2-hydroxypropyl methacrylate (HPMA), *N*-isopropylacrylamide (NIPAM), *N*,*N*-diethylacrylamide or 2-methyoxyethyl acrylate [12, 17, 22, 30-36]. The construction of phase diagrams enables the reproducible targeting of each copolymer morphology for a stabilizer block of a given mean degree of polymerization (DP), with the two synthesis variables being the target DP of the core-forming block and the overall copolymer concentration (or total solids concentration) [12, 22, 34]. Perhaps the most intensively studied formulations involve the chain extension of poly(glycerol monomethacrylate) (PGMA) [22, 32, 33], poly(2-(methacryloyloxy)ethyl phosphorylcholine) (PMPC) [12] or poly(ethylene glycol) (PEG) [34] macro-CTAs using HPMA to generate the core-forming PHPMA block. Such sterically-stabilized nanoparticles have several potential applications, including coatings [37], drug delivery [38], sterilizable gels [39] and novel Pickering emulsifiers [40]. More complex morphologies have also been reported for certain RAFT aqueous dispersion polymerization formulations, including so-called ‘lumpy rods’ [41], ‘framboidal’ vesicles [23], and oligolamellar vesicles [34].

Despite the extensive literature based on RAFT *aqueous* dispersion polymerization [12, 17, 22, 30-36], there are relatively few reports of RAFT *non-aqueous* dispersion formulations. There are various studies describing dispersion polymerization syntheses conducted in water/(m)ethanol or water/1,4-dioxane mixtures [42-51]. However, in this review article we will focus on examples of RAFT dispersion polymerization *in the absence of water as a co-solvent*. In most cases, this means either lower alcohols or various *n*-alkanes, although a few other solvents and solvent mixtures will also be considered. The various RAFT chain transfer agents (CTAs) and polymer blocks that have been deployed in such syntheses are summarized in Figure 2.



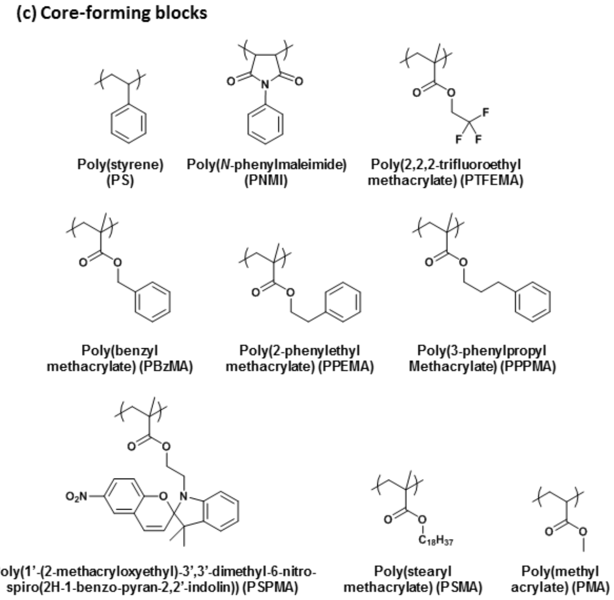


Figure 2. (a) Chemical structures of the chain transfer agents (CTAs), (b) stabilizer blocks and (c) core-forming blocks used in various RAFT non-aqueous dispersion formulations reported in the literature.

2. RAFT alcoholic dispersion polymerization

2.1.Dispersion polymerization of styrene

One of the first RAFT-mediated non-aqueous PISA formulations was the dispersion polymerization of styrene in lower alcohols. Pan and co-workers [28, 52-57] have utilized a trithiocarbonate-based chain transfer agent (DDMAT, see Figure 2a) to prepare a range of poly(4-vinylpyridine) (P4VP) macro-CTAs for the subsequent dispersion polymerization of styrene in methanol. The resulting poly(4-vinylpyridine)-polystyrene (P4VP-PS) nanoparticles formed a wide range of copolymer morphologies (Figure 3 andFigure **4**) [28, 52-57]. Like the analogous RAFT *aqueous* dispersion formulations [17, 25, 58], purely spherical, worm-like or vesicular morphologies could be targeted by tuning the block composition, which is consistent with the geometric packing argument for surfactant self-assembly introduced by Israelachvili and co-workers [6], and subsequently extended to block copolymer self-assembly by Antonietti and Förster [7]. This provides a conceptual framework that offers qualitative insights when considering mechanisms for morphological transitions as well as some aspects of phase diagrams. However, as yet this approach cannot be used to gain even a semi-quantitative understanding of the multiple morphological transformations that can occur during an in situ PISA synthesis. This is because the core-forming blocks within the block copolymer nano-objects are almost certainly solvated by both monomer and solvent, but the *local* concentrations of these two species are not known. Since this degree of solvation necessarily dictates the *effective* volume fraction of the core-forming block, calculation of the variation in the packing parameter, *P*, during a PISA synthesis is currently an intractable problem. In principle, theoretical advances in this area should enable phase diagrams to be calculated for a given PISA formulation, which would in turn minimize the intensive synthetic effort currently required to identify the phase space for each copolymer morphology. Nevertheless, such empirical experimental studies can be very instructive.

Pan and co-workers have used TEM to investigate in situ morphological transformations that occur when targeting vesicles. Perhaps surprisingly, no evidence of an intermediate worm-like morphology was reported [28, 54, 55], but worms are observed as a final nanoparticle morphology [52, 54]. Huang et al. [59] statistically copolymerized a small amount (5 mmol eq.) of the photochromatic spiropyran analogue 1’-(2-methacryloxyethyl)-3’,3’-dimethyl-6-nitro-spiro(2H-1-benzo-pyran-2,2’-indolin) (SPMA, Figure 2c) with 4VP to produce a light-responsive stabilizer macro-CTA. This enabled enhanced fluorescence properties of the resulting vesicles upon exposure to UV radiation as a result of photoisomerization of the SPMA repeat units.

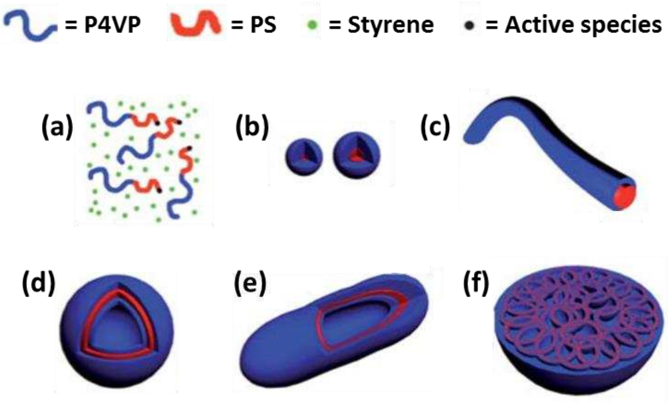


Figure 3. Formation of various poly(4-vinylpyridine)-polystyrene (P4VP-PS) diblock copolymer nanoparticles from initially soluble poly(4-vinylpyridine) chains via RAFT dispersion polymerization of styrene in methanol. Copolymer morphologies that can be obtained using this PISA formulation include (a) soluble chains, (b) spheres, (c) worms, (d) vesicles, (e) nanotubes and (f) large compound vesicles. Figure adapted with permission from ref. [54].

In addition to spheres, worms and vesicles, P4VP-PS block copolymer nanoparticles have been used to access more complex structures such as the so-called ‘yolk/shell’ morphology (Figure 4d) [53]. In this case, PS homopolymer chains were present during the PISA synthesis of P4VP-PS vesicles. The former component was subsequently stabilized by the P4VP-PS diblock copolymer chains, resulting in the formation of PS spherical nanoparticles within the vesicle lumen and hence the ‘yolk/shell’ morphology. More recently, Zhang et al.

[57] reported the formation of 'multi-shelled' vesicles when targeting highly asymmetric (e.g. $P4VP_{73}$-PS_{9400}) diblock copolymers in methanol (Figure 4e). These formulations indicate the complexity of block copolymer morphologies that can be achieved when utilizing PISA formulations in methanol. However, it must be emphasized that the RAFT dispersion polymerization of styrene invariably suffers from substantially incomplete conversions (e.g. 30-70% after 48 h at 80 °C), despite such syntheses being conducted at relatively high solids. Moreover, the relatively large volume of unreacted monomer solvates the insoluble core-forming PS block and hence most likely influences the nanoparticle morphology.

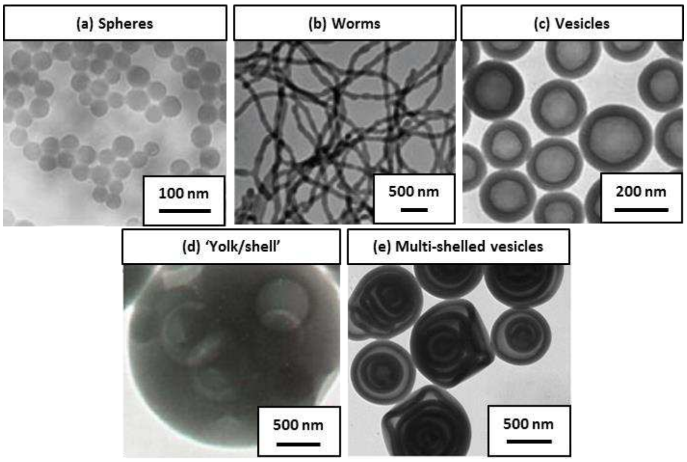


Figure 4. Transmission electron micrographs obtained for various diblock copolymer morphologies reported by Pan and co-workers via RAFT dispersion polymerization of styrene in methanol using various P4VP macro-CTAs: (a) spheres, (b) worms, (c) vesicles, (d) 'yolk/shell' and (e) multi-shelled vesicles. Figure adapted with permission from refs. [53], [54] and [57].

Subsequent studies have also examined the RAFT dispersion polymerization of styrene in methanol. A trithiocarbonate-based DDMAT CTA (Figure 2a) was used to prepare poly(ethylene oxide)-polystyrene (PEO-PS) [60] and poly(acrylic acid)-polystyrene (PAA-PS) [26] block copolymer nano-objects in methanol, where access to the full range of morphologies (spheres, worms or vesicles) was observed in both cases. Similarly, a dithiobenzoate-based CTA (cyanoisopropyl dithiobenzoate or CPDB, Figure 2a) was utilized for the synthesis of poly(2-(dimethylamino)ethyl methacrylate)-polystyrene (PDMA-PS) diblock copolymer spheres, worms or vesicles [27], in addition to the P4VP-PS formulations previously discussed [57]. However, relatively low styrene conversions again remained a significant problem when targeting a pure PS core-forming block. Yang et al. [61] reported that high comonomer conversions (> 90%) could be achieved when conducting the RAFT dispersion alternating copolymerization of styrene with *N*-phenylmaleimide (NMI) using a poly(methacrylic acid) (PMAA) macro-CTA in a solvent mixture. More specifically, PMAA-

P(S-*alt*-NMI) block copolymers formed spheres, worms or lamellae in 50:50 w/w ethanol/1,4-dioxane at ≥ 15% w/w solids [61]. Unusually, the latter morphology was obtained instead of vesicles, which was attributed to the relatively stiff, inflexible nature of the core-forming alternating copolymer chains (T_g > 200 °C).

2.2.Dispersion polymerization of benzyl methacrylate

Although styrene is a relatively cheap monomer, it suffers from a relatively slow rate of polymerization when utilized in non-aqueous PISA formulations [28, 52-57]. In contrast, Charleux et al. reported that RAFT *aqueous emulsion* polymerization of styrene led to almost complete conversion within 5 h [62, 63]. There are also various examples of alcohol/water mixtures that enable relatively high styrene conversions to be achieved via RAFT dispersion polymerization [44-47, 64-66]. However, for RAFT alcoholic dispersion polymerization formulations conducted in the *absence* of water as a co-solvent, benzyl methacrylate (BzMA) provides a pragmatic alternative to styrene for the core-forming block. For example, Armes and co-workers [67-71] reported that the RAFT dispersion polymerization of BzMA conducted in lower alcohols (i.e. methanol, ethanol or isopropanol) usually leads to monomer conversions exceeding 95% within 24 h at 70 °C. The versatility of such a protocol was highlighted by Semsarilar et al. [67], who synthesized PDMA, PMAA, PGMA and PMPC macro-CTAs using 4-cyano-4-(2-phenylethanesulfanylthiocarbonyl)sulfanylpentanoic acid (PETTC, Figure 2a), followed by chain extension of each macro-CTA in turn with BzMA to produce a range of pure spheres, worms or vesicles in ethanol (Figure 5a, b and c respectively).

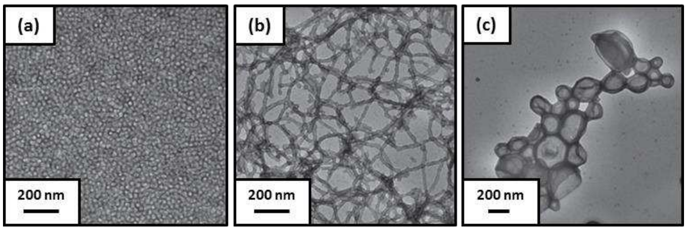


Figure 5. Transmission electron micrographs of (a) $PMAA_{67}$-$PBzMA_{50}$ spheres, (b) $PMAA_{67}$-$PBzMA_{100}$ worms and (c) $PMAA_{67}$-$PBzMA_{200}$ vesicles prepared by RAFT dispersion polymerization of benzyl methacrylate in ethanol at 70 °C. In each case relatively high monomer conversions were obtained (> 95%). Figure adapted with permission from ref. [67].

Construction of a suitable phase diagram allowed reproducible targeting of a desired morphology for a given $PMAA_{71}$-$PBzMA_x$ block copolymer composition (Figure 6). Generally, only a relatively weak concentration dependence on copolymer morphology was observed. However, only spherical nanoparticles could be obtained at 5% w/w solids regardless of the target DP for the PBzMA core-forming block, which suggests that a kinetically-trapped morphology under these conditions.[22] Presumably, this simply reflects the reduced probability of efficient inter-sphere fusion occurring on the time scale of the BzMA polymerization for PISA syntheses conducted under more dilute conditions.

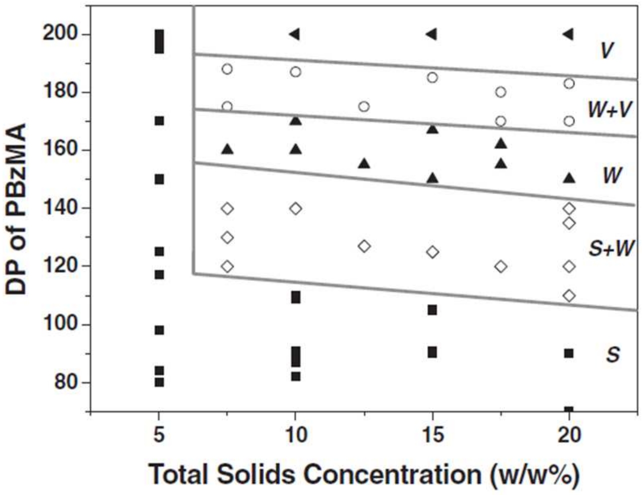


Figure 6. Phase diagram constructed for $PMAA_{71}$-$PBzMA_x$ diblock copolymer nanoparticles prepared by RAFT dispersion polymerization of BzMA in ethanol at 70 °C, where S, W and V represent spheres, worms and vesicles respectively. Figure reproduced with permission from ref. [67].

The PDMA, PMAA, PGMA and PMPC stabilizer blocks are soluble in both ethanol and water, hence facile transfer of diblock copolymer nano-objects into aqueous solution was conveniently achieved by dialysis of the as-synthesized ethanolic dispersion against water [67, 68]. This transfer allowed nanoparticle characterization by aqueous electrophoresis, which confirmed the expected cationic character of $PDMA_{31}$-$PBzMA_{37}$ spheres below pH 9 as a result of protonation of the stabilizer chains. Similarly, the anionic character of $PMAA_{67}$-$PBzMA_{50}$ spheres over a wide pH range was verified, whereas $PGMA_{60}$-$PBzMA_{50}$ and $PMPC_{30}$-$PBzMA_{380}$ spheres exhibited almost neutral (slightly anionic) character from pH 3 to pH 10 [67]. Thus these alcoholic PISA formulations offer a reasonably efficient route for the preparation of highly charged block copolymer nano-objects. Previously, Semsarilar et al. demonstrated that the direct preparation of highly anionic or cationic nanoparticles via aqueous PISA formulations is problematic in the absence of added salt. This is because strong lateral electrostatic repulsion between neighboring polyelectrolytic chains impedes in situ self-assembly [24, 72]. In collaboration with Meldrum and co-workers, we have recently shown that anionic $PMAA_x$-$PBzMA_y$ nano-objects can be efficiently occluded within single crystals of calcite, leading to a series of novel organic-inorganic nanocomposites that exhibit superior mechanical properties to that of calcite alone [73, 74]. Additionally, anionic $PMAA_{71}$-$PBzMA_{200}$ vesicles were successfully coated with cationic 12 nm alumina-coated silica particles (Ludox CL) to form ‘armoured’ vesicles [67].

Zehm et al. [69] reported the preparation of poly(2-hydroxypropyl methacrylate)-poly(benzyl methacrylate) (PHPMA-PBzMA) block copolymer spheres, worms and vesicles in either ethanol or isopropanol. This study highlighted the importance of the choice of solvent and the DP of the stabilizer macro-CTA (in addition to the target PBzMA DP and copolymer concentration) in dictating the final morphology of diblock copolymer nanoparticles in alcoholic media. These findings are also consistent with earlier reports of block copolymer nanoparticles prepared via RAFT aqueous dispersion polymerization [12, 22]. Zehm et al. also provided the first evidence that the worm-to-vesicle transition in non-aqueous PISA formulations proceeds via a transient ‘jellyfish’ morphology (Figure 7). This observation is in good agreement with TEM studies conducted by Blanazs et al., who examined the evolution in copolymer morphology during the synthesis of PGMA-PHPMA vesicles via RAFT aqueous dispersion polymerization [33].

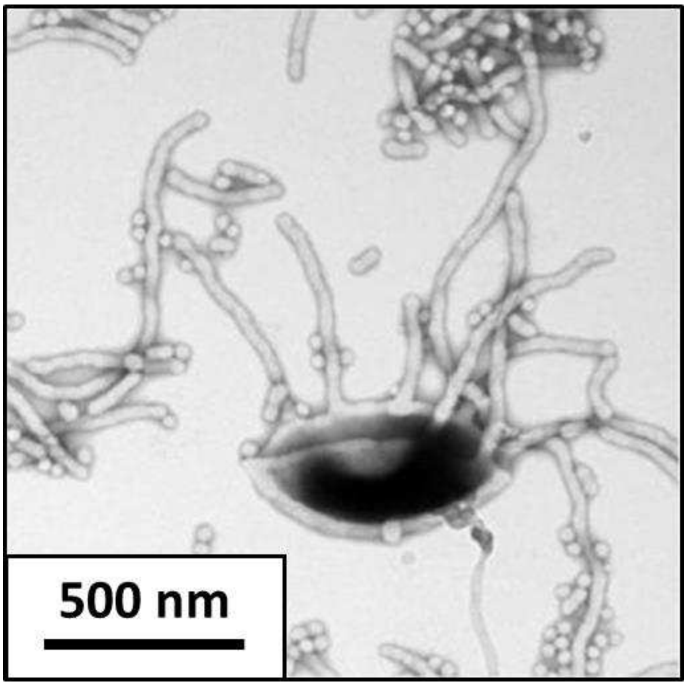
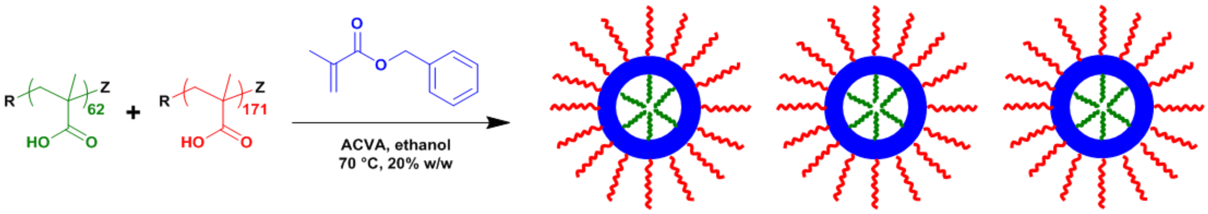


Figure 7. Transmission electron micrograph of the ‘jellyfish’ morphology observed during the formation of $PHPMA_{63}$-$PBzMA_{200}$ diblock copolymer nanoparticles prepared via RAFT dispersion polymerization of BzMA in ethanol [69]. Similar transient copolymer morphologies have been observed for RAFT aqueous dispersion polymerization formulations [33], and also during post-polymerization processing of block copolymers [25]. This strongly suggests that the ‘jellyfish’ is a *generic* intermediate for block copolymer self-assembly, rather than a PISA-specific species. Figure reproduced with permission from ref. [69].

More recently, Gonzato et al. [71] reported the synthesis of low-polydispersity PMAA-PBzMA vesicles via RAFT dispersion polymerization of BzMA in ethanol. This was achieved by selecting an appropriate binary mixture of a $PMAA_{171}$ and a $PMAA_{62}$ stabilizer macro-CTA, which preferentially occupy the outer and inner leaflets of the vesicle membrane respectively (Scheme 1). Control experiments confirmed that, if just the shorter $PMAA_{62}$ stabilizer macro-CTA was utilized for the PISA synthesis, then only relatively large vesicles with broad size distribution could be obtained. Systematic variation of the relative proportions of the two PMAA stabilizer blocks allowed construction of a phase diagram that enabled optimization of the vesicle size distribution, as judged by TEM, dynamic light scattering (DLS) and small-angle X-ray scattering (SAXS) studies. Given their high efficiency, such rational syntheses of well-defined vesicles are expected to be useful in the context of drug delivery vehicles, for *in vivo* imaging, the design of artificial organelles, for encapsulation and also for potential use as nanoreactors [75-78].



Scheme 1. Synthesis of low polydispersity diblock copolymer vesicles in ethanol via RAFT dispersion polymerization of BzMA using a binary mixture of two PMAA macro-CTAs (with DPs of x and y, respectively). Redrawn scheme from ref. [71].

2.3.Living character of RAFT alcoholic dispersion polymerization

The success of the various RAFT alcoholic dispersion polymerization formulations based on BzMA inspired a direct comparison of the pseudo-living character of RAFT polymerization conducted under homogeneous and heterogeneous conditions. This was facilitated by the serendipitous discovery that RAFT dispersion polymerization of 2,2,2-trifluoroethyl methacrylate (TFEMA) in ethanol using either PDMA or PMAA stabilizer macro-CTAs results in the formation of diblock copolymer nanoparticle dispersions with minimal turbidity [79]. This is a consequence of very similar refractive indices for PTFEMA and ethanol, which means that UV-visible spectroscopy can be used to record absorption spectra during PISA syntheses with essentially no background scattering from the nanoparticles. By monitoring the chromophore corresponding to the trithiocarbonate species at 305 nm, Semsarilar and co-workers were able to show that a significantly higher proportion of RAFT chain-ends ($\geq$ 73%) remained active during *dispersion* polymerizations conducted in ethanol, whereas only 55-60% RAFT chain-ends survived the corresponding *solution* polymerization conducted in THF (Figure 8). These findings suggest that, in addition to the enhanced rate of polymerization and low viscosity compared to conventional solution polymerization, the enhanced living character of such RAFT dispersion polymerization formulations is likely to enable higher blocking efficiencies to be achieved when targeting ABC triblock copolymers [23, 70].

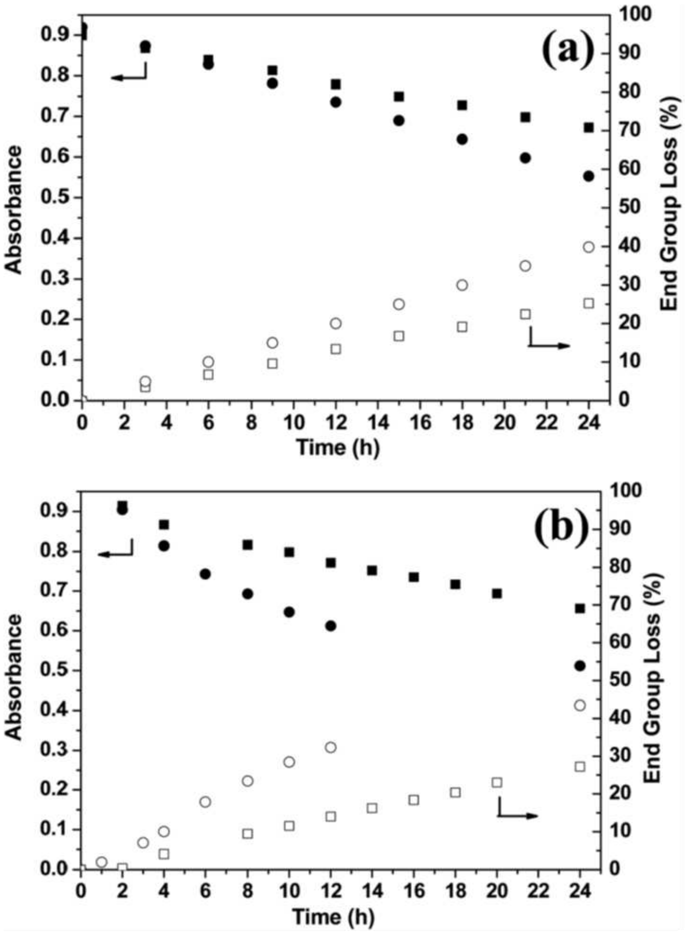


Figure 8. Comparison of the pseudo-living character of the RAFT *dispersion* polymerization of TFEMA in ethanol (squares) and the RAFT *solution* polymerization of TFEMA in THF (circles) when targeting (a) $PDMA_{94}$-$PTFEMA_{300}$ and (b) $PMAA_{70}$-$PTFEMA_{300}$ diblock copolymers. The observed absorbance at 305 nm is indicated by the filled symbols, whereas the calculated loss of RAFT chain ends is indicated by the open symbols. Figure reproduced with permission from ref. [79].

2.4.Alternative core-forming blocks for RAFT alcoholic dispersion polymerization

Following the elegant studies of crystallization-driven block copolymer self-assembly reported by Manners and Winnik [80-85], PISA syntheses of diblock copolymer nano-objects with semi-crystalline cores have been recently reported in the literature. For example, Charleux and co-workers conducted the RAFT dispersion polymerization of a bespoke cholestryl-based (meth)acrylic core-forming monomer in an ethanol/water mixture to produce well-defined diblock copolymer nanorods and nanofibers [44]. Similarly, Armes and co-workers conducted the RAFT dispersion polymerization of stearyl methacrylate (SMA) in pure ethanol using a PDMA macro-CTA (Figure 2c) [86]. The latter approach yielded PDMA-PSMA spheres, worms or vesicles with semi-crystalline stearyl side-chains in the PSMA core-forming block [86]. Potential advantages for such nano-objects could be the preparation of relatively stiff worms of tunable flexibility and perhaps also vesicles with less permeable membranes, thus offering enhanced encapsulation efficiency.

Recently, Lowe and co-workers [29, 87, 88] extended the RAFT dispersion polymerization formulation originally pioneered by Armes et al. [67-71] and Charleux and co-workers [17, 18, 31, 42, 63, 66]. A series of PDMA macro-CTAs were chain-extended via RAFT dispersion polymerization of either 2-phenylethyl methacrylate (PEMA) or 3-phenylpropyl methacrylate (PPMA) in ethanol at 70 °C to produce spheres, worms or vesicles [29, 87]. Moreover, a 21% w/w dispersion of $PDMA_{20}$-$PPPMA_{47}$ worms formed a free-standing gel at room temperature, but heating this dispersion to 70 °C for 1 min resulted in the formation of a free-flowing fluid. According to TEM studies, degelation is the result of a reversible worm-to-sphere order-order transition (Figure 9). Variable temperature ^{1}H NMR studies revealed that this change in copolymer morphology coincided with greater solvation of the PPPMA core block at elevated temperatures. This alters the relative volume fraction of the two blocks and hence the effective packing parameter for the diblock copolymer chains [87]. Such thermo-reversible degelation has been previously reported for diblock copolymer worms prepared by RAFT *aqueous* dispersion polymerization, where a worm-to-sphere transition was observed upon *cooling* [39, 89]. This is related to the well-known inverse temperature solubility (LCST-type) behavior exhibited by many non-ionic water-soluble polymers [90], whereas conventional solvent-soluble polymers typically exhibit UCST-type behaviour in common organic solvents [91].

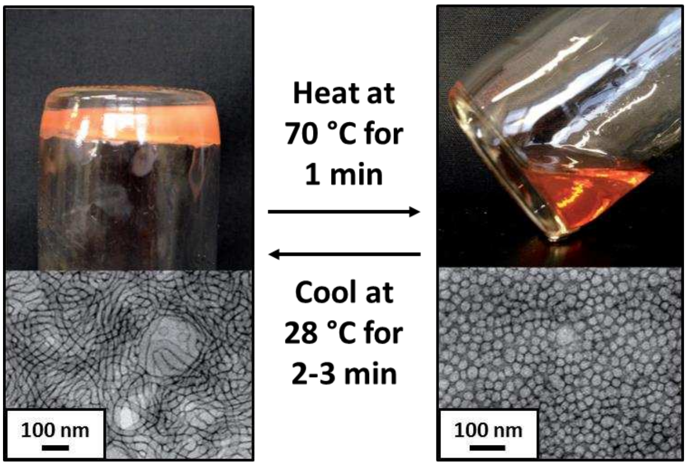


Figure 9. Digital photographs of a 21% w/w dispersion of $PDMA_{20}$-$PPPPMA_{47}$ diblock copolymer nano-objects in ethanol at room temperature (left) and 70 °C (right), and the corresponding transmission electron micrographs obtained after dilution showing worm-like nanoparticles at room temperature (left) and spherical nanoparticles at 70 °C (right). Figure reproduced with permission from [87].

3. RAFT non-polar dispersion polymerization

Compared to RAFT alcoholic dispersion polymerization, there are relatively few reports of RAFT dispersion polymerization being conducted in *non-polar* solvents [92-99]. Charleux and co-workers [92-94] reported an all-acrylic RAFT non-polar dispersion polymerization formulation that produced poly(2-ethylhexyl acrylate)-poly(methyl acrylate) (PEHA-PMA) diblock copolymer nanoparticles in *iso*-dodecane. However, it is emphasized that only spherical nanoparticles could be accessed in this study. Moreover, using a dithiobenzoate-based CTA led to strong rate retardation and extremely poor RAFT control ($M_w/M_n > 6.00$) at ≥ 85% conversion for the chain extension of a PEHA macro-CTA using methyl acrylate (MA) compared to a trithiocarbonate-based maco-CTA [92]. Thus it is perhaps debatable whether this constitutes a genuinely successful RAFT formulation. In 2013, Fielding et al. [95] reported the first well-controlled RAFT dispersion polymerization to be conducted in non-polar media. This all-methacrylic formulation utilized cumyl dithiobenzoate (CDB, Figure 2a) to prepare poly(lauryl methacrylate)-poly(benzyl methacrylate) (PLMA-PBzMA) diblock copolymer spheres, worms or vesicles in *n*-heptane. A phase diagram containing all three copolymer morphologies (see TEM images in Figure 10a) was constructed for a series of $PLMA_{17}$-$PBzMA_x$ (L_{17}-B_x) diblock copolymers. In contrast, using a relatively long $PLMA_{37}$ stabilizer block restricted the morphology to kinetically-trapped spheres (Figure 10b). In this case, the mean sphere diameter could be tuned by simply adjusting the target DP of the PBzMA core-forming block, with longer PBzMA blocks resulting in the formation of larger spheres, as previously reported for spherical nanoparticles prepared via RAFT *aqueous* dispersion polymerization [32]. This suggests some potential for using such spherical methacrylic nanoparticles as lubricity modifiers for automotive engine base oils, as reported by Zheng et al. for all-acrylic nanoparticles prepared via ATRP [100]. One important advantage of the former nanoparticles is that they are likely to be more resistant to *in situ* hydrolysis at elevated temperatures. Moreover, several other disadvantages such as possible copper catalyst contamination, oil discoloration during photo-crosslinking and the undesirable use of protecting chemistry are also avoided by utilizing RAFT-mediated PISA syntheses.

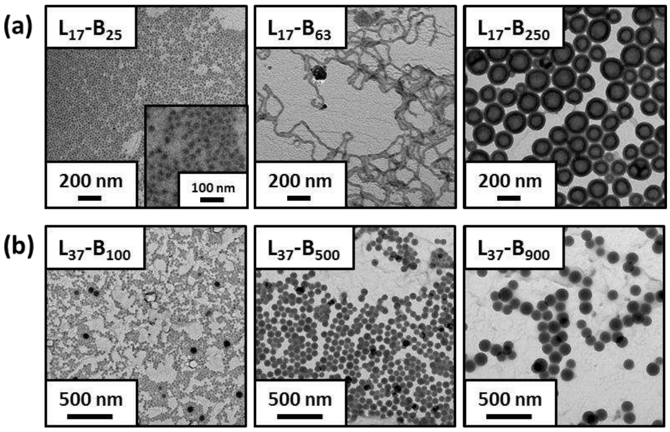


Figure 10. Transmission electron micrographs recorded for (a) $PLMA_{17}$-$PBzMA_x$ (L_{17}-B_x) diblock copolymer nanoparticles, where spherical, worm-like and vesicular morphologies are accessible in *n*-heptane, and (b) $PLMA_{37}$-$PBzMA_x$ (L_{37}-B_x) diblock copolymer spheres in the same solvent. Figure adapted with permission from ref. [95].

This PLMA-PBzMA formulation was subsequently extended from *n*-heptane to *n*-dodecane [96]. This may seem like a trivial advance, but the high boiling point of the latter solvent facilitates high temperature studies of PLMA-PBzMA nanoparticles and in particular, characterization of the thermo-responsive behavior of a $PLMA_{16}$-$PBzMA_{37}$ worm gel via rheology. TEM studies confirm that a worm-to-sphere transition is responsible for the degelation of a 20% w/w $PLMA_{16}$-$PBzMA_{37}$ worm gel that is observed upon heating to 90 °C. Variable temperature DLS, rheology and SAXS studies provided important insights into this morphological transformation, while ^{1}H NMR studies similar to those described by Lowe and co-workers were also undertaken [87]. In particular, it was determined that the worm-to-sphere transition was essentially irreversible when performed at copolymer concentrations below 5% w/w (Figure 11). Presumably, this is because the formation of worm-like nanoparticles from the fusion of multiple spheres is highly inefficient for dilute dispersions.

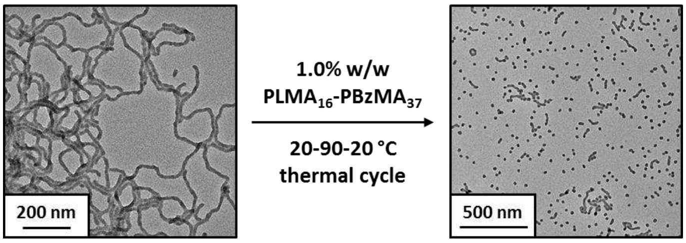


Figure 11. Transmission electron micrographs showing the irreversible worm-to-sphere transition of a 1.0% w/w dispersion of $PLMA_{16}$-$PBzMA_{37}$ diblock copolymer nanoparticles in *n*-dodecane. Figure reproduced with permission from [96].

Moreover, it was not necessary to convert all of the worms into spheres in order to induce degelation of the $PLMA_{16}$-$PBzMA_{37}$ worm gel. Rheological studies indicated that the onset of degelation occurred at approximately 47 °C. In contrast, SAXS studies confirmed that pure spheres (which have a zero gradient at low *q*) were only obtained when the original worms (which have a gradient close to -1 in the Guinier regime) were heated up to 160 °C (Figure 12) [96]. This suggests that degelation is a consequence of the reduction in the mean worm length, since this leads to fewer inter-worm contacts *per worm*. Two possible mechanisms were considered for the worm-to-sphere transition: (i) sequential budding of spheres from worm ends or (ii) random worm cleavage to produce gradually shorter worms (see Figure 12c). Variable temperature SAXS studies suggested that the former process was more likely to be the dominant mechanism. Finally, it is perhaps worth emphasizing that solvation of the core-forming PBzMA block is a necessary but not sufficient condition to account for the worm-to-sphere transition. If *uniform* plasticization of the core-forming block occurred on heating, this would simply lead to an increase in its effective volume fraction, which would be expected to induce a worm-to-vesicle transition. The worm-to-sphere transition that is actually observed can only be rationalized in terms of a subtle change in packing parameter if *surface* plasticization of the core-forming block occurs. This is physically reasonable for partial solvent ingress and leads to the BzMA repeat units nearest to the PLMA stabilizer becoming solvated. This increases the effective volume fraction of the *stabilizer* block, which *lowers* the packing parameter and hence accounts for the observed worm-to-sphere transition.

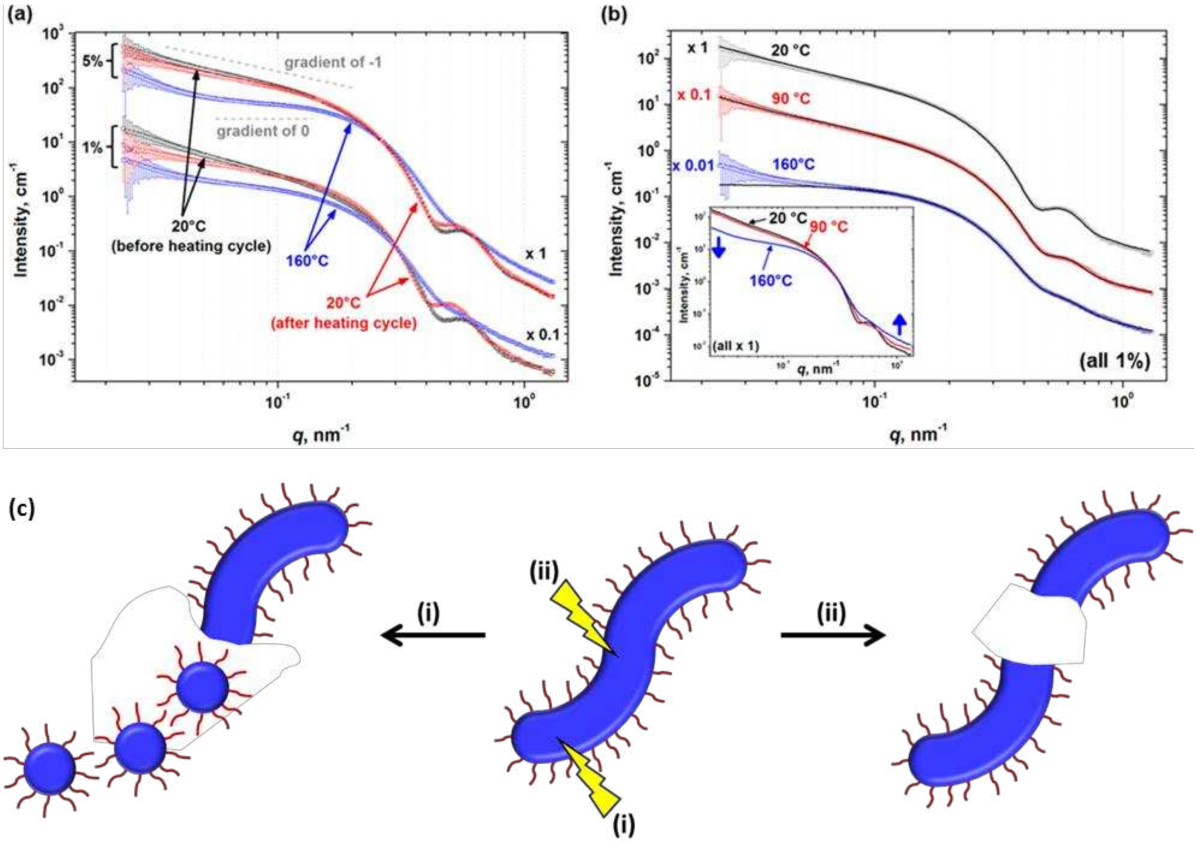


Figure 12. (a) Representative SAXS patterns for 5.0 and 1.0% w/w $PLMA_{16}$-$PBzMA_{37}$ diblock copolymer nanoparticles in *n*-dodecane before a 20-160-20 °C thermal cycle (black data), at 160 °C (blue data) and after the thermal cycle (red data). (b) Representative SAXS patterns for the same 1.0% w/w $PLMA_{16}$-$PBzMA_{37}$ diblock copolymer dispersion in *n*-dodecane recorded at 20 °C (black data), 90 °C (red data) and 160 °C (blue data). Data were fitted to a worm-like micelle model, where the scattering pattern at 160 °C indicated the presence of isotropic (spherical) particles. (c) Two possible mechanisms for the thermally-induced worm-to-sphere transition: (i) sequential budding and (ii) random worm cleavage. Figure adapted with permission from ref. [96].

Recently, Derry et al. reported the synthesis of PLMA-PBzMA spheres, worms and vesicles via RAFT dispersion polymerization of BzMA conducted in either mineral oil or a synthetic poly(*α*-olefin) in addition to *n*-dodecane [101]. Depending on the nature of the solvent, worm gels exhibited subtle differences in their storage modulus (*G*'), critical gelation temperature (CGT) and critical gelation concentration (CGC). Moreover, spherical nanoparticles could be prepared at up to 50% w/w solids, although a relatively high solution viscosity was observed above 40% w/w solids. An efficient 'one-pot' protocol was developed for the synthesis of 39 nm diameter $PLMA_{50}$-$PBzMA_{100}$ spheres in mineral oil, whereby the RAFT *solution* polymerization of LMA at 70% w/w solids was immediately followed by the RAFT *dispersion* polymerization of BzMA at 30% w/w solids (Figure 13). Each stage of the polymerization lead to more than 95% conversion and a high blocking efficiency was observed. Moreover, a relatively low final polydispersity ($M_w/M_n < 1.20$) was obtained and this one-pot synthesis was completed within 9 h. TEM studies of kinetic samples extracted during the RAFT *dispersion* polymerization of BzMA provided clear evidence of the onset of micellization at an approximate composition of PLMA$_{50}$-PBzMA$_{30}$ (Figure 13, images a-d), which correlated with the observation of an approximate five-fold increase in the rate of BzMA polymerization. This is believed to be as a result of the relatively high local BzMA concentration within the cores of the nascent growing micelles, as suggested by Blanazs et al. [33].

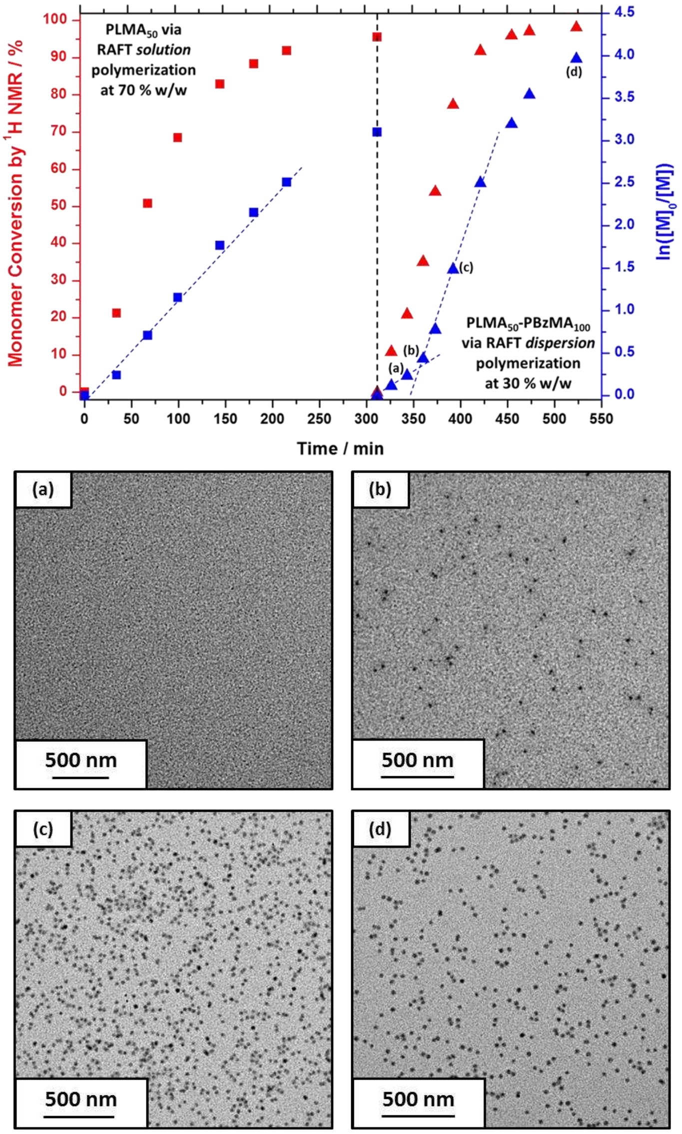


Figure 13. Conversion vs. time plots for the 'one-pot' synthesis of PLMA$_{50}$-PBzMA$_{100}$ spheres in mineral oil via RAFT solution polymerization of LMA at 70% w/w solids (squares) followed by the RAFT dispersion polymerization of BzMA at 30% w/w solids (triangles). TEM images (a), (b), (c) and (d) represent various time points during the RAFT dispersion polymerization of BzMA and indicate the onset of micellization at (b). Figure reproduced with permission from ref. [101].

In the patent literature, RAFT dispersion polymerization formulations are described that utilize methyl methacrylate (MAA), 2-hydroxypropyl methacrylate (HPMA) or glycidyl methacrylate (GlyMA) as core-forming monomers for the chain extension of PLMA macro-CTAs [102]. However, it is not yet clear whether such PISA formulations are as well-behaved as those based on BzMA. Lowe and co-workers recently reported using SMA instead of LMA to prepare PSMA stabilizer macro-CTAs (Figure 2b) for the synthesis of PSMA-PPPMA diblock copolymer nanoparticles in *n*-tetradecane [97] and *n*-octane [98]. Pure phases of spheres, worms or vesicles were accessible and a thermo-reversible worm-to-sphere transition was characterized by variable temperature TEM, DLS and ^{1}H NMR studies. Like the PLMA$_{16}$-PBzMA$_{37}$ worms in *n*-dodecane [96], this worm-to-sphere transition is most likely triggered by the surface plasticization of the PPPMA core block at elevated temperatures. These formulations were later extended by Pei et al. by introducing pentafluorophenyl methacrylate (PFPMA) residues into the PSMA macro-CTA to enable post-polymerization modification of this stabilizer block via nucleophilic acyl substitution [99]. A further RAFT dispersion polymerization formulation in non-polar media was recently reported by Lopez-Oliva et al. [103]. A near-monodisperse monocarbinol-functionalized polydimethylsiloxane (PDMS) was esterified using PETTC, with the resulting macro-CTA being subsequently used for the RAFT dispersion polymerization of BzMA in *n*-heptane at 70 °C (Figure 14a). In principle, preparing non-vinyl macro-CTAs such as PDMS-PETTC via end-group modification of an existing commercial precursor should provide reproducible access to the same mean stabilizer DP. This is expected to be useful for the construction of phase diagrams, for which remarkably narrow region was observed for the pure worm phase (Figure 14c) [103].

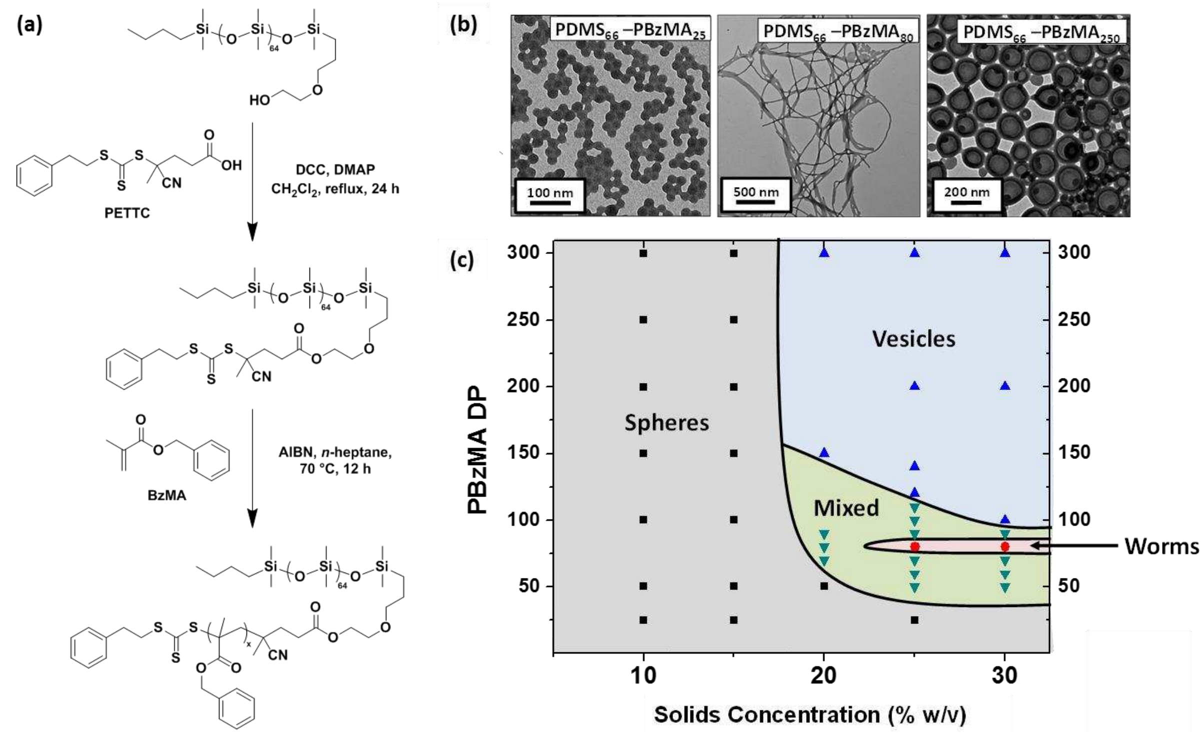


Figure 14. (a) Chain-end modification of monocarbinol-functionalized $PDMS_{66}$ and its subsequent chain-extension via RAFT dispersion polymerization of benzyl methacrylate in *n*-heptane at 70 °C. (b) Representative TEM images of $PDMS_{66}$-$PBzMA_{25}$ spheres, $PDMA_{66}$-$PBzMA_{80}$ worms and $PDMS_{66}$-$PBzMA_{250}$ vesicles in *n*-heptane. (c) Phase diagram constructed for $PDMS_{66}$-$PBzMA_x$ diblock copolymer nanoparticles prepared by RAFT dispersion polymerization of BzMA in *n*-heptane at 70 °C. Figure adapted with permission from ref. [103].

4. Non-aqueous Pickering emulsions using nanoparticles synthesized via RAFT dispersion polymerization

The use of various latex or microgel particles as Pickering emulsifiers to stabilize either oil or water droplets has been widely reported [104-107]. It is well known that the Pickering emulsion type is dictated primarily by the particle contact angle or surface wettability. In essence, hydrophilic particles typically form oil-in-water (o/w) emulsions, whereas hydrophobic particles usually stabilize water-in-oil (w/o) emulsions. The development of robust PISA formulations provided a timely opportunity to compare the performance of hydrophilic block copolymer spheres, worms or vesicles synthesized via RAFT *aqueous* dispersion polymerization for the preparation of o/w Pickering emulsions [20, 40, 108]. One interesting question in this context is whether worms offer any advantages over spheres. A rudimentary analysis suggests that worms should be more effective Pickering emulsifiers since they possess a relatively high specific surface area yet are much more strongly adsorbed at the oil/water interface [40, 109]. However, PGMA-PHPMA diblock copolymer worms prepared in aqueous media do not survive the high shear conditions required to generate the emulsion droplets. Fortunately this problem can be overcome by reinforcing the weakly hydrophobic core-forming block, either by covalent cross-linking or by introducing stronger inter-chain forces [40]. Very recently, Thompson et al. reported that hydrophobic $PLMA_{16}$-$PBzMA_{37}$ (or L_{16}-B_{37}) worms can be utilized to prepare w/o emulsions [109]. These worms undergo a worm-to-sphere transition on heating to 150 °C [96]. Since this change in morphology is essentially irreversible for sufficiently dilute dispersions (< 2 % w/w copolymer), *chemically identical* worms and spheres can be prepared that enable a direct comparison of their respective performance as Pickering emulsifiers [109]. The L_{16}-B_{37} *worms* proved to be more effective emulsifiers than L_{16}-B_{37} *spheres* when examined under identical conditions, since the former produced smaller, more stable droplets in the preparation of water-in-*n*-dodecane emulsions [109]. Moreover, these worm-stabilized Pickering emulsions became demulsified on heating as a result of a thermally-induced worm-to-sphere transition [109]. Thus the thermo-responsive nature of the particles is conferred on the Pickering emulsion.

In related work, Thompson et al. reported that the judicious combination of *hydrophilic* worms and *hydrophobic* worms enabled the preparation of highly stable Pickering *double emulsions* using either water or oil as the continuous phase (Figure 15) [110]. For example, fluorescence microscopy studies confirmed that water-in-*n*-dodecane-in-water double emulsions were successfully formed, since the fluorescein-labeled aqueous droplets were observed within oil droplets distributed in an aqueous continuous phase (Figure 15c). Moreover, addition of an oil-soluble Nile Red dye to *n*-dodecane confirmed that this oil was only present in the form of droplets (Figure 15d).

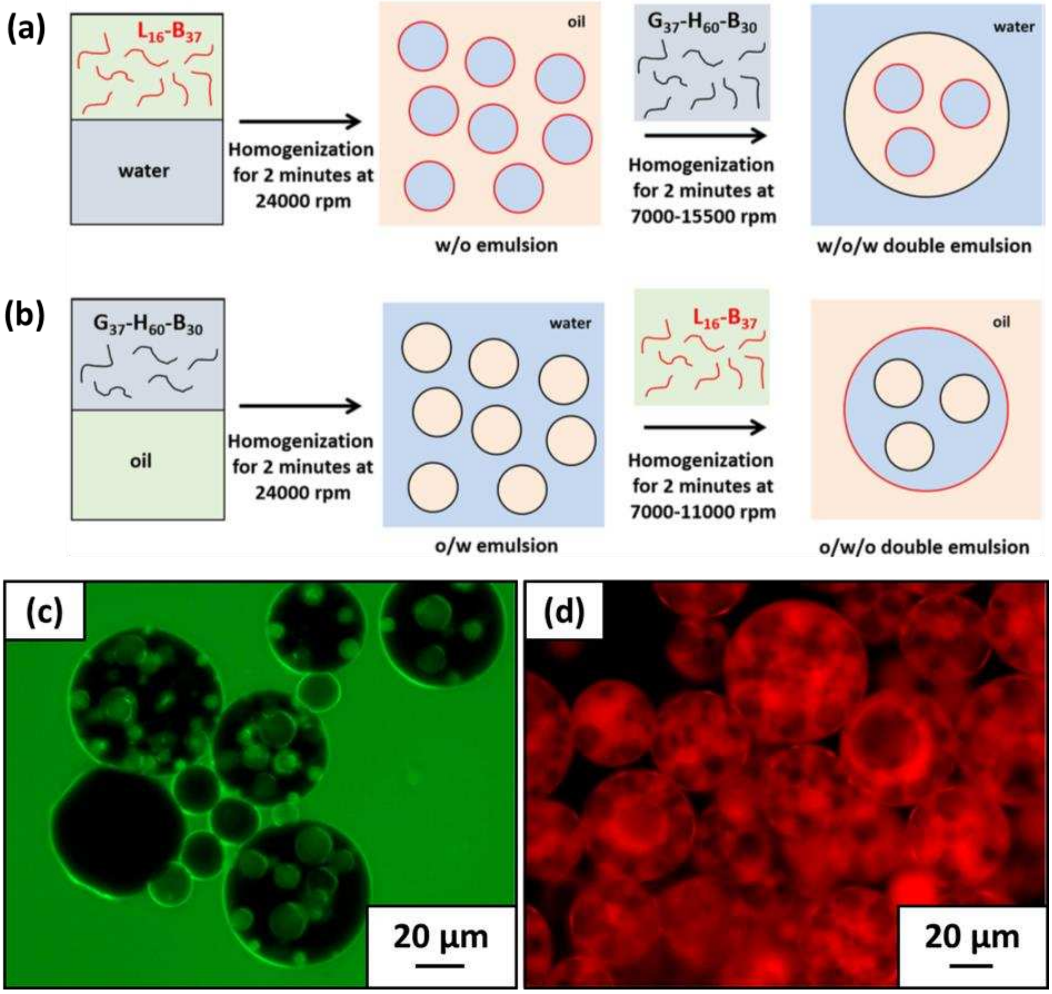


Figure 15. Schematic representation of the preparation of (a) water-in-oil-in-water (w/o/w) and (b) oil-in-water-in-oil (o/w/o) Pickering double emulsions using the judicious combination of hydrophilic and hydrophobic diblock copolymer worms synthesized by RAFT aqueous dispersion polymerization (G_{37}-H_{60}-B_{30}) and RAFT non-aqueous dispersion polymerization (L_{16}-B_{37}), respectively. Fluorescence microscopy images confirm the successful formation of w/o/w Pickering double emulsions where (c) the aqueous phase is labeled with fluorescein and (d) the *n*-dodecane phase is labeled with Nile Red. Figure adapted with permission from ref. [110].

Finally, Thompson et al. just reported the preparation of *non-aqueous* Pickering emulsions [111]. In this case the water phase is replaced with ethylene glycol, which is immiscible with a wide range of *n*-alkanes. Interestingly, judicious selection of an appropriate *n*-alkane with approximately the same refractive index as that of ethylene glycol enables the production of *near-isorefractive* emulsions. More specifically, emulsification of ethylene glycol (EG) with *n*-tetradecane using L_{16}-B_{37} worms dispersed in *n*-tetradecane produces almost transparent EG-in-*n*-tetradecane Pickering emulsions that exhibited up to 81% transmittance across the visible spectrum [111].

5. Summary and Outlook

RAFT dispersion polymerization is an extremely versatile synthetic tool for the formation of block copolymer nanoparticles in non-aqueous media. Initially, the RAFT dispersion polymerization of styrene in ethanol or methanol received considerable attention, with a wide range of block copolymer morphologies being obtained. However, relatively slow rates of polymerizations and substantially incomplete monomer conversions are highly problematic for such formulations and would most likely preclude industrial scale-up. Replacing styrene with benzyl methacrylate as an alternative core-forming monomer for PISA via RAFT dispersion polymerization conducted in *alcoholic* solvents allows more than 95% monomer conversion to be achieved within 24 h at 70 °C. Predictive phase diagrams have been constructed for various PISA syntheses, which is essential for reproducible targeting of the desired pure copolymer morphology. Such a systematic approach is particularly recommended if block copolymer worms are desired, since this morphology usually occupies rather narrow phase space. Like RAFT aqueous dispersion polymerization formulations, the evolution of copolymer morphology from worms to vesicles proceeds via a transient 'jellyfish' structure. A robust synthetic protocol has been established for the formation of relatively small, low-polydispersity vesicles via judicious selection of a binary mixture of a relatively long and a relatively short stabilizer macro-CTA. Initial studies indicate that RAFT *dispersion* polymerization is more efficient than RAFT *solution* polymerization. In particular, analysis of an *isorefractive* PISA formulation utilizing a semi-fluorinated methacrylic monomer in ethanol suggests that significantly more RAFT chain ends survive under the former conditions. Block copolymer worms can form free-standing gels and thermo-reversible worm-to-sphere transitions have been observed for both polar (alcoholic) and non-polar (*n*-alkane) PISA formulations, as judged by DLS, TEM and rheology experiments. Variable temperature ^{1}H NMR and SAXS studies indicate that such transitions involve surface plasticization of the worms, since this leads to a reduction in the packing parameter. Recently, a robust and highly attractive 'one-pot' protocol at high solids has been developed for the synthesis of diblock copolymer spheres via RAFT dispersion polymerization of benzyl methacrylate using a poly(lauryl methacrylate) macro-CTA in mineral oil. Selected diblock copolymer worms and spheres have been evaluated as bespoke Pickering emulsifiers for the production of o/w and w/o emulsions, as well as various multiple emulsions. However, RAFT dispersion polymerization in non-aqueous media remains a relatively unexplored field compared to the corresponding aqueous formulations. In particular, various questions regarding the evolution of copolymer morphology remain unanswered. For example, what happens *during* the PISA synthesis? As a complement to TEM studies, SAXS has proven to be a particularly powerful tool for the characterization of nanoparticle morphologies and also to provide mechanistic information regarding the precise nature of morphological transitions. If SAXS studies were to be conducted *during* RAFT dispersion polymerizations, important additional details concerning the various *in situ* morphological transitions (i.e. sphere-to-worm and worm-to-vesicle) should be forthcoming; this hypothesis is currently being tested in our laboratory. We believe that such research is warranted in order to gain a deeper understanding of PISA syntheses, which is likely to be a pre-requisite for the development of genuine commercial applications for this platform technology.

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Vitae

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