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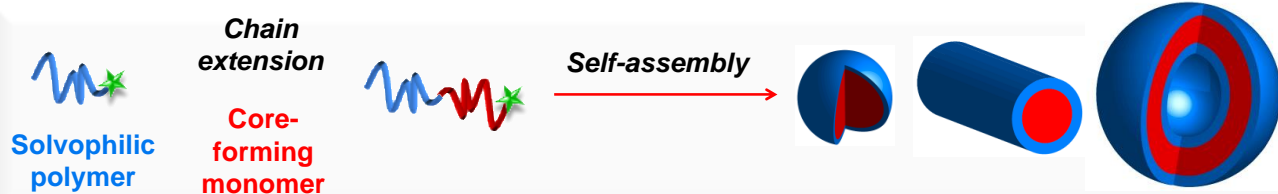
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## RAFT-mediated polymerization-induced self-assembly

Franck D'Agosto,<sup>\*[a]</sup> Jutta Rieger,<sup>\*[b]</sup> Muriel Lansalot<sup>\*[a]</sup>

### RAFT-MEDIATED PISA

versatile  
 By Dispersion In Water  
 By Emulsion One-pot In Organic solvents  
 Broad range of monomers



Particle dispersion latex block copolymers  
 Functional particles various morphologies  
 Surfactant-free High solids

For polymer chemists  
 For physical chemists  
 For physicists

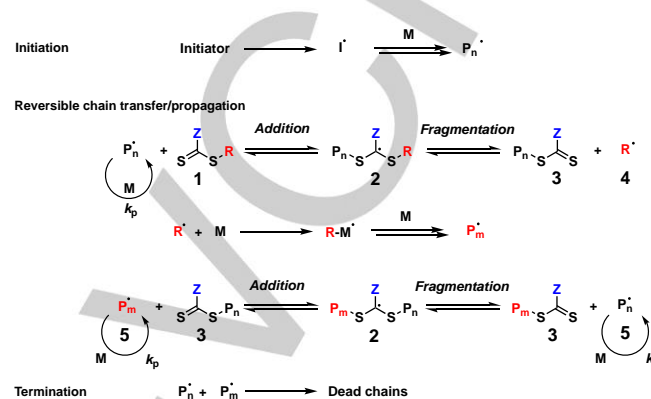
**Abstract:** After a brief history that positions polymerization-induced self-assembly (PISA) in the field of polymer chemistry, this review will cover the fundamentals of the PISA mechanism and review some features and limitations of RAFT-mediated PISA in terms of the choice of the components involved, the nature of the nano-objects that is achievable, the morphologies that are accessible and how they can be controlled, and some potential applications. This review will be part of the forthcoming second edition of 'The Handbook of RAFT' (Wiley, co-edited by G. Moad, E. Rizzardo, S.H. Thang) as a comprehensive chapter on RAFT-mediated PISA.

## 1. INTRODUCTION

There is today no doubt that among the available reversible-deactivation radical polymerization (RDRP) techniques, reversible addition-fragmentation chain transfer (RAFT) is the most versatile and powerful way to combine the tolerance of a radical process with a controlled chain growth for the production of well-defined polymers.<sup>[1]</sup> It proceeds via the use of a low concentration of radical initiator in combination with a comparatively large amount of thiocarbonylthio compounds used as controlling agents (1, R-C(=S)-Z in Fig. 1.). These molecules also called chain transfer agents (CTA) react with the (macro)radicals (5,  $P_n^*$  or  $P_m^*$ ) formed in the presence of monomer according to a reversible addition-fragmentation reaction ensuring an exchange mechanism between dormant chains (3,  $P_n$ -S-C(=S)-Z) and active species (4 and 5) via the formation an intermediate radical (2). The RAFT process thus obeys the same initiation, propagation termination steps as a classical free radical polymerization superimposed to this additional reversible addition-fragmentation steps. If the initiator concentration is low enough, the number of chains is fixed by the CTA concentration, and the majority of the chains possesses the same chemical structure ( $P_n$ -S-C(=S)-Z). This ensures the homogeneity of the chains in terms of molar mass and end-functionality compared to a free radical process. Carrying a thiocarbonylthio moiety on their  $\omega$ -end, the chains are thus reactivatable if they are used as a macromolecular chain transfer agent (macroCTA) for the polymerization of the same or another monomer to allow the formation of block copolymers.

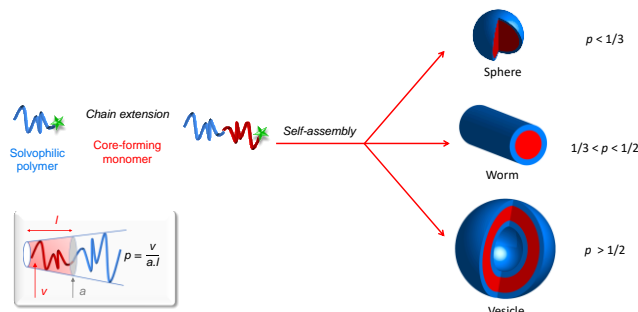
Since the edition of the first handbook on RAFT published by Wiley in 2008,<sup>[2]</sup> RAFT has been confirming its fame and great potential over the existing RDRP techniques. This is attested by

its ever growing interest since the first report on RAFT polymerization in the open literature in 1998,<sup>[3]</sup> and by constantly improving the control on molar mass while expanding the range of controllable monomers<sup>[4-7]</sup>. In addition, the development of RAFT in heterogeneous media<sup>[8]</sup> has provided new tools to design macromolecular objects, contributing to the development of new and original applications.<sup>[9]</sup>



**Figure 1.** Reversible addition-fragmentation chain transfer (RAFT) process.

As we will see in this review, polymerization-induced self-assembly (PISA) is probably the best example of this evolution. Indeed, as mentioned above, the myriad of macromolecular architectures that have been obtained through the use of RDRP techniques lies in the fact that the formed chains can be further extended for the generation of a second block. While this feature was extensively used for the production of block copolymers in solution or bulk polymerizations,<sup>[10, 11]</sup> PISA makes the most of polymerizations in dispersed media, by chain extending a solvophilic polymer obtained by RDRP with a solvophobic block and inducing, concomitantly to the growth of a second solvophobic block, the self-assembly of the resulting block copolymers. This is made possible by the choice of a dispersing phase that is a selective solvent of the first block. As a result, PISA is not only an extremely valuable tool to efficiently produce block copolymers, generally including amphiphilic ones, but has also rapidly reached interest as a technique of choice to form nanoobjects<sup>[12, 13]</sup> that can exhibit various morphologies (Fig. 2).<sup>[14-16]</sup>



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## REVIEW

**Figure 2.** RAFT-mediated polymerization-induced self-assembly and illustration of the packing parameter  $p$  (by analogy to surfactants,  $a$  is the area of the hydrophilic segment and  $v$  and  $l$  are the volume and length of the hydrophobic segment) and the impact of the solvophobic block molar mass on the packing parameter/morphology.

Theoretically, any RDRP technique or living polymerization technique can be selected to produce these block copolymer nano-objects by PISA. Indeed, nitroxide mediated polymerization (NMP),<sup>[14, 17-20]</sup> atom transfer radical polymerization (ATRP)<sup>[21-26]</sup> or Cu-mediated controlled polymerization,<sup>[27]</sup> iodine transfer polymerization (ITP),<sup>[28]</sup> organotellurium-mediated radical polymerization (TERP),<sup>[29-31]</sup> Co-mediated radical polymerization,<sup>[32]</sup> ring-opening metathesis polymerization (ROMP)<sup>[33-36]</sup> or reversible complexation mediated polymerization (RCMP)<sup>[37]</sup> have been successfully implemented. However, RAFT-mediated PISA remains the most employed strategy. In the above-mentioned first book edition in 2008, the pioneering works of Ferguson *et al.*<sup>[38]</sup> on chain extension of preformed poly(acrylic acid) (PAA) macromolecular RAFT agent (macroRAFT) in water with a slow feed of *n*-butyl acrylate (BA) were the only mention to this strategy, not yet called PISA. Since then, the vast majority of the studies conducted on PISA deals with RAFT, which confirms the general adoption of this fast maturing subdiscipline. It is worth mentioning that a process that probably strongly inspired RAFT inventors and called addition-fragmentation chain transfer<sup>[39-42]</sup> (AFCT) exploits the reactivity of radicals towards vinyl moiety such as methacrylates to form an adduct radical that is known to proceed mainly via fragmentation, with a minimal contribution of copolymerization. Although the level of control is not comparable to RAFT carried out in the presence of thiocarbonylthio compounds, it allows the production of block copolymers if the methacrylate controlling agent is carried by a macromolecular chain. It is thus worth mentioning that AFCT-mediated PISA has also recently been investigated<sup>[43-45]</sup> but will not be the focus of the present review.

To date, more than twenty reviews have already been published on PISA, mainly on RAFT-mediated PISA, covering the general concepts of the strategy,<sup>[12, 13, 46-58]</sup> the corresponding design of reactive nano-objects,<sup>[59]</sup> and their biomedical applications.<sup>[60-63]</sup> The aim of this review is thus not to be an additional contribution of this type but rather to provide the reader, both inquirer to the field or experts, with a general overview of the topic. For a detailed account of specific features of RAFT-mediated PISA, the reader should thus be referred to these reviews. After a brief history that positions PISA in the field of polymer chemistry, this review will cover the fundamentals of the PISA mechanism and review some features and limitations of RAFT-mediated PISA in terms of the choice of the components involved, the nature of the nano-objects that is achievable, the morphologies that are accessible and how they can be controlled and some potential applications.

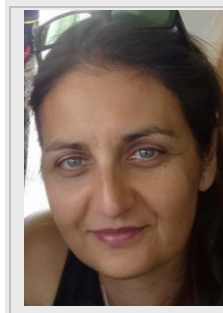
Franck D'Agosto completed a PhD in Polymer Chemistry at the joined unit between CNRS and bioMérieux (University of Lyon, France) before working at the University of Sydney (Australia) as a postdoctoral fellow in the Key Center for Polymer Colloids. Since 2002, he is researcher at the CNRS in the Chemistry and Process of Polymerization Team in C2P2 laboratory (Lyon, France). His research interests focus on the control of polymer architectures by the use of different polymerization chemistries - such as catalytic and controlled free radical polymerizations - either performed in solution or in dispersed media.



Jutta Rieger received her PhD from the University of Liège (Belgium) and the University of Grenoble (France). After a postdoctoral fellowship at ICMMO (Orsay, France) in collaboration with Macopharma, she joined the LCP at UPMC (now Sorbonne University) and started working on RAFT polymerization in heterogeneous media. Since 2009 she is an independent CNRS researcher at IPCM in the same institution. Her current research focuses on the synthesis of functional polymeric materials using homogeneous or heterogeneous controlled radical polymerization processes, and in particular PISA.



Muriel Lansalot completed her doctoral studies on transposition of RDRP (namely nitroxide-mediated polymerization and degenerative transfer) to dispersed media at the University Pierre et Marie Curie (Paris, France) under the supervision of Prof. Bernadette Charleux. After post-doctoral fellowships in France and Australia, she joined the CNRS as a researcher in 2004. Since 2008, she is working at the laboratory for Chemistry, Catalysis, Polymers and Processes (C2P2, Lyon, France), where her research interests focus on both RAFT and conventional free-radical polymerization in dispersed media, directed towards the synthesis of pure polymer and hybrid organic/inorganic particles.



## 2. HISTORY/ORIGINS OF PISA

Block copolymers are very attractive materials that have raised attention in many high-performance applications. These polymers are particularly interesting when the chemical nature of both blocks is such that the corresponding properties are not compatible with each other (polar/apolar, attractive/repulsive, hydrophilic/hydrophobic). The resulting materials generally exhibit



a unique behavior originating from hybrid properties. However, the synthesis of A-B diblock copolymers with such properties is often tricky. In the particular field of amphiphilic block copolymers, the conditions for the preparation of each block are sometimes incompatible and the synthesis of the block copolymer then requires two (or more) steps. The main strategies are (i) the synthesis of one block followed by the initiation of the second block, (ii) the selective post-modification of a preformed diblock copolymer composed of compatible blocks, or (iii) a polymer-polymer coupling reaction. In any case, the choice of the solvent for an efficient chemistry is narrowed by the nature of the monomers involved or the targeted polymers.

PISA can find its origins in different fields of polymer science. Polymer chemists will see in PISA a very original strategy to produce (amphiphilic) block copolymers. Indeed, PISA that can be in essence defined as the self-assembly of (amphiphilic) block copolymers during polymerization is a way to alleviate the problems mentioned above. Works published by polymer chemists almost 25 years ago, exploiting the livingness of poly(*t*-butyl styryl)-lithium chains to initiate the anionic dispersion polymerization of styrene (St)<sup>[64]</sup> or divinylbenzene (DVB)<sup>[65]</sup> in *n*-hexane, did indeed probably pioneer the concept of what is called today a PISA process. More recently, Yamauchi *et al.*<sup>[66]</sup> observed what they named a polymerization-reaction-induced molecular self-assembling process when simultaneously polymerizing isoprene and St in deuterated benzene by living anionic polymerization initiated by *sec*-butyllithium. Indeed, the reactivity ratios are such that a polyisoprene-*b*-polystyrene block copolymer is formed, and the authors set up experiments by means of time resolved SANS measurements to visualize the self-assembly upon the growth of the polystyrene block from the polyisoprene first block.

For the emulsion polymer chemists, however, PISA is the result of constant efforts from researchers in the field of latex synthesis, particularly for coating applications. These efforts were concentrated on both finding appropriate ways to get rid of molecular surfactants and transposing all the features of homogeneous RDRP (solution or bulk) to polymerization in dispersed media.<sup>[8, 67]</sup> As already mentioned, the pioneering works on RAFT-mediated PISA from Hawket and Gilbert<sup>[38]</sup> consisted in the starve-feed addition of BA to an aqueous solution of a PAA macroRAFT. The low solubility of BA in water was sufficient to induce chain extension of PAA and form a PBA block. The resulting PAA-*b*-PBA amphiphilic block copolymers then self-assembled into micellar aggregates that could swell with BA. The polymerization thus quickly switched from the aqueous phase to the particle core with a constant feed of radicals coming from water. These seminal works launched a series of important patents from the University of Sydney related to coating applications.<sup>[68, 69]</sup> It is worth mentioning here that, very soon after the simultaneous discovery of RAFT by Dupont<sup>[70]</sup> and macromolecular interchange of xanthate (MADIX)<sup>[71, 72]</sup> by Rhodia Chimie, and two years before the works patented and published by Hawket and Gilbert,<sup>[38]</sup> Rhodia Chimie patented the use of hydrophilic macroxanthates for particle surface functionalization using however some molecular surfactant in emulsion polymerization.<sup>[1, 73]</sup> These last works clearly did not aim at

producing well-defined block copolymers but targeted the formation of latex particles (formed through conventional emulsion polymerization) stabilized by the *in situ* formation of a fraction of block copolymers, which concomitantly allowed the surface modification of the particles by the hydrophilic macroxanthate structure.

As mentioned in the Introduction, these works performed in aqueous emulsion polymerization were the first PISA systems based on RAFT and more generally speaking on a RDRP technique. RAFT-mediated PISA was then quickly transposed to aqueous<sup>[12, 13, 48]</sup> and organic dispersion polymerization.<sup>[46, 50]</sup>

### 3. THE PISA PROCESS

#### 3.1. Emulsion, dispersion and precipitation polymerizations: The reference processes

As already mentioned, PISA proceeds by polymerization in dispersed media, by the chain extension of a solvophilic polymer obtained by RDRP with a monomer for which the corresponding polymer is not soluble. Emulsion, dispersion and precipitation polymerizations are the three relevant processes to produce polymers in dispersed media and they are briefly depicted below.

- **Emulsion polymerization.** The main ingredients of an emulsion polymerization are water, a water soluble initiator, a surfactant and a hydrophobic monomer, mostly located in micrometric droplets and in nanometric surfactant micelles, with however a slight solubility in water. The decomposition of the initiator in water generates hydrosoluble radicals that start to add monomer units in the aqueous phase and produce oligoradicals. Beyond a critical degree of polymerization, the growing oligomeric species become insoluble and migrate into the monomer-swollen surfactant micelles that then become nucleated particles, where the polymerization continues. This is called micellar nucleation. In the absence of micelles, homogeneous nucleation takes place and consists in the precipitation of these oligomers generating nuclei that are stabilized by the surfactant. Whatever the nucleation, the growing particles are swollen with monomer diffusing from large monomer droplets through the aqueous phase, and the polymerization continues until full monomer consumption. The stability of the final particles is thus achieved by a key component in the process: the surfactant.

- **Dispersion polymerization.** In a dispersion polymerization, the situation is different since the monomer is soluble in the continuous phase, that can be aqueous or organic. However, the corresponding polymer is not. The stability of the nuclei formed upon polymerization is generally ensured by the *in situ* formation of grafted macromolecular stabilizers resulting from chain transfer reactions occurring along solvophilic polymer chains or protective colloids used in the formulation.

- **Precipitation polymerization.** Precipitation polymerization is a particular case of dispersion polymerization for which the monomer does not or poorly swell its polymer. This is for example the case for *N*-isopropylacrylamide (NIPAM) in water for which the

polymerization can be conducted in the absence of surfactant.<sup>[74, 75]</sup>

Replacing the surfactant or stabilizer by a solvophilic chain prepared by RAFT has led to successful PISA under both emulsion and dispersion polymerization conditions, to generate block copolymer particles in a few hours at similar high solids content (up to 50 wt%<sup>[76]</sup>) and under the same undemanding conditions as in emulsion or dispersion polymerization. This is in striking contrast to the strategies used so far to obtain the same nano-objects, such as e.g. the co-solvent method used to self-assemble preformed block copolymers that requires extended periods of time and results in very low polymer concentrations (< 2 wt%).<sup>[77]</sup>

Whatever the polymerization process, most of the studies dealing with PISA employs a preformed, well-defined solvophilic macroRAFT agent. However, several examples showed that this macroRAFT could be synthesized in the same reactor as the solvophobic block. This led to the development of so-called one-pot processes either starting with a hydrophilic monomer such as AA or MAA in water for emulsion,<sup>[56, 78, 79]</sup> or after hydrolysis of a monomer such as glycidyl methacrylate (GlyMA) followed by the RAFT polymerization of the formed glycerol methacrylate (GMA) and dispersion polymerization of hydroxypropyl methacrylate (HPMA),<sup>[80]</sup> or using a monomer soluble in mineral oil, such as lauroyl methacrylate (LMA), in dispersion polymerization.<sup>[76]</sup>

In addition, the simultaneous *in situ* formation and self-assembly in water of amphiphilic block copolymers should give rise to the formation of morphologies that have already been observed when self-assembling preformed block copolymers in a selective solvent of one of the two blocks.<sup>[77]</sup> The full range of expected morphologies (spheres, worms, fibers, vesicles, lamellae) was indeed obtained by RAFT-PISA by varying the nature and molar mass of the solvophilic macroRAFT and of the solvophobic block, and/or the solids content. So far, the vast majority of the non-spherical morphologies have been obtained in dispersion polymerization. The monomer-swollen spherical block copolymer particles initially formed during the process fuse together according to a polymerization-induced reorganization mechanism,<sup>[47]</sup> as visualized in transmission electron microscopy (TEM) studies by Armes and coworkers.<sup>[81]</sup> Although, the same process could take place in emulsion polymerization,<sup>[82-87]</sup> kinetically trapped spheres are most of the time obtained.<sup>[88-91]</sup> (see section 5).

### 3.2. The main parameters at play for a successful PISA at a glance

- **MacroRAFT type.** Whatever the polymerization process (emulsion, dispersion, precipitation) the large majority of the solvophilic macroRAFT employed are based on dithioesters or trithiocarbonates. A slight preference goes to trithiocarbonates when water is used as the dispersing phase, since these compounds have been shown to be less sensitive to hydrolysis. As a result, almost all the papers published on RAFT mediated PISA deal with the formation of solvophobic blocks from more activated monomers. Indeed, as far as we know, only five papers depict the use of solvophilic macroRAFT carrying a

dithiocarbonate chain end for the formation of block copolymer particles based on less activated monomers such as vinyl acetate (VAc)<sup>[92-94]</sup> or *N*-vinylcaprolactam.<sup>[94-96]</sup>

- **Initiation in RAFT-PISA.** Contrary to other RDRP techniques such as NMP or ATRP for instance, RAFT generally requires an external source of radicals usually provided through the decomposition of organic molecules under thermal-, redox- or photo-activation. The initiating step in RAFT is complex and the control partly depends on the fine tuning of the relative amounts of initiator and chain transfer agent. This is a disadvantage compared to other techniques, particularly when considering block copolymer syntheses and particularly PISA. Indeed, the formation of the second block will be unavoidably accompanied by the formation of its homopolymer as a side product, which may impact the efficiency of the self-assembly. In emulsion polymerization for example, the desired block copolymer self-assembly may thus compete with homogeneous nucleation leading to precipitation of solvophobic oligomers. This situation is indeed also favored when the chain transfer efficiency to the solvophilic macroRAFT is too low.<sup>[84]</sup> This is however not the case for the vast majority of RAFT-mediated PISA studies. Regardless whether PISA is performed in emulsion or dispersion, the initiator concentration is generally optimized like in conventional RAFT to minimize the quantity of homopolymer produced. As demonstrated by the successful PICA (polymerization-induced cooperative assembly) process (detailed below) for which the formation of the homopolymer is exacerbated, this low proportion of homopolymer probably helps in the nucleation of the block copolymer particles. It is worth mentioning here that promoting the formation of homopolymer to the detriment of block copolymer is not without interest as it may boost up the development surfactant-free emulsion polymerization based on PISA,<sup>[56]</sup> as discussed in section 3.4.

In conclusion, most of the conventional initiators employed to conduct conventional emulsion or dispersion polymerization such as azo-initiators or photoactive molecules can be employed to perform RAFT-PISA. When the dispersing phase is water, ionic azo-initiators or persulfates are preferred.

Photoinitiators can also be used in PISA<sup>[55]</sup> under appropriate irradiation conditions using UV<sup>[97]</sup> or visible light.<sup>[98]</sup> Original and efficient photoinitiating systems based on horseradish peroxidase have also been successfully developed in combination with hydrogen peroxide and ascorbic acid.<sup>[99]</sup> A way to get around the additional use of free radical initiator can be the recourse to photoinitiated systems (photo-induced electron/energy transfer RAFT (PET-RAFT)) in absence of molecular photoinitiators (iniferter type RAFT). Indeed, the photosensitivity of the thiothiocarbonylated chain ends of the solvophilic macroRAFT can also be exploited, circumventing the undesired formation of homopolymer when targeting block copolymers. In this case, visible light is preferred over UV to keep the integrity of the RAFT end all along the PISA process.<sup>[100, 101]</sup> It is worth mentioning here that the livingness is not necessarily better in these last systems as termination does lead to loss of RAFT moieties, while it does not with normal RAFT.

- **Chemical nature of the blocks.** The solvophilic macroRAFT can be obtained by post-modification of a preformed polymer as

observed when poly(ethylene glycol) (PEG) or polydimethylsiloxane is employed for example. It is however generally obtained by RAFT polymerization of the corresponding solvophilic monomer either performed in organic solution, purified and redissolved in the continuous phase, or directly in water. As mentioned above, a one-pot strategy, for which the whole PISA process is performed in the same solvent and reactor, is thus possible.<sup>[76, 78-80]</sup> The solvophobic core monomer is selected with respect to the nature of the thiothiocarbonyl chain end of the solvophilic macroRAFT to ensure a good blocking efficiency<sup>[10, 11]</sup> and thus a fast reinitiation (fast consumption of the starting macroRAFT) that often favors the homogeneity of the resulting block copolymer particle size and morphology.

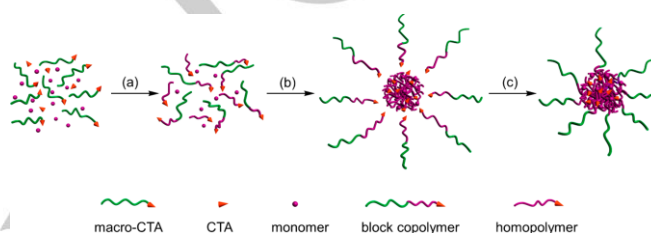
The remainder of the present review will provide the reader with a representative range of solvophilic monomers and macroRAFT, solvophobic monomers and solvents to perform RAFT-PISA.

### 3.3. PITSA, PICA, PIESA, PIHSA: Different acronyms however all boiling down to PISA

The vast majority of the RAFT-PISA systems are operating according to the process explained above, *i.e.* chain extension of a preformed solvophilic macroRAFT with a solvophobic block either by emulsion or dispersion polymerization. However, considering the tremendous amount of systems and operating conditions used to conduct RAFT-PISA, the researchers sometimes observed peculiar behaviors and different acronyms related to PISA can be found in the literature.

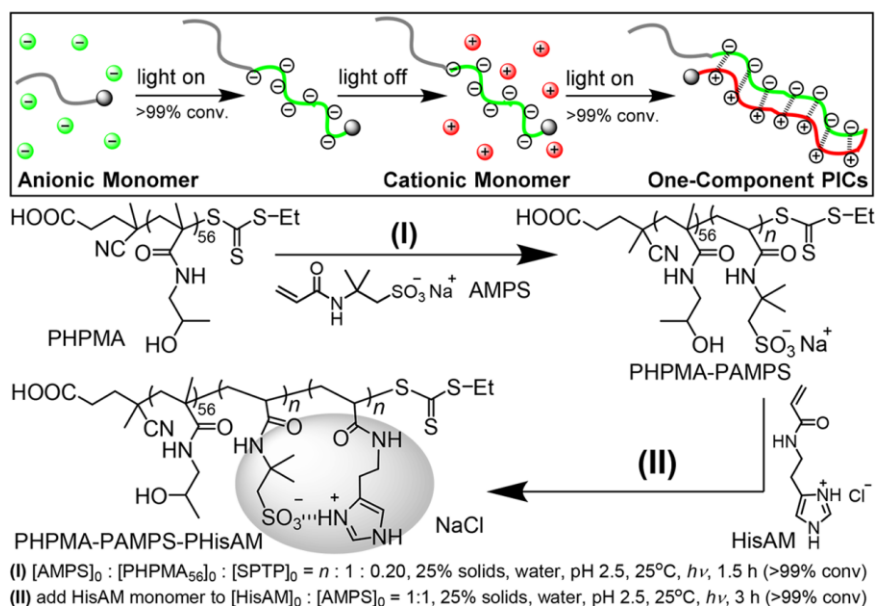
Polymerization-induced thermal self-assembly (PITSA) was coined by Figg *et al.*<sup>[102]</sup> but developed for the first time by An *et al.*<sup>[103]</sup> Starting from a poly(*N,N*-dimethyl acrylamide) (PDAAm) macroRAFT, NIPAM was polymerized under precipitation conditions in the presence of a crosslinker in water at 70 °C. The chain extension, performed above the LCST of PNIPAM, led to the self-assembly of the resulting PDMAAm-*b*-PNIPAM triggered both by the growth of the hydrophobic PNIPAM block and the polymerization temperature. Compared to particles formed by PISA, PITSA results in amphiphilic block copolymer assemblies that disassemble by cooling the resulting nanoobject dispersion

and thus requires crosslinking during the block copolymer particles formation to keep their integrity at room temperature. Polymerization-induced cooperative assembly (PICA) was recently coined by Zhu *et al.*<sup>[104]</sup> and contemporaneously reported by Tan *et al.*<sup>[105, 106]</sup> It consists in performing RAFT-PISA in the presence of both a macroRAFT and a molecular RAFT agent (Fig. 3). Consequently, amphiphilic block copolymers form simultaneously to a solvophobic homopolymer, and particles are generated from homopolymer-based nuclei stabilized by amphiphilic block copolymers. The additional presence of homopolymer can to some extent help the transition from the spherical morphology to higher order morphologies as explained in section 5.3.



**Figure 3.** Polymerization-induced cooperative assembly (PICA). Reprinted with permission from reference<sup>[104]</sup> Copyright 2017, American Chemical Society.

PIESA stands for polymerization-induced electrostatic self-assembly. It consists in synthesizing a double hydrophilic block copolymer by RAFT in water in which the second block is a polyelectrolyte. The self-assembly is then induced by *in situ* polyion complexation either by the presence of a preformed polyelectrolyte homopolymer during PISA<sup>[107, 108]</sup> and the growth of a polyelectrolyte block of opposite charge from the macroRAFT, or by the chain extension of the resulting soluble diblock copolymer with a monomer of opposite charge.<sup>[109]</sup> In this last case, this leads to the formation of a third block strongly interacting upon its growth with the second block through electrostatic interactions inducing the self-assembly (Fig. 4).



**Figure 4.** Polymerization-induced electrostatic self-assembly (PIESA). Reprinted with permission from reference <sup>[109]</sup> Copyright 2018, American Chemical Society.

Eventually, polymerization-induced hierarchical self-assembly (PIHSA)<sup>[110]</sup> was performed in ethanol by chain extending a poly(methacrylic acid) (PMAA) macroRAFT with a monomer containing an azobenzene side-group. While the formed block copolymers self-assemble as a result of the solvophobicity of the second block, the liquid crystalline property of the azobenzene group allows the core block to organize at the same time. This system not only consists in hierarchical self-assembly leading to formation of unconventional morphologies and their transitions (cuboids, short belts, ellipsoidal vesicles) but also produces light sensitive nano-objects thanks to the configuration switch of the azobenzene group (see section 5.3.1).

### 3.4. PISA-inspired synthesis of surfactant-free latexes

In the first works reporting the use of macroRAFTs to mediate polymerization in dispersed media, the main motivation was to introduce a reactive stabilizer, which was covalently anchored to the final latex particles, or to functionalize the particle surface (a molecular surfactant being still present) with less emphasis placed on their ability to control the polymerization of the core-forming block. With this in mind, PISA has been used for the synthesis of polystyrene (PS) particles using macroRAFT of polysoaps,<sup>[111]</sup> poly(2-diethylaminoethyl methacrylate) (PDEAEMA),<sup>[112]</sup> poly(ethylene oxide) (PEG), poly(2-dimethylaminoethyl methacrylate) (PDMAEMA) and PEG-*b*-PDMAEMA,<sup>[113]</sup> or PMAA,<sup>[114]</sup> PVAc particles using a dextran-based macroxanthate<sup>[92]</sup> or PBA particles from a galactopyranose-functionalized poly(*N*-acryloylmorpholine) (PNAM) macroRAFT<sup>[115]</sup> have also been reported. These latter systems involved low amount of macroRAFT, high amount of

initiator and/or the use of macroRAFT with a poor reinitiation efficiency.

The PISA process can thus also provide a valuable pathway of performing surfactant-free emulsion polymerization, expanding the range of strategies based on the use of reactive surfactants that have been investigated for many years.<sup>[116]</sup> It is worth mentioning here that most of the PISA systems reported in the literature require important amount of solvophilic species, typically 3 to 15 wt% with respect to the core-forming polymer. Considering the restrictions on the use of low molar mass surfactants, using low amount of macroRAFT consists in an interesting and economically viable approach to synthesize high solids content surfactant-free latexes. So far, little attention has been paid to produce such industrially relevant colloidal formulations. For instance, Lansalot, D'Agosto and coworkers recently demonstrated that different kinds of latex particles (40 wt.% solids), incorporating less than 2 wt.% of hydrophilic PEG, PAA, PMAA or poly(sodium 4-styrene sulfonate) (PSSNa), could be produced using this strategy, starting from the corresponding hydrophilic macroRAFT agent: poly(vinylidene chloride),<sup>[117, 118]</sup> poly(vinylidene fluoride) (PVDF)<sup>[119]</sup> and acrylic latexes.<sup>[120-123]</sup> In the latter case, it was also demonstrated that the strategy was compatible with well-established film crosslinking strategies (namely, 2-(acetoacetoxy)ethyl methacrylate (AAEM)/hexamethylenediamine, and diacetone acrylamide (DAAm)/adipic acid dihydrazide (ADH)) and that water barrier properties of the resulting films could be improved with regard to the use of low molar mass surfactants. Using a similar low quantity of stabilizer, Rieger and coworkers had prepared PAA-*b*-PBA latex nanoparticles<sup>[124]</sup> to create soft films<sup>[125]</sup> possessing a percolating network of PAA which allowed to combine high stiffness with extensibility in addition to water-and solvent resistance.<sup>[126]</sup>



## 4. REACTIVE/FUNCTIONAL NANO-OBJECTS

As demonstrated in the previous sections, the focus of PISA was initially the control of the macromolecular architecture via heterogeneous polymerization processes, progressively associated with the control of particle morphology. The robustness of the PISA process has now opened up many possibilities to provide the nano-objects with reactivity and/or functionality, which can be introduced at various stages of the process: in the initial RAFT agent, in the macroRAFT and/or in the particle core. Whatever the chosen strategy, the aim is either the introduction of a specific function for a specific goal or a targeted application, or the incorporation of reactive groups allowing post-synthesis modification of the particles by further coupling or crosslinking reactions. Both options can also be combined. In addition, many studies report the introduction of functional groups able to induce morphological transitions and these examples are discussed in section 5. Moreover, potential applications of the formed nano-objects are sometimes mentioned in the present section, even if those developed for very specific applications (e.g. catalysis, bioimaging) are presented in more details in section 6. As mentioned in the Introduction, PISA is a rapidly expanding field, and the literature is regularly enriched with new studies. Our aim is not to provide an exhaustive list of all the functional particles already prepared by PISA, but rather to provide the reader with some specific examples illustrating the different synthetic strategies. A thorough review on the synthesis of reactive and functional nano-objects has recently been published by Delaitre and coworkers.<sup>[59]</sup>

Most of the examples detailed below rely on either dispersion or emulsion polymerization. However, for the sake of simplicity, the process used in each case is not systematically indicated.

### 4.2. Via the solvophilic block: functionalization along the shell polymer

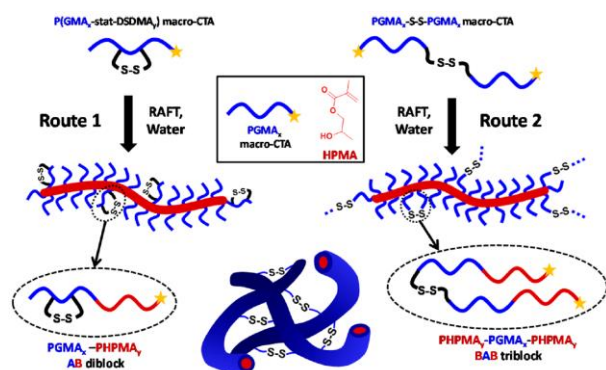
An easy way to produce particles with a functional shell is to use a RAFT agent with a functional R reinitiating group, producing solvophilic polymers with functional  $\square\square$  ends. In most cases, the goal is to functionalize the particle surface. One of the very first works reporting the synthesis of surface-functional particles relying on this strategy was made by An *et al.*,<sup>[127]</sup> who used an azido-functionalized RAFT agent to prepare poly(*N,N*-dimethyl acrylamide) (PDMAAm) polymers then used for the aqueous microwave-assisted polymerization of NIPAM in the presence of *N,N'*-methylene bisacrylamide as a crosslinker. The surface reactivity of the obtained nanogels (size < 100 nm) was demonstrated via copper-catalyzed azide-alkyne cycloaddition with a dansyl probe, leading to the production of fluorescent particles. Later on, alkoxyamine-functionalized particles were prepared by St Thomas *et al.* starting from a symmetrical trithiocarbonate holding two alkoxyamine moieties.<sup>[128]</sup> The PAA macroRAFT prepared from this RAFT agent was used for the synthesis of triblock copolymer nanoparticles of either PS or PBA in water. NMP of either St or SSNa was then triggered from the particle surface, leading to morphological changes under certain conditions. Aiming at the synthesis of building blocks for larger

supramolecular structures, Ebeling *et al.*<sup>[129]</sup> have recently reported the synthesis of PS particles carrying naphthalene units initially present at the  $\alpha$ -chain end of the macroRAFT agent. They overcame the challenge to localize an intrinsically hydrophobic moiety at the surface of particles dispersed in water, by using charged PAA as a stabilizer. Similarly, György *et al.*<sup>[130]</sup> aimed at inserting one reactive epoxy group per chain on average in the shell of poly(benzyl methacrylate) (PBzMA) nanospheres, either with an epoxy-functional RAFT agent or through a stepwise copolymerization strategy using GlyMA as a comonomer. They demonstrated that the epoxy function was much more resistant towards hydrolysis when it was inserted within the polymer chain than when it was exposed at the  $\alpha$ -chain end. Amine or carboxylic acid functionalities were then introduced via reaction of the epoxy groups with various thiols.

### 4.3. Via the RAFT agent: functionalization of the $\alpha$ -end of the shell polymer

Unlike the previous approach that allows functionalization of the  $\alpha$ -end of the solvophilic block only, the use of functional monomers leads to the introduction of reactive/functional groups, distributed along the solvophilic block, increasing the density of functional groups of the particle surface. It also broadens the range of accessible functionalities. Again, the aim is to design shell-functionalized nano-objects, which are sometimes further crosslinked to freeze their morphology or to design nano-objects for specific applications.

• **A variety of functions.** Two strategies were developed by Warren *et al.* to introduce disulfide groups at the surface of PGMA-*b*-PHPMA diblock copolymer worms, allowing the introduction of a latent thiol functionality (Fig. 5).<sup>[131]</sup> In the first route, a disulfide dimethacrylate (DSDMA) was copolymerized with GMA, while the second one involved the use of a bifunctional disulfide-based RAFT agent (DSDB). Each of these macroRAFT was used in varying proportions with a non-functional PGMA macroRAFT for HPMA dispersion polymerization leading to different disulfide-functionalized worm gels. For both kinds of formulation, it was shown that higher disulfide contents led to stronger gels, presumably as a result of inter-worm covalent bond formation via disulfide/thiol exchange. The gels produced by the DSDMA strategy are promising materials to prepare thermoreversible 3D matrix for sheet-based cell cultures.<sup>[132]</sup> DSDMA was also used to produce thiol functionalized vesicles.<sup>[133]</sup> Indeed, the reductive cleavage of the disulfide bonds generates thiol groups that readily react with an acrylate containing a quaternary ammonium to produce cationic vesicles, or with a Rhodamine B isothiocyanate reagent to produce fluorescent vesicles. In the former case, drug delivery applications were targeted because enhanced muco-adhesion was anticipated for these cationic vesicles. Core-crosslinked thiol-functional vesicles were also readily prepared by the addition of ethylene glycol dimethacrylate at the end of the polymerization of HPMA.



**Figure 5.** Incorporation of disulfide functionality into PGMA-*b*-PHPMA worm gels using either a disulfide-based methacrylate (DSDMA) or a disulfide-based RAFT agent (DSDB). Reprinted with permission from reference [131] Copyright 2015, American Chemical Society.

Targeting a cheaper and more straightforward synthetic strategy, another approach was developed by Armes' group to introduce disulfide groups at the outer surface of worms. Ratcliffe *et al.*<sup>[134]</sup> prepared epoxy-functionalized worm particles of P(GMA-*co*-GlyMA)-*b*-PHPMA that were reacted with cystamine allowing the introduction of disulfide groups in the worm shell. The simultaneous formation of secondary amine groups conferred a cationic character to the nano-objects in water. Depending on the cystamine/epoxy molar ratio either covalently crosslinked disulfide-bridged worm gels (stoichiometric amount) or linear primary amine-functionalized worm gels (large excess of cystamine) were obtained. Again, such amine-functional hydrogels are expected to offer enhanced mucoadhesive properties.

Yao *et al.*<sup>[135]</sup> used a similar approach to form vesicles of P(GMA-*co*-GlyMA)-*b*-PHPMA however decorated with  $\beta$ -cyclodextrin ( $\beta$ -CD) *via* reaction of the epoxy groups with amine-functionalized  $\beta$ -CD. Taking advantage of the host-guest chemistry operating between  $\beta$ -CD and azobenzene groups, azobenzene-functionalized PEG chains were attached to the vesicle surface, inducing morphological transition to worms and/or spheres.

Thiol-ene chemistry was also investigated. Oleic acid decorated nano-objects of various morphologies were first synthesized using a macroRAFT of poly(2-(methacryloyloxy)ethyl oleate) for BzMA dispersion polymerization in *n*-heptane.<sup>[136]</sup> Alkyl, carboxyl, hydroxyl and protected amine functionalities could then be introduced onto the particle surface *via* reaction of the corresponding thiols with the pendant double bond of the stabilizer.

Core-shell particles with an organic photosensitizer incorporated in the shell were recently prepared by Save and Lacombe.<sup>[137]</sup> Indeed, a photoreactive monomer, 2-Rose Bengal ethyl acrylate, was successfully incorporated in the PAA shell of PBA particles, which were then used to produce photoactive films exhibiting photo-oxidation activity.

Finally, a last example worth to be mentioned reports the possibility to produce shell-crosslinked spheres using DAAM as the shell constituting monomer.<sup>[138]</sup> Polymerization of *tert*-butyl acrylate led to the formation of various particle morphologies, the shell of which could be crosslinked *via* a ketone-amine reaction.

• **Surface functionalization by sugar moieties and amino acids.** PISA has also revealed to be a powerful tool to produce particles stabilized by various polysaccharides or glycopolymers. Ting *et al.*<sup>[139]</sup> prepared a macroRAFT from a glucopyranose-based methacrylamide, that was subsequently used for the synthesis of PS particles crosslinked with a degradable disulfide crosslinker, thus enabling eventual degradation to the corresponding linear glycopolymers by a reductant for drug release application. Effective degradation of the particles by a thiol reagent and successful binding of lectins to the glucose moieties were both demonstrated. Ladmiraal *et al.*<sup>[140]</sup> later used a similar approach with a galactose-based methacrylate for the shell and HPMA for the core to form particles of various morphologies. The availability of the galactose moieties on the particle surface was confirmed by effective interaction with galectins, and the vesicles proved to be biocompatible and allowed intracellular delivery of encapsulated Rhodamine B. Another variety of carbohydrate functional PS nanoparticles was successfully obtained from glycuronan macromonomers derived from alginates.<sup>[86]</sup> The synthesis of xyloglucan (XG) functionalized poly(methyl methacrylate) (PMMA) particles, a natural hemicellulose, was also recently reported.<sup>[141]</sup> In this case XG was functionalized with a dithioester chain end and used for MMA emulsion polymerization. Relying on the known affinity of XG for cellulose, XG-PMMA particles were adsorbed on various cellulosic substrates.

Another class of functional particles of interest is the one decorated with amino acids. In the first system studied by Ladmiraal *et al.*,<sup>[142]</sup> cysteine (Cys) or glutathione (GSH)-based solvophilic macroRAFT were prepared from the corresponding methacrylic monomers. They were then chain extended with a PHPMA block to produce nano-objects of various morphologies. The obtained worm aqueous dispersions formed soft free-standing thermoresponsive gels that underwent degelation on cooling resulting from worm to sphere transition. In the second system developed by Bauri *et al.*<sup>[143]</sup> a side-chain L-alanine containing macroRAFT was used to form PBzMA particles of various morphologies. One of their formulations led to pure worms forming a free-standing gel, but in this case degelation occurred upon heating. Besides, the molecular chirality coming from the L-alanine groups was maintained in the polymer, and the hydrogen bonding interactions between these side-chain chiral amino acids in the fibers led to the formation of one-handed helical ropes through the hierarchical self-assembly of the block copolymers nanofibers. Finally, films made from such diblock copolymers formed a wrinkle surface where the fibers were twisted and weaved together. Such nanostructured materials could for instance be applied in adhesive materials or to create platforms for tissue engineering and enhanced cell growth.

• **Fluoroparticles.** A few groups also worked on the introduction of fluorinated moieties in the particle shell. For instance, Pei *et al.* prepared particles with pentafluorophenyl (PFP) shell-units.<sup>[144]</sup> Passerini reaction-derived methacrylates containing PFP groups were first copolymerized with DMAEMA. The use of the obtained macroRAFT for dispersion polymerization of 3-phenylpropyl

methacrylate resulted in the formation of different particle morphologies. Reaction of the PFP residues with various functional thiols allowed the preparation of surface-modified nanoparticles. The same group also described the synthesis of pentafluorophenyl methacrylate (PFPMA)-decorated particles, and their shell-functionalization using various primary amines.<sup>[145]</sup> In the study from Shen *et al.*,<sup>[146]</sup> fluoro moieties were introduced both in the shell and the core of different particles. In all cases, the core was composed of poly(heptadecafluorodecyl methacrylate) (PHDFDMA), which is a semi-fluorinated liquid-crystalline (SFLC) polymer. Dispersion polymerization to form the particles was performed in various solvents using various macroRAFT, *i.e.* PEG, PDMAEMA, PMMA, poly(stearyl methacrylate) (PSMA) and finally poly(2,2,2-trifluoroethyl methacrylate) (PTFEMA). Thus, depending on the molar mass of the blocks, PTFEMA-*b*-PHDFDMA ellipsoidal nanoparticles and vesicles comprising two different semi-fluorinated blocks (respectively amorphous and crystalline) could be obtained through dispersion polymerizations performed in DMF. Finally, an interesting study reported the formation of particles with a fluorinated shell for imaging purposes.<sup>[147]</sup>

- **PISA and CO<sub>2</sub>.** Supercritical carbon dioxide (scCO<sub>2</sub>) is an attractive alternative solvent for dispersion polymerization. Fluorinated stabilizers have shown their ability to provide efficient steric stabilization to prevent particle aggregation in scCO<sub>2</sub>, and of course, the use of fluorinated macroRAFT was investigated in PISA. The very first report was made by Zong *et al.*<sup>[148]</sup> who used a poly(1*H*,1*H*,2*H*,2*H*-perfluorooctyl methacrylate) (PFOMA) macroRAFT to mediate MMA dispersion polymerization in scCO<sub>2</sub>. Micrometric spherical particles with a broad size distribution and stabilized by a fluoro-shell were obtained. The presence of fluorine inside the particles was also shown indicating that scCO<sub>2</sub> acted as a compatibilizer between the PFOMA and PMMA phases. More recently, Xu *et al.* also reported MMA dispersion polymerization in scCO<sub>2</sub>, but using a poly(dodecafluoroheptyl methacrylate) macroRAFT.<sup>[149]</sup> The influence of the molar mass of both blocks as well as the pressure was studied, and nanoparticles with low size distribution were formed in the best cases, with particle sizes ranging from 80 to 260 nm depending on the block copolymer composition.

CO<sub>2</sub> has also been used to tune particle morphology. A macroRAFT of poly(4-vinylpyridine) (P4VP) was used to mediate the dispersion polymerization of styrene in isopropanol, without CO<sub>2</sub> or with a low pressure of CO<sub>2</sub> (8.0 MPa, *i.e.* 80 bar).<sup>[150]</sup> The presence of CO<sub>2</sub> had a strong effect on the particle morphology. Indeed, the properties of the continuous phase are altered by generating a gas expanded liquid in the presence of CO<sub>2</sub>, and the formation of nano-objects with a high interfacial core/corona curvature was favoured relative to the corresponding system without CO<sub>2</sub>, *e.g.* rods were formed (with CO<sub>2</sub>) under conditions where vesicles (no CO<sub>2</sub>) would otherwise form. In a later work, the same team used a CO<sub>2</sub>-responsive macroRAFT (namely a statistical copolymer comprising *N,N*-diethylaminoethyl methacrylate (DEAEMA) and poly(ethylene glycol) methyl ether methacrylate ( $M_n = 475 \text{ g mol}^{-1}$ )) for the dispersion polymerization of 2-hydroxypropyl methacrylate in water and water/MeOH.<sup>[151]</sup>

Pressurization with CO<sub>2</sub> led to protonation of DEAEMA units, thereby offering a means of adjusting the charge density of the stabilizing layer. The authors demonstrated that a wide range of tunable particle morphologies were accessible by simply varying the CO<sub>2</sub> pressure during polymerization in the range of 10–45 bar. CO<sub>2</sub> use was also valued in a different way, by the preparation of CO<sub>2</sub>-responsive particles. Among other approaches, PISA has been used for the synthesis of CO<sub>2</sub> switchable latexes. The team of Cunningham<sup>[152]</sup> used a PDEAEMA macroRAFT for the synthesis of PS or PMMA particles, with a shell which was both pH and CO<sub>2</sub>-responsive, which are actually related properties. The tertiary amine groups of the DEAEMA units can be protonated by introducing CO<sub>2</sub> and reversibly deprotonated by CO<sub>2</sub> removal allowing particle coagulation/redispersion cycles.

#### 4.4. Via the solvophobic block: core functionalization

Most of the reported works dealing with core functionalization aim at introducing specific functional groups inside the particle core and/or provide enhanced particle stabilization by core-crosslinking. In essence, the thiocarbonylthio chain end of the polymer chains is buried inside the particles formed by PISA. One of the most straightforward ways to introduce functionality inside the particle core thus consists in converting this chain end into a thiol. An *et al.* used this strategy to functionalize the PNIPAM-core-crosslinked/PDMAAm-shell particles discussed above in section 4.1.<sup>[127]</sup> Before surface functionalization with dansyl probes, the core was functionalized with fluorescein groups by one-pot aminolysis (with 2-hydroxyethylamine)/Michael addition (with fluorescein *o*-acrylate). In most cases though, functionalization comes from the use of a functional comonomer in the core formation step, allowing access to a broad range of nano-objects.

- **Fluoroparticles.** A significant amount of work has been dedicated to the synthesis of fluorine-core containing particles, one of the main goals being the preparation of (super)hydrophobic surfaces (SHS). In the study from Shen *et al.* described above for shell functionalization,<sup>[146]</sup> fluoro moieties were present in the core of different PHDFDMA particles prepared from macroRAFT of PEG, PDMAEMA, PMMA, PSMA and PTFEMA. Depending on the macroRAFT, particles with different properties could be obtained. Indeed, the core was in all cases crystalline, whereas the shells could be either amorphous (PDMAEMA, PMMA and PTFEMA) or crystalline (PEG and PSMA). The liquid crystalline nature of the core-forming PHDFDMA was responsible for the general formation of non-spherical morphologies. The PHDFDMA containing nanoparticles demonstrated to be robust Pickering emulsifiers leading to the formation of several types of stable oil-in-water or oil-in-oil emulsions.

PTFEMA can also be used as core forming block.<sup>[90]</sup> The aim of the study was to design particles with a high core mass density to determine the effective particle density and the thickness of the PGMA stabilizer layer using both SAXS and disk centrifuge photosedimentometry. The same core polymer was used for the formation of PMAA-*b*-PTFEMA<sup>[153]</sup> and PMAA-*b*-PBzMA-*b*-PTFEMA<sup>[154]</sup> particles. PTFEMA was also selected to prepare



SHS.<sup>[155]</sup> A copolymer of 4-vinyl pyridine (4VP) and vinyl triethoxysilane (VTES) in which the 4VP units were quaternized was used for the emulsion polymerization of TFEMA. The particles were thus not only core-functionalized, but also possessed shell-reactive groups. Indeed, the VTES units allowed further grafting of silica nanoparticles onto the particles. The film formed from these hybrid latexes exhibited a nanostructured surface and modification with fluorinated trichlorosilane led to SHS. Such coatings were also prepared from spin-coating of a mixture of PMAA-*b*-PBA-*b*-P(BA-co-FDA) nanoparticles and silica beads (with FDA: 1*H*,1*H*,2*H*,2*H*-perfluorodecyl acrylate).<sup>[156]</sup> In the study of Qiao *et al.*, a symmetrical RAFT agent was used to prepare triblock copolymer nanoparticles of poly(acrylic acid)-*b*-poly(2,2,3,3,4,4,4-hexafluorobutyl acrylate)-*b*-poly(acrylic acid).<sup>[157]</sup> Transparent films with elastomer properties were obtained from these latexes, and further thermal annealing provided hydrophobic coatings.

Another very interesting fluoropolymer is PVDF. The only attempt to perform PISA starting from VDF was recently reported by Guerre *et al.*<sup>[158]</sup> PVAc-*b*-PVDF block copolymers were formed in dimethyl carbonate (DMC). The occurrence of head-to-head additions for both VAc and VDF homopolymerization, combined with transfer to DMC in the case of VDF, however led to the concomitant formation of PVAc and PVDF homopolymers. Nevertheless, original micrometric (1-5  $\mu$ m) ovoidal flake morphologies, able to stack on each other, were observed, likely driven by PVDF crystallization.

Finally, two recent studies describe the synthesis of reactive fluorinated core-crosslinked block copolymer particles. Couturaud *et al.*<sup>[159]</sup> proposed the use of a linear PEG macroRAFT for the polymerization of PFPMA as a core monomer yielding spherical particles. Similarly to the work of Pei *et al.* discussed above for shell functionalization,<sup>[145]</sup> the particles could be crosslinked after polymerization by reaction of the PFP groups with diamines and thus remained stable in water. In particular, the use of cystamine allowed the formation of redox responsive particles, which could be disassembled by the addition of glutathione. These core-crosslinked micelles also demonstrated cytocompatibility. Alternatively, Busatto *et al.*<sup>[160]</sup> reported the dispersion polymerization of 2,3,4,5,6-pentafluorobenzyl methacrylate mediated by a PPEGMA macroRAFT. Depending of the respective molar mass of both blocks, the particles exhibited spherical, worm-like, or vesicular morphologies. Thermoreversible morphological changes were observed, notably worm-to-sphere transitions. The morphology could however be locked by crosslinking reaction through thiol-*para*-fluoro substitution reactions using dithiols, enabling the morphology to be maintained across a temperature range and in nonselective solvents.

• **Core-crosslinking.** One of the very first examples reporting core-crosslinking, where the aim was to freeze particle morphology, was published by Zheng and Pan.<sup>[161]</sup> A PS macroRAFT was used for the dispersion copolymerization of 4VP and DVB in cyclohexane. Since then, and as mentioned above, crosslinking has been the focus of many studies dealing with core functionalization. While in the previous section GlyMA was used

in many instances to introduce reactive epoxy groups in the particle shell, it can also be used for core functionalization. It was the case in the work of Lovett *et al.*<sup>[162]</sup> who prepared PGMA-shell/P(HPMA-co-GlyMA)-core worms. The epoxy groups could be ring-opened using 3-aminopropyltriethoxysilane (APTES) in order to prepare core-crosslinked worms *via* hydrolysis-condensation with siloxane groups and/or hydroxyl groups on the HPMA residues. The ring opening and crosslinking reactions occurred on similar time scales. Crosslinking led to stiffer worm gels which remained intact when exposed to methanol or an anionic surfactant. In addition, the worm aspect ratio could be tuned by the temperature at which APTES is added, and the cross-linked worms were evaluated as emulsifiers for the stabilization of *n*-dodecane-in-water emulsions.<sup>[163]</sup> A similar study was conducted with vesicles crosslinked by addition of various diamines.<sup>[164]</sup> More recently, Armes' group was able to produce PGMA-*b*-PGlyMA block copolymer nanoparticles by emulsion polymerization, preserving most of the epoxy groups from hydrolysis.<sup>[91]</sup> A third PBMA block could also be attached to the PGlyMA one. For PGMA-*b*-PGlyMA, reaction with NaN<sub>3</sub> provided azide-functional nanoparticles, and the possibility to crosslink the particle core by the addition of diamines was evidenced. Interestingly, using a shorter PGMA block led to the formation of worms, a morphology that is not very often obtained by emulsion polymerization.<sup>[165]</sup> Subsequent reaction with 4-amino-2,2,6,6-tetramethylpiperidin-1-oxyl produced crosslinked worms bearing a high local concentration of stable nitroxide groups within the worm cores. Such anisotropic nanoparticles could offer potential applications for charge storage and transport. In all of these studies, some residual pendent amine groups could be protonated to provide cationic nano-objects. In the work of Tan *et al.*<sup>[166]</sup> particles of pure PGlyMA were also prepared, through photoinitiated dispersion polymerization using a linear PEG macroRAFT. Different morphologies were obtained, and worms and vesicles were crosslinked by addition of ethylene diamine. Residual amine groups could be used to complex Ag salts, then reduced to form vesicles loaded with silver nanoparticles. Their catalytic activity was demonstrated by reduction of methyl blue. An and coworkers used AAEM, another interesting monomer employed in section 3.4 as a co-monomer to induce crosslinking with amines, however employed here as core-forming monomer to form nanospheres and vesicles stabilized by PPEGMA chains.<sup>[167]</sup> These nano-objects could be further functionalized or crosslinked *via* keto-alkoxylamine chemistry. *In situ* formation of silver nanoparticles by metal complexation and reduction was also demonstrated. The same team reported the synthesis of ketone functionalized particles.<sup>[168]</sup> Using a PDMAAm macroRAFT, both spheres and vesicles composed of a PDAAm core were prepared by dispersion polymerization of DAAM. The nano-objects could be functionalized using oxime (addition of *O*-allyl hydroxylamine) or hydrazine (fluorescein-based semicarbazide) chemistry. They also formed crosslinked vesicles by copolymerization of allyl acrylamide and DAAM, crosslinking being delayed to the late stage of the polymerization (when morphology transition was completed), due to the different reactivities of the two vinyl groups.<sup>[169]</sup> Byard *et al.* prepared PDMAAm-*b*-PDAAm particles but in addition to spheres and



vesicles, worms could also be obtained.<sup>[170]</sup> Addition of adipic acid dihydrazide (ADH) led to crosslinked nano-objects. An interesting class of reactive particles was reported by Jiang *et al.* who prepared nanospheres by chain extension of a poly(2-hydroxypropyl methacrylamide) macroRAFT with DAAm and an ammonium-based *N*-2-aminoethyl acrylamide hydrochloride.<sup>[98]</sup> Conjugation with pyridine-2,6-dicarboxaldehyde led to core-crosslinking forming terdentate ligands able to coordinate Zn(II) species. Using the same copolymer, the same group also reported the formation of pore-switchable nanotubes (or long cylindrical vesicles) driven by hydrogen bondings.<sup>[171]</sup>

As mentioned above, PS particles decorated with glucopyranose units could be crosslinked by copolymerization with a degradable disulfide diacrylate crosslinker.<sup>[139]</sup> Addition of 1,4-dithiothreitol as reductant led to particle degradation into the corresponding linear chains, demonstrating potential use as drug carriers.

Another way of inducing core-crosslinking is the use of light. This was achieved by Huang *et al.* who prepared particles of poly(2-((3-(4-(diethylamino)phenyl)acryloyl)oxy)ethyl methacrylate) in the presence of PHPMA macroRAFT.<sup>[172]</sup> Crosslinking occurred upon UV irradiation, by photoinduced [2+2] cycloaddition of the cinnamate groups. The crosslinked nano-objects were used as templates for *in situ* formation of gold nanoparticles. An original crosslinking strategy was reported by the same team.<sup>[173]</sup> Different particle morphologies were obtained by dispersion polymerization of 3-formyl-4-hydroxybenzyl methacrylate (FHMA) mediated by a PHPMA macroRAFT. Reaction of dihydrazine with the salicylaldehyde groups of PFHMA not only formed salicylaldazine crosslinks, but also conferred fluorescence properties by aggregation-induced emission.

• **Adding a function allowing degradation of the particle core.**

As illustrated in the previous examples, core-crosslinking can provide particles with additional properties. But dissolution of the particle core could also be a powerful tool. In that vein, an original work reporting the synthesis of degradable block copolymer nanoparticles was recently published by Guegain *et al.*<sup>[174]</sup> Radical ring-opening copolymerization-induced self-assembly (rROPISA) was performed by copolymerizing BzMA and cyclic ketene acetals (CKA), such as 2-methylene-4-phenyl-1,3-dioxolane or 5,6-benzo-2-methylene-1,3-dioxepane, in heptane from a poly(lauryl methacrylate) macroRAFT, leading to spherical particles whatever the copolymer compositions investigated. The amount of CKA in the copolymers ranged from 4 to ca. 40 mol %, leading to nearly complete degradation for CKA contents above ca. 15 mol %. Such degradable vinyl polymer nanoparticles may find applications in the biomedical field or for environmental protection.

Finally, as mentioned in the previous section, CO<sub>2</sub>-responsive particles can present interesting properties. In the work of Tan *et al.*<sup>[175]</sup> the CO<sub>2</sub>-sensitive units were located in the core of P(HPMA-co-DMAEMA) particles prepared from a PPEGMA macroRAFT. The responsive properties of the particles were illustrated by the CO<sub>2</sub>-triggered release of BSA used as a model protein.

## 5. CONTROL OVER THE PARTICLE MORPHOLOGY

The main objective of *section 5* is to establish and explain the fundamental principles that control particle morphology in PISA; where the term “morphology” refers to the particle shape or morphological structure, typically spheres, worms or vesicles. Again, we will not provide an exhaustive list of all examples reported in the literature, but rather illustrate the different factors that determine morphology by citing both pioneering works and most recent studies.

### 5.1. From spherical to anisotropic block copolymer particles

As mentioned in the Introduction of this review, at the start of RAFT-mediated PISA, independently of the polymerization mechanism, only *spherical* particles were reported. In some cases, the size of the particles increased with increasing degree of polymerization ( $DP_n$ ) of the solvophobic block,<sup>[176-178]</sup> but in other reports, no correlation was observed. It rapidly appeared that the particle formation mechanism in PISA was rather complex and strongly dependent on the studied system. It generally includes the aggregation of primary particles and their fusion to larger particles.<sup>[179]</sup> The first examples of *non-spherical* particles were described in 2009, by the groups of Charleux and of C. Y. Pan, reporting a NMP polymerization system in water,<sup>[14]</sup> and a RAFT-mediated dispersion polymerization in methanol,<sup>[15, 16, 180]</sup> respectively. Shortly after, Armes group reported for the first time the formation of vesicles in water, also obtained in RAFT dispersion polymerization conditions.<sup>[181]</sup> These morphologies were composed of PGMA-*b*-PHPMA copolymers. Continuous monitoring of the polymerizations by <sup>1</sup>H-NMR, SEC, TEM, cryo-TEM, DLS, SLS, SAXS provided important insights into the formation mechanism of the different morphologies.<sup>[49, 182]</sup> The first nanostructures to form are always spherical micelles. As the polymerization continues within the particles, (increase of  $DP_n$ ), nonspherical morphologies can form. It is now well-established that worm-like particles are formed through fusion of spherical particles following inelastic particle collisions. In the course of the polymerization, these 1D structures become branched and the resulting flat octipi-like morphologies reorganize to form vesicles. Such morphological transition during polymerization are driven by the increase of the hydrophobic volume fraction (see *section 5.2*). Morphological transitions during polymerization require a reorganization of the macromolecular chains within the assembly. As such, it has been shown that particles swelling by the monomer plasticizes the core chains increasing their mobility and promoting chain reorganization.

Today, a myriad of solvophilic macroRAFT and solvophobic polymers have been successfully used to form higher-order morphologies in RAFT dispersion polymerization conditions. In *water* however, the number of suitable solvophobic polymers is very limited. The most frequently studied solvophobic polymers are PHPMA<sup>[53, 182]</sup> and PDAAm,<sup>[168, 170, 183]</sup> but poly(2-methoxyethyl acrylate) (PMEA),<sup>[184]</sup> PNIPAM<sup>[102]</sup> and poly( $\alpha$ -hydroxymethyl acrylates)<sup>[185]</sup> could also be used to prepare non-spherical

morphologies. Recently, Foster *et al.* reported an *in silico* method based on octanol-water partition coefficients, to predict additional suitable monomers for the use in PISA in aqueous dispersion. Although the predicted monomers were less common and not all commercially available, this method might be a valuable tool, not only to predict new monomers but also to predict their self-assembly behaviour, that is morphologies.<sup>[186]</sup>

While the choice of monomers for aqueous dispersion remains restricted, all kind of stabilizer blocks, neutral, ionic or functionalized polymers (e.g. PGMA,<sup>[181]</sup> PEG<sup>[187]</sup> P(PEGMA),<sup>[188]</sup> poly(2-(methacryloyloxy)ethylphosphorylcholine),<sup>[81]</sup> poly(2-(methacryloyloxy)ethyl dimethyl(3-sulfopropyl)ammonium hydroxide),<sup>[189]</sup> poly(2-ethyl-2-oxazoline),<sup>[190]</sup> dextran<sup>[191]</sup> etc.), have successfully been used to obtain particles of various morphologies. However, particle fusion and consequently the formation of higher-order morphologies can be hampered by a too strong particle repulsion,<sup>[49]</sup> typically by using charged polymers as stabilizers, for instance using weak polyacids or polybases (e.g. PAA)<sup>[89, 192]</sup> or cationic stabilizers<sup>[193]</sup> or using high molar mass stabilizing blocks.<sup>[194]</sup>

In *emulsion polymerization* conditions, the monomer forms a separate reservoir phase and the formed diblock copolymer particles are swollen by the monomer. The first description of non-spherical particles dates back to 2010<sup>[192]</sup> reporting the emulsion polymerization of styrene using graft copolymers based on AA and PEGA, namely P(AA-co-PEGA), as macroRAFT. By adjusting the targeted  $DP_n$  of the PS block, worm-like micelles and small vesicles were obtained. Moreover, a transition from spheres to fibers was observed with increasing monomer conversion, *i.e.*, with an increase in the  $DP_n$  of the PS block. Again, these changes in morphologies directly relate to the relative hydrophilic/hydrophobic block volume fractions. Interestingly, higher-order non-spherical morphologies were only found for the graft copolymer, while linear PAA or PEG homopolymers used as macroRAFT only yielded spherical particles. In addition, the morphologies were very sensitive to changes in pH or ionic strength of the polymerization medium. The authors postulated that the particular structure of the macroRAFT, composed of AA and EO units capable of forming hydrophobic complexes, was the key element for the formation of non-spherical particles.

Since then, additional systems have been described where non-spherical particles could be obtained in emulsion polymerization conditions, but the number of examples remains limited compared to the booming development of higher-order morphologies *via* dispersion/precipitation polymerization. In terms of hydrophobic monomers, mainly styrene has been studied<sup>[82, 83, 85, 87-89, 176, 177, 192]</sup> but it was shown that also *t*-butyl acrylate<sup>[195]</sup> and more water-soluble monomers such as MMA,<sup>[84]</sup> 2-hydroxybutyl methacrylate (HBMA),<sup>[196]</sup> GlyMA<sup>[165]</sup> and 2-methoxyethyl methacrylate (MOEMA)<sup>[197]</sup> could provide non-spherical morphologies. It should be mentioned that – except for the last two monomers – for all other examples graft copolymers comprising PEG(M)A macromonomers were used as stabilizers (copolymers of PEG(M)A with either (M)AA,<sup>[82, 83, 177, 192, 198]</sup> NAM,<sup>[85]</sup> or hydroxyethyl acrylamide (HEAAm)).<sup>[87]</sup> There are a few other reports of higher-order morphologies by RAFT aqueous emulsion

polymerization, but these routes typically required small quantities of either a surfactant and/or a plasticizer.<sup>[199-202]</sup>

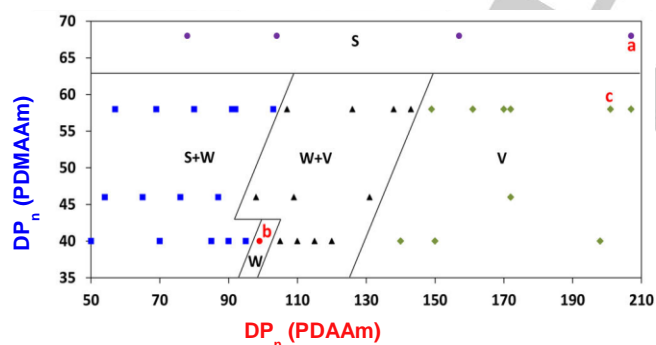
## 5.2. Main parameters that impact the particle morphology

It is nowadays well established that the particle morphology obtained by PISA depends on various parameters, notably factors that influence the packing parameter  $P$ , such as the type of polymers used, the solvent and the molar mass and architecture of the polymers. These factors have been widely studied for block copolymer assemblies prepared by traditional post-polymerization assembly methods.<sup>[77]</sup> In contrast to these latter methods, in PISA, the assembly forms while the solvophobic block grows, meaning that not only the properties of the polymer change during the process, but that also the solvent properties evolve constantly during polymerization (as the monomer is consumed). While at the beginning of the polymerization thermodynamic assemblies might be formed, kinetically frozen assemblies are often obtained at the end of the polymerization. Morphology prediction in PISA remains thus difficult. Actually, in addition to intrinsic changes in the chemical nature of the polymer and the solvent, in PISA the experimental polymerization conditions, for instance stirring, temperature, initiating system and monomer concentration and conversion, play also a role. As mentioned above, particle fusion following inelastic collisions and chain reorganization are prerequisites for the formation of higher order morphologies. As such, the impact of stirring speed on morphology has been clearly evidenced in a PISA emulsion polymerization system.<sup>[203]</sup> In dispersion polymerization formulations, more and more authors decrease the volume of the experimental set-ups (< 1 mL NMR tubes<sup>[186]</sup>, or microliter scales such as in 96-well microtiter plates<sup>[204]</sup>) and monitor PISA *in situ* by NMR or SAXS in unstirred set-ups, but it is questionable whether such unstirred PISA provides “valuable” results on morphologies.

Another important parameter, which determines morphology in PISA, is the monomer concentration. As mentioned above, a higher monomer concentration promotes the formation of higher-order morphologies through plasticizing of the core chains and an increased number of particles per volume unit in the reaction medium.<sup>[184, 187, 205]</sup> The polymerization temperature is another parameter to be taken into account. Indeed, modification of the polymerization temperature affects the polymer/polymer and polymer/solvent interaction parameters and may result in morphological changes through the alteration of the packing parameter (see also section 5.4). In addition, the temperature has also an effect on the particle formation mechanism through changes in the propagation rate constant  $k_p$ , or on the polymerization control through alteration in radical flux (in the case of thermal initiation).<sup>[84]</sup> Furthermore, an impact of the initiator concentration<sup>[87, 206]</sup> or the type of initiating system (thermal PISA vs photo-PISA) has also been reported.<sup>[207]</sup> Indeed, the self-assembly of diblock copolymers has been rationalized by the packing parameter  $p$  (Fig. 2),<sup>[208]</sup> a concept which was initially developed for small amphiphilic molecules (surfactants).  $p$  is defined as  $v/(a l)$ , where  $a$  is the area of the

surfactant head group and  $v$  and  $l$  are the volume and length of the surfactant tail, respectively. The self-assembly and the resulting morphology are essentially a balance between the degree of stretching of the core-forming chains, the interfacial tension between the solvophobic core and its external environment, and repulsive interactions between shell chains.<sup>[77]</sup> In essence, the morphology changes with the increasing volume ratio between the solvophilic and the solvophobic segment, from spheres ( $p \leq 1/3$ ) to cylinders ( $1/3 \leq p \leq 1/2$ ) to vesicles ( $1/2 \leq p \leq 1$ ) (Fig. 2). Strictly speaking, this concept holds only for morphologies at thermodynamic equilibrium. With the discovery of higher-order morphologies by PISA, the concept was however rapidly applied to PISA derived assemblies – which are not necessarily at equilibrium – by varying a certain number of features that are listed below.

- Varying the molar mass.** A direct way to control the morphology is thus to tune the volume fraction of the solvophobic and solvophilic segments through the adjustment of the molar mass of each block. For a given solvophilic block, by increasing the molar mass of the solvophobic block the morphology can thus be transformed from spheres towards worms to vesicles – provided that a morphological transition is possible.<sup>[13, 49, 51, 83, 194]</sup> This has been widely explored in the literature, and many, rather complete pseudo-phase diagrams have been constructed. As the packing parameter is the result of the interplay of polymer/polymer and solvent/polymer interactions, the absolute molar mass of the block segments depends on the polymer type and the solvent used for the polymerization. The packing parameter and thus the morphology is very sensitive to small changes in molar mass<sup>[209]</sup>, and generally, the pure worms are typically accessible in a very narrow window of composition (Fig. 6).



**Figure 6.** Phase diagram constructed for a series of PDMAAm-*b*-PDAAm diblock copolymer nanoobjects. S = spheres, S + W = mixed spheres and worms, W = worms, W + V = mixed worms and vesicles and V = vesicles. Reprinted with permission from reference<sup>[170]</sup> Copyright 2017, American Chemical Society.

- Varying the chemical nature of the solvophobic block.** As mentioned above, Mathers and O'Reilly and coworkers have shown a correlation between the chemical nature of the monomers to be polymerized and the particles morphology by comparing the aqueous dispersion polymerization of increasingly hydrophobic monomers using an *in silico* method. In identical

experimental conditions, the morphologies changed from spherical particles to worms and vesicles with increasing hydrophobicity of the monomers.<sup>[186]</sup> An and coworkers synthesized a series of alkyl  $\alpha$ -hydroxymethyl acrylates of tunable water solubility to study systematically the impact of the monomer solubility on morphology.<sup>[185]</sup> They have notably observed that the less water-soluble monomers, *ethyl-* and *isopropyl*  $\alpha$ -hydroxymethyl acrylate in particular, promoted the formation of higher order morphologies at lower  $DP_n$ s of the solvophobic block. The former systems were based on monomers with relatively high water-solubility, so that the polymerization mechanism was essentially that of a dispersion polymerization formulation. As mentioned above, monomers classically used in aqueous *emulsion* polymerization formulations often lead to kinetically trapped spheres – unless stabilizers comprising PEG grafts were used. It should be noted that the effect of the monomer water solubility on morphology has also been assessed for monomers that possess a lower solubility in water, and which are polymerized at a much higher concentration. For instance, replacing BzMA (aqueous solubility = 0.4 g L<sup>-1</sup> at 70°C) by HBMA (aqueous solubility = 20 g L<sup>-1</sup> at 70 °C)<sup>[196]</sup> (using a PMAA macroRAFT at pH 5) allowed to form unusual so-termed “monkey nut” morphologies, whereas spheres were obtained with the less soluble BzMA. Such an effect of the monomer solubility had already been reported before comparing the emulsion polymerization of MMA with that of styrene (aqueous solubility of MMA = 15 g L<sup>-1</sup> at 30 °C, of styrene = 0.3 g L<sup>-1</sup> at 20 °C).<sup>[84]</sup> It seemed that the formation of higher order morphologies was favored in the case of more soluble monomer MMA, but an influence of the differences in rate constant was also postulated. An interesting alternative to exchanging monomer or designing new monomers to tune morphology is the incorporation of solvophilic monomer units in the solvophobic block. Since 2015, this concept has been reported by several authors. For instance, 4VP<sup>[210]</sup> or MMA<sup>[211]</sup> were added as a comonomer to the dispersion polymerization of styrene. It was possible to tune the morphology by the molar ratio of 4VP/styrene in the monomer feed, in addition to adjusting the ratio of monomer/RAFT ratio ( $DP_n$ ). Besides, while for styrene alone only spherical micelles were generated, the insertion of 25 mol% of MMA into the solvophobic block enhanced its mobility promoting morphological transitions and the formation of worms and vesicles. Both examples showed that the incorporation of a solvophilic monomer was beneficial for the formation of high order morphologies. More recently the same concept has also been explored by Figg *et al.* in the aqueous dispersion polymerization of DAAm with DMAAm demonstrating the general validity of this concept.<sup>[212]</sup> Based on SLS analysis, the authors suggested that the insertion of a hydrophilic monomer alters the thermodynamics of the aggregation, promoting morphological reorganization.

- Varying the topology of the shell or the core.** As mentioned above, in emulsion polymerization formulations non-spherical morphologies are scarce. They had exclusively been observed for formulations using graft copolymers as macroRAFT, obtained by copolymerization of PEG macromonomers. In 2016, the group of Lansalot and D'Agosto has shown that the topology of the



stabilizer composed of PNAM, to which an average of three PEGA units as pendant chains were incorporated, had a critical impact on the particle morphology obtained in the emulsion polymerization of styrene.<sup>[85]</sup> Depending on the presence or not and the position of the pendant PEG chains (at the beginning, randomly distributed, or at the end of the chain), different morphologies, notably spheres, nanometric vesicles or large vesicles were obtained. Again, only spherical particles were obtained for the linear, non-branched polymer, *i.e.* PNAM homopolymer.

Instead of tuning the topology of the solvophilic macroRAFT agent, Yuan group inserted bulky and solvophobic comonomers, namely stearyl acrylate<sup>[213]</sup> and 2-(perfluorooctyl)ethyl methacrylate<sup>[214]</sup>, in the solvophobic block. They showed that the vesicle size could be tuned by the molar fraction of the comonomer.

• **Varying the solvent quality.** Instead of varying the monomer, others have studied the effect of the solvent on the morphological phase diagram. In one of the first reports it was shown that the addition of organic co-solvents (ethanol or dioxane) to the aqueous emulsion polymerization of BzMA was beneficial for morphological transitions and the formation of higher-order morphologies. It was also shown that the morphologies strongly depended on the co-solvent properties: whereas small amounts of 1,4-dioxane led to huge morphological changes, much higher amounts of ethanol were necessary to tune morphology.<sup>[198]</sup> More recently, the introduction of non-reactive PEG in the polymerization medium as a means to alter morphology and promote the formation of complex membrane morphologies<sup>[215]</sup> and to produce vesicles of uniform size was also described.<sup>[216]</sup> A particular case is the combination of specific monomers (styrene/*N*-phenylmaleimide) with the mixture of specific solvents (ethanol/methyl ethyl ketone) allowing the formation of complex morphologies, such as micrometric particles comprising inverse bicontinuous phases.<sup>[217]</sup>

Instead of co-solvents, additives have also been added to traditional PISA formulations in order to alter the solubility of the monomers. As such cyclodextrin (CD) has been added to aid dissolution of a water-immiscible monomer (styrene), allowing for its aqueous dispersion polymerization thanks to host-guest complex formation.<sup>[218]</sup> Performing PISA of the CD-styrene complexes in the presence of a PEG macroRAFT gave access to the direct synthesis of various kinetically trapped PS-based nanostructures in water, in particular hollow nanotubes.

• **PISA in aqueous media: varying pH and/or ionic strength.**

One should not forget the possibility to greatly tune the solvent properties of water by addition of salts or by changing the pH, which is of greatest importance whenever weak polyacids or polybases are used as macroRAFT. For instance, the effect of pH on morphology had been largely studied for the aqueous emulsion polymerization of styrene using P[(M)AA-co-PEG(M)A] macroRAFT as stabilizers.<sup>[83, 192]</sup> In addition to being sensitive to changes in pH, a strong impact of the ionic strength and the salt type was evidenced, both in emulsion<sup>[192, 203]</sup> and dispersion polymerization formulations.<sup>[219]</sup> The presence of salts may directly alter the packing parameter through changes in

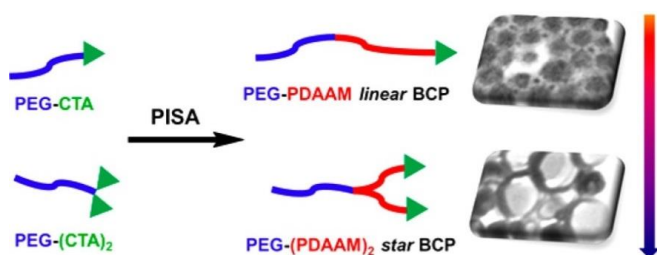
interaction parameters, which may explain the observed changes in morphology. In addition, salts diminish the electrostatic repulsion between individual particles therefore promoting particle fusion.

Whereas these former examples demonstrate the pH- and salt-sensitivity of PISA when weak polyacids or polybases were used, the surprising effect of a single charged moiety present in non-ionic macroRAFT agents has also been demonstrated. Several articles report indeed a great impact of pH on nanoparticles stabilized by a neutral polymer and terminated by a single weak acid group or a charged unit, but in the majority of cases the morphological transitions were induced through pH variation post-synthesis (cf section 5.4).<sup>[220-222]</sup> To demonstrate the importance of such an  $\alpha$ -end-group during PISA, Khor *et al.* had compared the aqueous emulsion polymerization of styrene using two types of P(HEAm-co-PEGA) macroRAFT agents, the first one bearing a carboxylic acid  $\alpha$ -end-group while the second one was the methyl ester.<sup>[87]</sup> Their study revealed a great effect of the end group on the morphologies over a large range of pH.

• **Varying the block copolymer architecture via the RAFT agent.**

Whereas the impact of the respective molar masses, polymer nature and solvent has been extensively studied, much less attention has been paid on the macromolecular architecture. In most of the studies monofunctional RAFT agents are used, generating *linear* copolymers, mostly AB diblock copolymers (A is the solvophilic block synthesized in the first step and B the solvophobic block synthesized in the second step), but ABC triblock copolymers have also been reported. Virtually from the start of PISA, bifunctional symmetrical RAFT agents producing ABA structures have also been implemented successfully,<sup>[223-226]</sup> but more recently, trifunctional<sup>[227]</sup> or tetrafunctional RAFT agents<sup>[228]</sup> - leading to the formation of triarm or tetraarm star polymers - have also been used. These articles show that the structure of the RAFT agent, *i.e.* the number of functionality (mono-, bi- or multifunctional), the inversion of the Z and R groups leading to BAB<sup>[183, 229-231]</sup> or (BA)<sub>n</sub> stars<sup>[228, 232, 233]</sup> has a crucial impact not only on the polymerization mechanism and control but also on the resulting particle morphology. Whereas it was not always straightforward to correlate macromolecular architecture and morphology in the former examples,<sup>[227, 229]</sup> An's group<sup>[234]</sup> has proposed an elegant approach to rationally increase the packing parameter *via* macromolecular architecture design. They synthesized a bifunctional asymmetric RAFT agent to which a PEG chain was coupled through an additional functional group at the symmetry point of the RAFT agent (Fig. 7). Compared to linear AB architectures, the resulting A(B)<sub>2</sub> triarm star copolymers clearly promoted the formation of vesicles as expected for copolymers with bulky hydrophobic segments, considering the packing parameter theory (Fig. 2).





**Figure 7.** A(B)<sub>2</sub> star architecture promoting the formation of complex morphologies compared to linear diblock copolymers. Reprinted with permission from reference [234] Copyright 2017, American Chemical Society.

### 5.3. Strategies to steer specific morphologies

Besides from studying systematically different parameters and assessing their impact on particle morphology, recently several strategies have been devised to control morphology instead of suffering from it. In the previous section, we have reported that the formation of higher-order morphologies can be promoted by increasing the volume fraction of the hydrophobic block through the rational design of the RAFT agents.<sup>[234]</sup>

Besides from increasing the hydrophobic volume to increase the packing parameter promoting the formation of vesicles/lamellae, other strategies aimed at synthesizing a targeted particle morphology in *robust synthesis conditions* and to obtain it as a pure phase, which is not mixed with other morphologies as often observed in PISA. As an example, the worm morphology is generally obtained in a narrow experimental window<sup>[53, 170]</sup> (Fig. 6) and in view of the possible applications, it would be of great interest to find means to enlarge the experimental window in which worms can be obtained. In addition, other research projects aim at producing particular anisotropic particle morphologies that are not observed in simple PISA formulations, for instance cuboids or ellipsoids.

#### 5.3.1 Using PICA

As mentioned in section 3.3, Zhu *et al.* used binary mixtures of macroRAFT and the parent molecular RAFT agent to promote the formation of higher order morphologies through the concomitant formation of solvophobic homopolymer in a derived-PISA system called PICA.<sup>[104]</sup> It should be mentioned that this concept of mixing a macroRAFT with a molecular RAFT agent has also been explored by the group of J. Tan and L. Zhang using a PEG macroRAFT instead of a PDMAEMA one.<sup>[105, 106]</sup> Finally, Zhang's group who has worked a lot on inverted RAFT agent structures leading to loop stabilized particles, has shown that the mixture of monofunctional PEG trithiocarbonate (TTC) macroRAFT with its

bifunctional analogue TTC-PEG-TTC promoted the formation of compartmentalized vesicles.<sup>[230]</sup>

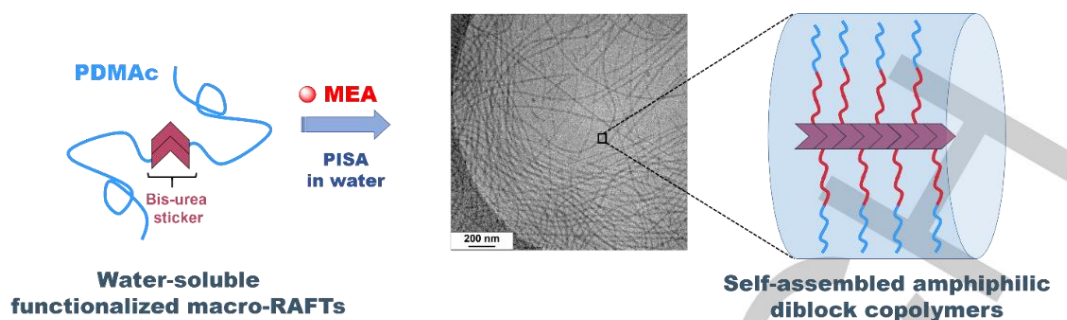
#### 5.3.2 Using PIHSA

In order to form anisotropic nanoparticles, such as cylinders,<sup>[235]</sup> cuboids<sup>[110]</sup> or ellipsoids,<sup>[146, 236]</sup> a known strategy in post-synthesis block copolymer self-assembly relies on the use of polymers that are able to organize within the core into (semi)crystalline or liquid crystalline domains.<sup>[237, 238]</sup> In this respect, mesogenic monomers, containing cholesteryl,<sup>[235]</sup> azobenzene<sup>[110]</sup> or long (semi)fluorinated chains<sup>[146, 236]</sup> have been used, generally in non-aqueous dispersion polymerization formulations. Particles with unusual shapes were obtained in all examples, which were attributed to the internal liquid crystalline (mostly smectic phases) organization as determined by SAXS. As discussed in section 3.3, the formation of such anisotropic nanoparticles by PISA containing liquid crystalline mesogens in their core has also been termed PIHSA.<sup>[110]</sup>

#### 5.3.3 Using ionic complexes (PIESA) and hydrogen-bonding units

Other authors have shown that using particular monomers that can undergo supramolecular interactions, such as H-bonding or the formation of polymeric ionic complexes (PIC) is also a means to tune morphology in PISA and to produce rather exotic morphologies (section 3.3). For instance, acrylamides such as DAAM,<sup>[171]</sup> or nucleobase-based monomers<sup>[239, 240]</sup> are capable of forming H-bondings with themselves or with mediator molecules leading to specific structures, while charged monomers can generate PICs with polyelectrolytes added to PISA<sup>[108]</sup> or formed through chain extension of double hydrophilic AB block copolymers with a third block of opposite charge.<sup>[107]</sup> This latter strategy is PIEESA, as discussed in section 3.3.

The previous examples show that there is a current trend to combine supramolecular chemistry and PISA. Whereas the latter examples were based on supramolecular interactions between monomer units of the core chains, Rieger, Stoffelbach and coworkers have very recently devised a templating strategy based on interactions between a single sticker unit placed at the  $\omega$ -end of each chain. They actually designed a macroRAFT functionalized by a hydrogen-bonded bis-urea sticker<sup>[241]</sup> in order to drive PISA towards the nanofiber morphology, *via* one-dimensional, directed assembly of the sticker units, which is reinforced by the creation of hydrophobic domains during PISA (Fig. 8). This concept was tested in the synthesis of poly(*N,N*-dimethylacrylamide)-*b*-poly(2-methoxyethyl acrylate) diblock copolymers prepared by dispersion polymerization in water. The results clearly showed that the developed strategy promotes the formation of nanofibers in a large experimental window.<sup>[242]</sup>



**Figure 8.** Using bis-urea functional macro-RAFT agent for "templated PISA" in water. Reprinted with permission from reference <sup>[241]</sup>. Copyright 2018, Wiley.

### 5.3.5 Hierarchical assembly between particles

Finally, one should also mention the possibility to construct complex hierarchical assemblies from primary nanoparticles (obtained by PISA) through supramolecular interparticle interactions. As an example, raspberry-like nanoparticles have been produced by controlled heterocoagulation of PEG-stabilized and PAA-stabilized nanoparticles *via* hydrogen bonding interactions between PAA and PEG chains.<sup>[243]</sup> More recently, the possibility to functionalize the surface of PS particles by naphthalene units, present at the  $\alpha$ -chain end of the PAA macroRAFT, was also demonstrated.<sup>[129]</sup> The latter particles should be useful as building blocks to construct larger supramolecular structures through host-guest interactions.

### 5.4. Post-polymerization morphological transitions/chain reorganization

It is well known that amphiphilic block copolymer assemblies prepared by traditional assembly methods (such as nanoprecipitation or solvent displacement) can undergo morphological transitions if one of the blocks is responsive to external stimuli - such as pH or temperature in the simplest case. The result is either the dissociation of the assembly (also called "order-to-disorder transition") or a change in morphology (termed "order-to-order transition" or "morphological transition"). Whereas the former case has been largely explored, the latter case was actually rarely reported for such conventional block copolymer assemblies. In contrast, post-polymerization morphological order-to-order transitions play nowadays a major role in PISA, probably because of the large variety of systems explored and the possibility to synthesize highly concentrated dispersions, which pave the way to new properties and applications. Firstly simply observed, such transitions are now understood (they are mainly the result of changes in the packing parameter) and have also found applications. It should be mentioned that they are not always desired, and that chain crosslinking is a means to prevent them by freezing the assembly (cf sections 4.2 and 4.3). On the other hand, the dynamics of the assembly must be favorable to the transition. In other words, a kinetically frozen assembly will not be able to rearrange chains resulting in a change of morphology (in reasonable timescales).

Several reviews have summarized and commented order-to-order transitions (among other aspects of PISA)<sup>[49, 51, 53, 59]</sup> or even dedicated the whole review to this subject.<sup>[54]</sup> We will thus only

briefly summarize the most important stimuli that have been reported to induce post-polymerization morphological transitions in PISA and illustrate them by some representative examples. Some of the examples will be detailed in the section dedicated to the applications.

- **Temperature.** Temperature-induced morphological transitions in water have first been reported for diblock copolymers possessing PHPMA as a core block.<sup>[244]</sup> It was shown that such PGMA-*b*-PHPMA block copolymer worms transformed into spherical micelles, when the solution was cooled from room temperature to 4 °C. The morphological transition resulted in a change in bulk properties: whereas entangled worms form free-standing gels, the corresponding sphere dispersion is a liquid of low viscosity. A possible application of such thermoresponsive gels is their use as sterilizable gels. Since then, other types of core polymers (generally rather "hydrophilic" polymers prepared through dispersion polymerization formulations) have also been reported, for instance using PDAAm.<sup>[170, 245]</sup> These post-polymerization transitions have been termed Temperature-Induced Morphological Transitions (TIMT) by Wang *et al.*<sup>[245]</sup> and they are usually explained by a change in surface-plasticization leading to a change in the packing parameter. The transition temperature is generally very sensitive to the molar mass of the polymers, and can thus be tuned by the  $DP_n$ <sup>[209]</sup> or by copolymerization. For instance, Warren and Plamper copolymerized NIPAM with *tert*-butyl acrylamide (tBuAAm) to afford PDMAAm-*b*-P(NIPAM-*co*-tBuAAm) assemblies for which morphological transitions could be induced by both temperature and hydrostatic pressure.<sup>[205]</sup>

TIMT have not only been reported in water, but also in non-aqueous media, such as in *n*-dodecane<sup>[246]</sup> or in mineral oil.<sup>[247]</sup> In the latter case, PSMA-*b*-PBzMA diblock copolymer assemblies were synthesized through a dispersion polymerization formulation.  $DP_n$  of the polymers was tuned in order to obtain vesicles, which underwent a vesicle-to-worm transition upon heating above a critical gelation temperature (at 135 °C, as the non-interacting vesicles are converted into weakly interacting worms). This concept provides a new mechanism for the high-temperature thickening of oils.

- **pH.** As mentioned above (section 5.2), morphological transitions can be triggered by a change of pH, in case the nano-objects are stabilized by a weak polyelectrolyte shell, or even by a neutral polymer possessing a single ionizable functional group (such as

## REVIEW

a carboxylic acid group<sup>[220, 221]</sup> or a morpholine end-groups<sup>[222]</sup>. In the case of a PGMA-*b*-PHPMA diblock copolymers synthesized from a carboxylic acid-functional RAFT agent, worm-to-sphere<sup>[220]</sup> or vesicles-to-worm (or sphere) transitions<sup>[221]</sup> could be induced by a pH increase. The ionization of the terminal carboxylic acid group should increase the volume of the hydrophilic segment, triggering the observed slow morphological transitions. Instead of triggering morphological transitions, it was also possible to trigger the inversion of the core and shell of spherical diblock copolymer micelles, possessing two pH-responsive blocks, in the example a polyamine and a hydrophobic polyacid block, prepared by PISA. Such pH-responsive spherical micelles are called “schizophrenic” micelles, and they offer the possibility to incorporate and release a payload on demand.<sup>[248]</sup> In addition to pH-responsive diblock copolymer self-assemblies, the concept was also reported for ABC triblock copolymers, where morphological transitions could be induced by the protonation of a polyamine middle block.<sup>[249]</sup>

- **“Reactive” groups.** As already mentioned in section 4, “reactive groups” that are able to interact or react in a larger sense may also induce morphological transitions.

- **Degradation.** As reported above, morphology is related to the packing parameter and thus in the simplest case to the  $DP_n$  of the hydrophilic and hydrophobic blocks. So finally, a means to alter morphology after polymerization is thus to alter the  $DP_n$  of the core block. An elegant while slow strategy to induce order-to-order morphological transitions was thus the design of a degradable core block by copolymerizing 3-methylidene-1,9-dioxo-5,12,13-trithiacyclopentadecane-2,8-dione (MTC), a disulfide-based cyclic monomer, yielding copolymers with degradable disulfide bonds in the main chain. The authors validated their concept and showed that worm could be transformed into sphere thanks to the chemical degradation of the hydrophobic P(HPMA-*co*-MTC) block.<sup>[250]</sup>

- **Initiators.** A particular type of reactive groups are initiators, *i.e.* groups that are capable of initiating the growth of a new polymer chain. As such, in the work of St Thomas *et al.*, alkoxyamine-functionalized latex nanoparticles were synthesized by RAFT-PISA and depicted in section 4.1. They were used in a second polymerization step performed at higher temperature (130 °C) to form of a double hydrophilic corona (PAA-*b*-PSSNa) which went along with a switch in morphology.<sup>[128]</sup>

- **Supramolecular interactions.** A completely different type of reactive groups are supramolecular interacting groups that may bind to a specific molecule by complexation. Armes group showed in 2017 how dynamic covalent chemistry can drive order-to-order morphological transitions in aqueous dispersions of PGMA-*b*-PHPMA diblock copolymer vesicles in order to release nanoparticle payloads from the vesicles.<sup>[251, 252]</sup> In the first example,<sup>[251]</sup> the addition of 3-aminophenylboronic acid (APBA) to such vesicles at pH ~ 10 resulted in specific binding of this reagent to some of the pendent cis-diol groups of the hydrophilic PGMA chains to form phenylboronate ester bonds. This led to a subtle increase in the effective volume fraction of this stabilizer block, which in turn caused a reduction in the packing parameter and hence induced a vesicle-to-worm (or vesicle-to-sphere) morphological transition, and eventually the release of silica

particles. In the same year, the same group also explored host-guest chemistry, another subclass of supramolecular chemistry, to modify the morphological transition of preformed diblock copolymer assemblies.<sup>[135]</sup> CD (host) - azobenzene (guest) interactions were exploited to tune in particular the rate of thermally-induced morphological transitions for  $\beta$ -CD-functionalized vesicles constituted of P(GMA-*co*-GlyMA)-*b*-PHPMA) diblock copolymers. Addition of azobenzene-methoxypoly(ethylene glycol) to such vesicles resulted in the formation of an inclusion complex with the  $\beta$ -CD groups present at the hydrophilic P(GMA-*co*-GlyMA) chains and led to a significantly faster change in copolymer morphology compared to the  $\beta$ -CD-functionalized vesicles alone.

- **Light.** In addition to being hydrophobic mesogenic moieties, which can arrange in a liquid crystalline order (see sections 5.3.2 and 4.2), and their ability to interact with CD, azobenzenes are also known to be light-responsive. Triggered by changes in wavelength they can undergo a reversible trans-cis isomerization, which results in a change in hydrophobicity. Already largely explored for assemblies prepared from preformed polymers, copolymers possessing pendant azobenzene groups in their core have also been synthesized by PISA. The UV-light-induced morphological transformations were again rationalized by the volume change of the hydrophobic block caused by the isomerization of the azobenzene moieties.<sup>[110, 253]</sup> Bagheri *et al.* proposed another strategy to use light as a trigger to change morphology. They actually incorporated 1-pyrenemethyl methacrylate as a comonomer in the solvophobic block of photoactive nanoparticles, as a means to photochemically trigger particle dissociation by cleavage of pyrene moieties leading to a solvophobic-solvophilic transition of the core polymer.<sup>[254]</sup>

- **Oxygen.** To finish with, the same group has also prepared nano-objects possessing core polymers sensitive to reactive oxygen species, namely poly(2-(methylthio)ethyl methacrylate), by a PISA process. In this work, particle disassembly rather than morphological transitions were observed through a hydrophobic-hydrophilic change in the block copolymer properties due to oxidation of the thioether groups.<sup>[255]</sup> Similarly, Sobotta *et al.* demonstrate that the cyclic thioether *N*-acryloyl thiomorpholine can be used in PISA to afford a hydrophobic block, which can be transformed upon oxidation into a highly water-soluble sulfoxide leading again to the disassembly of the particles.<sup>[256]</sup>

## 6. APPLICATIONS

As mentioned in previous sections, the possibility to produce nano-objects of various shapes in high amount and concentration opens the door towards their application in various fields. Whereas standard application of micellar objects /nanoparticles – such as their use as drug delivery vehicles - have been explored, original applications related to the possibility to synthesize them at high solids contents have also been reported. In the latter case, the bulk properties of these concentrated dispersions have been explored, typically in the case of worm dispersions that may form



free-standing gels and for which the rational design of the copolymer allowed to make them thermoresponsive. The following part summarizes the main applications of PISA-derived nanoparticles that have been explored. For each application, some representative examples are provided.

To date, the most explored field of application for PISA certainly concerns **biomedical applications**. Indeed, PISA allows the synthesis of core-shell nanoparticles directly in aqueous media without using co-solvents, combined with the possibility to encapsulate any kind of payload *in situ*, *i.e.* during polymerization. All main morphologies accessible by PISA have been explored for the encapsulation and delivery of drugs.<sup>[63]</sup> Whereas spherical and worm-like morphologies have been used to encapsulate hydrophobic drugs, vesicles (also termed polymersomes in the biomedical field) allow the encapsulation of both hydrophobic (in the bilayer membrane) and hydrophilic drugs (in the cavity) or other bio-relevant agents (such as enzymes). A related biomedical application concerns the encapsulation of any type of molecules or materials useful for imaging purposes. As such, fluorescent dyes, magnetic particles<sup>[257]</sup> or alternatively <sup>19</sup>F-containing fluorinated monomers<sup>[147, 257]</sup> have been incorporated. Some papers reported the synthesis of model stimuli-responsive vesicles by PISA able to release various species such as silica nanoparticles,<sup>[251, 258, 259]</sup> bovine serum albumin (BSA),<sup>[175, 258]</sup> Rhodamine B,<sup>[260]</sup> Nile red<sup>[261]</sup> or enzymes.<sup>[262]</sup>

Worm dispersions that form free-standing gels at room temperature (or physiological temperature) and that are less viscous at low temperature (due to reversible morphological worm-sphere transitions, see *section 5.4*) have also found interest for biomedical application as they are sterilizable by filtration at low temperature.<sup>[132, 244]</sup> Their potential use as drug delivery systems, for tissue engineering or for cell storage has been considered.<sup>[263]</sup> In contrast, vesicles have also found interest as mimicking systems for living cells.<sup>[62, 264]</sup> For instance, enzymes have successfully been encapsulated in vesicles and their permeability has been modulated, for instance by the incorporation of pores.<sup>[265]</sup> In addition to mimicking living cells, another aspect of such bio-hybrids is their use as enzymatic nanoreactors.<sup>[262, 266]</sup> For more details on biomedical applications of PISA-derived nano-objects, the reader can refer to recent reviews, which provide a good overview on the existing systems.<sup>[59, 61, 63]</sup>

Another application of particles produced by PISA is **catalysis**. PISA was employed to nanostructure the particles cores in order to generate catalytic nanoreactors dispersed in water. This was achieved by the use of hydrophobic monomers carrying triphenylphosphine ligands and a crosslinker introduced either at the beginning of the emulsion polymerization or at a later stage. After complexation of Ru, the resulting catalytic nanoreactors proved to be useful for hydroformylation of octene.<sup>[267-270]</sup> Metallic Pd(0) nanoparticles have also been introduced, for instance into nanogels obtained by PISA, and showed a remarkable stability in the solid state and in solution. This feature allowed their successful application as catalysts for the Mizoroki-Heck reaction between *n*-butyl acrylate and a series of bromo- and iodo-arenes.<sup>[271]</sup> In addition to the examples cited above, a large variety

of metal-hybrid nanocatalysts (most of the incorporating metal particles) have now been synthesized using PISA, but their detailed description is out of the scope of this review.

An expanding application of PISA-derived particles is their use for the stabilization of liquid-liquid interfaces to form so-called **Pickering emulsions**.<sup>[272]</sup> Block copolymer nanoparticles of various morphology, mainly spheres and worms,<sup>[163, 273, 274]</sup> but also vesicles<sup>[273]</sup> have been investigated. Furthermore, the utility of thermoresponsive particles that undergo worm-to-sphere morphological transitions in the field of Pickering emulsions has also been demonstrated.<sup>[275]</sup> The different studies revealed that not only the type of shell and core (crosslinked or not) polymer, but also the particle morphology play a crucial role in their efficiency to stabilize emulsions. Eventually, one may note that worm-like particles have also been used successfully to stabilize high internal phase emulsions (HIPEs).<sup>[276]</sup>

The main particle morphologies have also all been used as **templating agents** to produce hollow inorganic nanoparticles, porous materials or nanocomposites. One of the first examples was the use of nanoworms as soft templates to produce hollow silica nanotubes through calcination of the hybrid nanoworms prepared in a previous synthesis step.<sup>[277]</sup> More recently, spherical nanoparticles possessing a soft poly(hydroxyethyl acrylate) core have been used to prepare uniform mesoporous carbon materials.<sup>[101]</sup> Another type of inorganic material used in combination with nanoparticles made by PISA is calcite (CaCO<sub>3</sub>).<sup>[278, 279]</sup>

Other applications of PISA nanoparticles concern their **use as additives** in complex formulations. Anisotropic particles or particles that undergo morphological transitions are of particular interest for these applications. Aqueous dispersions of long fibers can be used as rheomodifiers to adjust the rheology of complex formulations,<sup>[280]</sup> whereas thermoresponsive vesicles that exhibit a heating-induced vesicle-to-worm morphological transition in mineral oil have a potential interest as lubricants for oils, as heat thickening is an unusual and desired rheological feature.<sup>[247]</sup> Another application is in the field of coatings, with the use of hollow particles (vesicles<sup>[281]</sup> or bicontinuous microparticles<sup>[282]</sup>) as opacifiers for paint films. Besides, the utility of high T<sub>g</sub> PISA nanofibers as mechanically reinforcing fillers for soft films has also been demonstrated,<sup>[283]</sup> while highly asymmetric diblock copolymer nanoparticles composed of a large soft PBA core block and a short hard PAA shell can be used to prepare films with enhanced properties.<sup>[125, 126]</sup>

Whereas most of the previous applications concern the individual nanoparticle itself or the bulk properties of a particle dispersion, other applications concern the films that can be produced after drying or processing the dispersions. For instance, **thin nanostructured films** of PISA nanoparticles (pure polymer particles<sup>[284, 285]</sup> or hybrids<sup>[286]</sup>) have been spin-coated as thin films to construct membranes for water ultrafiltration purposes.

As mentioned in the introduction, PISA was initially developed for emulsion polymerization formulations to produce **surfactant-free latexes**. The presence of free surfactants is still an important issue in the coating industry, and the current expiration of the RAFT patents is expecting to further boost the industrial demands



for developing PISA for coating applications, hopefully with the aid of academic collaborations.

## 7. SUMMARY AND OUTLOOK

As shown in the previous sections, PISA is a very simple and efficient tool to produce amphiphilic block copolymers in high concentrations and a way to self-assemble these block copolymers into nano-structured aggregates during their formation. PISA is attracting a broad range of interests from polymer chemists and physico-chemists to biologists and, as a direct consequence, PISA is generating a broad range of hopes for various applications. We believe that the reading of this overview on RAFT-mediated PISA will easily allow the reader to comprehend the vast potentialities of this technique. The transposition of new processes or technologies to industry is a challenge because it always faces the robustness and the experience gained on the existing systems. PISA will perform even better in a near future with the development of process parameters *e.g.* continuous processes<sup>[287-289]</sup> and will undoubtedly benefit from the well-established industrial field of polymerization in dispersed media.

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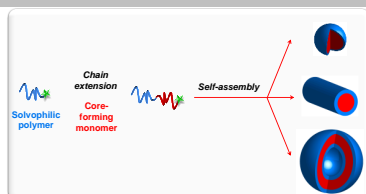
## REVIEW

Entry for the Table of Contents (Please choose one layout)

Layout 1:

## REVIEW

Polymerization-induced self-assembly (PISA) is based on the use of controlled/living polymerization (CLP) and consists in extending solvophilic living chains with a solvophobic segment to generate block copolymers that self-assemble to achieve various morphologies *in situ*. This review covers PISA mediated by reversible addition-fragmentation chain transfer (RAFT), one of the most popular radical CLP techniques.



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RAFT-mediated polymerization-induced self-assembly