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# Progress in Aqueous Dispersion RAFT PISA

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29 **Abstract.**

30 Polymerization induce self-assembly (PISA) is an emerging platform technology offering many advantages  
31 compared to the solvent switch methods. Aqueous dispersion reversible addition fragmentation chain transfer PISA  
32 (aqueous dispersion RAFT PISA) has progressively won over many research groups due to its green chemical  
33 process and amazing efficiency to produce wide range of morphologies. This review summarizes the recent works  
34 reported in the literature on the aqueous dispersion RAFT PISA. After a general introduction on the PISA process,  
35 exhaustive lists of the different RAFT activation techniques, the hydrophilic steric stabilizers, and the monomers  
36 used are shown and discussed. Our objective is to provide an overview for experts and a toolbox for nonexperts that  
37 aim to explore this robust and efficient route to produce block copolymer nano-objects for a specific application.

38 **Keywords.**

39 RAFT polymerization; PISA; Polymerization induced self-assembly, Aqueous; nano-object; dispersion

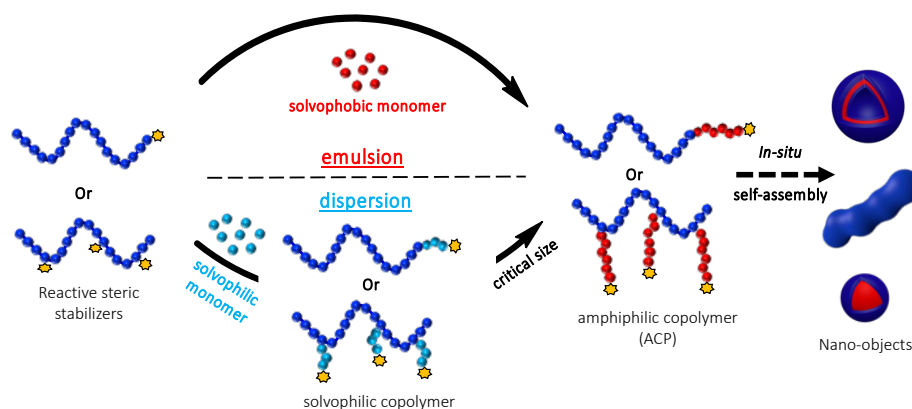
40

41 **1. Introduction.**

42 Over the past decades, considerable efforts have been made to design functional polymeric nano-objects of  
43 advanced physico-chemical properties, higher mechanical stability and modulable shape.[1-4] Such  
44 nanostructures have found applications in various area especially in nanomedicine to improve the  
45 bioavailability of drugs or to mimic natural cells,[5-7] and in cosmetic/food industries to stabilize  
46 emulsions for instance.[8, 9] Polymeric nano-objects resulting from self-assembly of amphiphilic  
47 copolymers (ACPs) are probably the most studied systems in the literature.[10-20] Thanks to the  
48 development of reversible deactivation radical polymerization (RDRP) techniques,[21, 22] including  
49 nitroxide-mediated polymerization (NMP),[23, 24] atom transfer radical polymerization (ATRP),[25, 26]  
50 and reversible addition fragmentation chain transfer (RAFT),[27] that facilitates and expands the synthesis  
51 of well-defined ACPs of various architectures (block, star and graft) compared to ionic polymerizations.  
52 Moreover, RDRP allowed introduction of new functional monomers hitherto difficult or impossible to  
53 achieve using ionic polymerization.[28] ACPs-based nano-objects have been traditionally prepared *via*  
54 direct dissolution in **water**[29, 30] or solvent switch methods[3, 4, 31, 32] such as nanoprecipitation,[33,  
55 34] film-rehydration[35-37] and emulsion-solvent evaporation.[38] In these self-assembly methods, pre-  
56 synthesized ACPs are dissolved in a common solvent for both blocks, followed by a gradual addition of a  
57 selective solvent of one specific block to form nano-objects. However, the low solid content (typically <1  
58 % wt) of suspensions produced and the multiple processing/purification steps required by these methods  
59 limit their potential upscaling.[39]

60 Polymerization induce self-assembly (PISA) is an attractive platform technology offering many advantages  
61 compared to the solvent switch methods.[40-43] PISA is an one-pot methodology leading to formulation of  
62 high solid content (up to 50 wt%) without performing additional purification steps. As shown in **Scheme 1**,  
63 a solvophilic macromolecular stabilizer is chain-extended by polymerizing a desired monomer that forms a

64 solvophobic block when reaching a critical chain-length. This results in a spontaneous assembly of the



65 ACPs into nano-objects of various morphologies, depending on the relative volume ratio of each block.

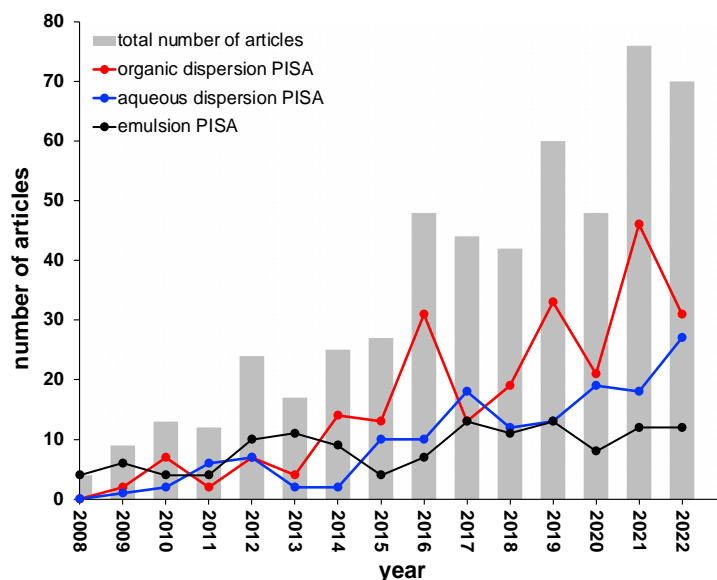
66 **Scheme 1.** Schematic Polymerization-Induced Self-Assembly conducted either in emulsion or in dispersion  
67 media. Cases of diblock and grafted amphiphilic copolymers.

68

69 In academia, PISA was first carried out in heterogeneous media, previously called “ab Initio Emulsion  
70 Polymerization”, today known as “emulsion PISA”. [44] In this case, the monomer is solvophobic such as  
71 benzyl methacrylate, [45-47] butyl acrylate, [48-51] glycidyl methacrylate, [52-56] methyl methacrylate, [57-  
72 59] styrene [60-65] and vinyl acetate. [66-68] However, this approach leads mainly to kinetically trapped  
73 nanospheres. [69] On the other hand, PISA in dispersion media, [70] either in aqueous [71, 72] or non-  
74 aqueous solvents, [17, 72, 73] offers an interesting alternative to produce nano-objects with advanced  
75 morphologies. [69, 72, 74, 75] In practice, this is achieved by polymerizing a solvophilic monomer which  
76 forms solvophobic polymer from a critical degree of polymerization. Several solvents have been used to  
77 conduct non-aqueous PISA including: i) polar solvents (methanol, [40, 76] ethanol, [77] isopropanol, [78]  
78 mixture of water and alcohol, [79-81] and acetic acid [82]) ii) non-polar solvents (dodecane, [83]  
79 heptane, [84] chloroform, [85] and toluene [86]), and iii) some specific organic media (supercritical  
80 CO<sub>2</sub>, [87] ionic liquids [88] and PEG of low molar masses [89]). Several monomers meeting the PISA  
81 prerequisites in non-aqueous dispersion have been reported in the literature such as benzyl  
82 methacrylate, [77, 81, 83, 84] methyl methacrylate, [89] and styrene. [40, 78, 80, 88]

83 Aqueous dispersion PISA [71, 90] has progressively won over many research groups regarding its green  
84 chemical process (use of water) and its efficiency to produce wide range of morphologies, as judged by the  
85 growth number of publications over the last fifteen years (**Fig. 1**). It has been successfully carried out using  
86 almost all living/controlled polymerization techniques. [91-96] However, RAFT polymerization remains  
87 the most used mechanism in PISA, [97, 98] thanks to its simplicity, its tolerance to water and its ability to  
88 control the polymerization of a wide variety of monomers. [22, 99, 100] We termed here this process  
89 “aqueous dispersion RAFT PISA”. The aim of this review is to provide an overview on the state of the  
90 current literature for experts and a tutorial for nonexperts on the aqueous dispersion RAFT PISA. Readers

91 can refer to some other recent reviews dealing with specific topics related to PISA process, including  
 92 mechanisms for initiating and controlling the PISA process,[90, 101-103] approaches used for  
 93 crosslinking[104, 105] and formulation of functional nano-objects[32, 106-108] for biomedical  
 94 applications.[109-113]



95  
 96 **Fig. 1** Published articles per year dealing with “polymerization induced self-assembly” (source Web of Science,  
 97 November 2022).

98 **2. Aqueous dispersion RAFT polymerization.**

99 RAFT polymerization is a conventional radical polymerization with a controlled and living behavior  
 100 reached by adding a chain transfer agent (CTA) to the reaction medium. It involves rapid reversible chain  
 101 transfer between the CTA and a growing macroradical *via* a degenerative chain transfer mechanism.[22,  
 102 27] **Table 1** shows an overview of the systems and the experimental conditions reported up today to  
 103 conduct aqueous dispersion RAFT PISA.

104  
 105 **Table 1.** Aqueous dispersion RAFT PISA of different water-soluble monomers from various steric stabilizer blocks.  
 106 *TI: thermal initiated, PI: photo-initiated, EI: enzymatic initiated, DD: direct dissociation, PET: photo electron*  
 107 *transfer. See Fig. 2-6 for the abbreviations of CTA, initiation systems, steric stabilizer blocks, monomers and nano-*  
 108 *objects morphology, respectively.*

Monomer	Steric stabilizer block	RAFT experimental conditions	Morphology	ref
HPMA	PGMA	TI CTA-1, CTA-3, CTA-4, CTA-6, V-501 (70°C), V-50 (56°C)	S, WLM, ULV, BW, J, OM, FV	[43, 114-123]
		PI CTA-4, CTA-7, CTA-10 SPTP (405nm, 0.095-17.1 mW/cm <sup>2</sup> , 0°C, 25°C, 70°C). SBAPO (465nm, 3.0 mW/cm <sup>2</sup> , RT). SPTP (405nm 0.45 mW/cm <sup>2</sup> , 25°C, 60°C)	S, WLM, ULV, TV, DV	[124-128]

	EI	CTA-7, HRP/ACAC/H <sub>2</sub> O <sub>2</sub> (RT)	ULV	[129]
	TI	CTA-1, CTA-4, CTA-7, CTA-10, CTA-21 VA-044 (37°C-50°C), V-50 (45°C-70°C)	S, WLM, ULV, MLV, J, R	[130- 134]
	PI	CTA-7, CTA-10, PP-OH (405nm, 160 – 800 mW, 37°C) SPTP (405nm, 0.4-0.5 mW/cm <sup>2</sup> , 25°C, 55°C)	S, WLM, ULV, BW, L, GULV, MLV	[132, 135- 139]
PEO	DD	CTA-7, CTA-10 (365nm, RT), (405nm, 37°C), (460nm, 0.8-1.6 mW/cm <sup>2</sup> , RT).	S, WLM, ULV, BW, L, GULV, MLV	[132, 140- 142]
	PET	CTA-7, CTA-10 Ru(bpy) <sub>3</sub> (450nm, 30°C), ZnTMPyP (595nm, 10.2 mW/cm <sup>2</sup> , RT), ZnPCS <sub>4</sub> (730nm, 60mW/cm <sup>2</sup> , RT)	S, WLM, ULV, MLV	[143- 146]
	EI	CTA-7, HRP/ACAC/H <sub>2</sub> O <sub>2</sub> (RT)	S, WLM, ULV	[147]
	Sono	CTA-10 (990 kHz, 23°C)	S, WLM, ULV	[148]
PPEGMA	PI	CTA-7, CTA-10, CTA-16 SPTP (405nm, 0.5 mW/cm <sup>2</sup> , 4-25°C), (530 nm, 10 mW/cm <sup>2</sup> , RT)	S, WLM, ULV	[127, 149- 153]
	RI	CTA-16, KPS/NaAs (30°C)	ULV	[151]
PHPMAc	TI	CTA-3, V-501 (70°C)	S, WLM, ULV	[154]
Dextran	DD	CTA-9, (365nm, 4-27 mW/cm <sup>2</sup> , RT)	M, OM, WLM, ULV, SNPs	[155, 156]
	PI	CTA-12, TPO-L (405nm, 10-60 mW/cm <sup>2</sup> , 20-60°C)	M, WLM, ULV, MCV	[157- 159]
PDMAEMA		CTA-10 (365nm, RT)	S, WLM, ULV	[141]
PSar		CTA-7 (405nm, 37°C)	S, WLM, EULV, ULV	[160]
BSA	PET	CTA-13, Ru(bpy) <sub>3</sub> Cl <sub>2</sub> (460 nm, 3 mW/cm <sup>2</sup> , RT)	SNPs	[161]
PNMEP		CTA-4, VA-044 (44°C)	SNPs	[162]
FNA (Nucleic acid)		CTA-2, SPTP, 405 nm, 0,5 mW/cm, (GOx), RT	S, W	[163]
PMPC		CTA-1, CTA-4, V-501 (70°C), VA-044 (50°C)	S, WLM, ULV, LR	[130, 164, 165]
PCysMA		CTA-4, V-501 (70°C)	S, WLM, ULV	[166]
PSBMA		CTA-1, V-501 (70°C)	S, WLM, ULV	[167]
PQDMA		CTA-1, CTA-9, V-501 (70°C)	S, SNPs	[43, 168]
PCoAEMACl		CTA-3, VA-044 (70°C)	SNPs	[169]
Polylysine		CTA-4, V-501 (60°C)	S, WLM, ULV	[170]
PKSPMA		CTA-1, CTA-9, V-501 (70°C)	S, SNPs	[43, 171]
PMAA		CTA-3, V-501 (70°C)	S, WLM	[172]
PSEMA		CTA-1, V-501 (70°C)	S	[43]
PGSHMA		CTA-4, V-501 (70°C)	SNPs	[166]
PGMA + PEG	TI	CTA-4, VA-044 (44°C)	S, WLM, ULV	[173]
PGMA + PMAA		CTA-3, V-501 (70°C)	S, WLM, ULV	[174]
PGMA + PAMA		CTA-4, V-50 (60°C)	S, WLM, ULV	[175]
PGMA + PQDMA		CTA-4, V-501 (70°C).	S, WLM, ULV	[176]
PGMA + PGalSMA		CTA-4, V-501 (70°C)	S, WLM, ULV	[177]
PGMA + PGSHMA		CTA-4, V-501 (70°C)	S, WLM, ULV	[166]
POE + PMPC		CTA-4, VA-044 (50°C), pH=6.8	S, ULV	[130]
P(GMA-co-MAm-GFF)		CTA-4, V-501 (70°C)	F, Sp	[178]
P(GMA-co-GlyMA)		CTA-3, VA-044 (50°C)	WLM	[179]
P(GMA <sub>43</sub> -co-DSDMA)		CTA-3, V-501 (70°C)	ULV	[180]
P(GMA-co-QDMA)		CTA-4, V-501 (70°C)	S, WLM, ULV	[168]
P(KSPMA-co-HEMA)		CTA-4, V-501 (70°C) pH=5.5	NPs	[171]
β-CD-POEGMA		CTA-10, VA-044 (50°C)	S, WLM, ULV	[181]
PPEGMA-co-		CTA-8, V-50 (52°C)	S, WLM, ULV	[182]

	PFBMA		CTA-18, CTA-19, CTA-21, CTA-26, CTA-27, CTA-29, CTA-32, V-501 (70°C), V-50 (70°C)	S, WLM, ULV, L	[183-193]
	PDMA	PI	CTA-18, SPTP (405nm, 0.45 mW/cm <sup>2</sup> , 70°C).	S, TV, ULV, L	[192]
		PET	CTA-1, CTA-20, Eosin Y/ Ascorbic acid (530nm, 2.65 mW/cm <sup>2</sup> )	S, WLM	[194, 195]
DAAM	PEO	TI	CTA-28, V-50 (70°C)	S, WLM, ULV, L	[196]
	PHPMAc	PI	CTA-7, SPTP (405nm, 0.20 mW/cm <sup>2</sup> , 25°C).	S, WLM, ULV, L	[197-199]
	PVBTMAC	TI	CTA-26, V-501 (70°C)	S, WLM, ULV	[200]
	PVP		CTA-34, V-50 (60°C)	S, ULV	[201]
	PHPMAc- <i>b</i> -PHisMA	PI	CTA-7, SPTP (405–577 nm, 0.20 mW/cm <sup>2</sup> , 25°C)	L	[202]
	PDMA	TI	CTA-17, CTA-21, CTA-22, APS (60°C), V-50 (70°C)	NG	[42, 203]
		PI	CTA-21, SPTP (405nm, 0.45 mW/cm <sup>2</sup> , 37 or 70°C).	S, WLM, ULV	[204]
NIPAm	PPEGMA	Sono	CTA-14 (490 kHz, 40 W, 45°C)	NG	[205]
	PDMA- <i>b</i> -P(DMA- <i>co</i> AA)		CTA-19, V-501 (70°C)	S, WLM, BW, ULV	[206]
	PDEGA- <i>b</i> -PDMA	TI	CTA-27, VA-044 (40°C)	NG	[207]
	PDMA		CTA-31, CTA-33, V-50 (60°C)	S, F	[208]
MEA		EI	CTA-7, HRP/ACAC/H <sub>2</sub> O <sub>2</sub> (30°C)	SNPs	[209]
	PPEGMA	RI	CTA-7, KPS/NaAs (30 or 40°C)	SNPs	[210]
		EI	CTA-7, HRP/ACAC/H <sub>2</sub> O <sub>2</sub> (30°C)	SNPs	[209]
	PEO	TI	CTA-21, V-501 (70°C)	S, WLM, ULV	[211]
	PGMA		CTA-5, KPS/NaAs, pH=3 (30°C)	S, WLM, ULV	[212]
HBA	PEO	RI	CTA-4, KPS/NaAs, pH=3 (30°C)	S, WLM, ULV	[213]
	PNAEP		CTA-21, KPS/NaAs, pH=3 (30°C)	S, WLM, ULV	[214]
	PHEA	TI	CTA-23, VA-044 (44°C)	S, WLM, ULV	[215]
DEAA	PPEGMA	PI	CTA-24, DOXO/TEA (485nm, 2.2 mW/cm <sup>2</sup> , 37°C)	S	[216]
	PEO- <i>b</i> -PDMA		CTA-21, V-50 (70°C)	NG	[217]
			CTA-21, V-50 (60°C)	NG	[218]
DMAEMA	PEO		CTA-21, V-501 (65°C)	NG	[219]
META-PF <sub>6</sub>			CTA-7, V-50 (80°C)	S, WLM, L	[220]
	PPEGMA		CTA-7, V-50 (80°C)	S, WLM, L	[220]
NAT	PNAM	TI	CTA-24, VA-044, (50°C, 90°C)	S, WLM, ULV, L	[221, 222]
PEGMA	PEO		CTA-7, CTA-10, V-50 (70°C)	NG	[223]
MAm-FGD	PGMA		CTA-4, V-501 (70°C)	Sp	[224]
CMAm	PDMA		CTA-25, VA-044 (45°C)	S, WLM, ULV	[225, 226]
CysMA	PHPMAc	PI	CTA-7, SPTP (405nm, 0.20 mW/cm <sup>2</sup> , 25°C)	S, L, ULV	[227]
NAGA	PPEGMA		CTA-14, PP-OH (365nm, 3°C)	NG	[228]
AEDIBr	PADEIBr	TI	CTA-19, V-501 (70°C)	S, WLM, ULV	[229]
	PGMA		CTA-3, VA-044 (50°C)	W	[230]
HPMA + GlyMA		PI	CTA-7, SPTP (405nm, 0.5 mW/cm <sup>2</sup> , GOx, RT)	S, WLM, ULV, FV	[127]
		EI	CTA-7, HRP/ACAC/H <sub>2</sub> O <sub>2</sub> (RT)	ULV	[129]
	PEO + PQDMA	TI	CTA-4, VA-044 (50°C) pH4.	S, WLM	[231]
	PEO		CTA-7, SPTP (405nm, 0.5 mW/cm <sup>2</sup> , RT)	ULV	[138]
	PPEGMA	PI	CTA-10, SPTP (405nm, 0.5 mW/cm <sup>2</sup> , RT)	S, WLM, ULV	[232]
HPMA + DMEAMA	PEO		CTA-7, SPTP (405nm, 0.5 mW/cm <sup>2</sup> , RT)	ULV	[137]
		PET	CTA-21, Ru(bpy) <sub>3</sub> Cl <sub>2</sub> ·6H <sub>2</sub> O (9 mW/cm <sup>2</sup> , 25°C)	S, WLM, ULV	[233]
	PGMA		CTA-10, SPTP (405nm, 0.5 mW/cm <sup>2</sup> , GOx, RT).	ULV	[234]
HPMA + METAC	PEO	PI	CTA-7, SPTP (405nm, 0.5 mW/cm <sup>2</sup> , RT)	ULV	[137]
HPMA + MTC	PGMA	TI	CTA-3, V-501 (70°C)	S, WLM, ULV	[235]
HPMA + NiPAM	PEO	PI	CTA-7, SPTP (405nm, 0.5 mW/cm <sup>2</sup> , 37°C)	ULV	[236]

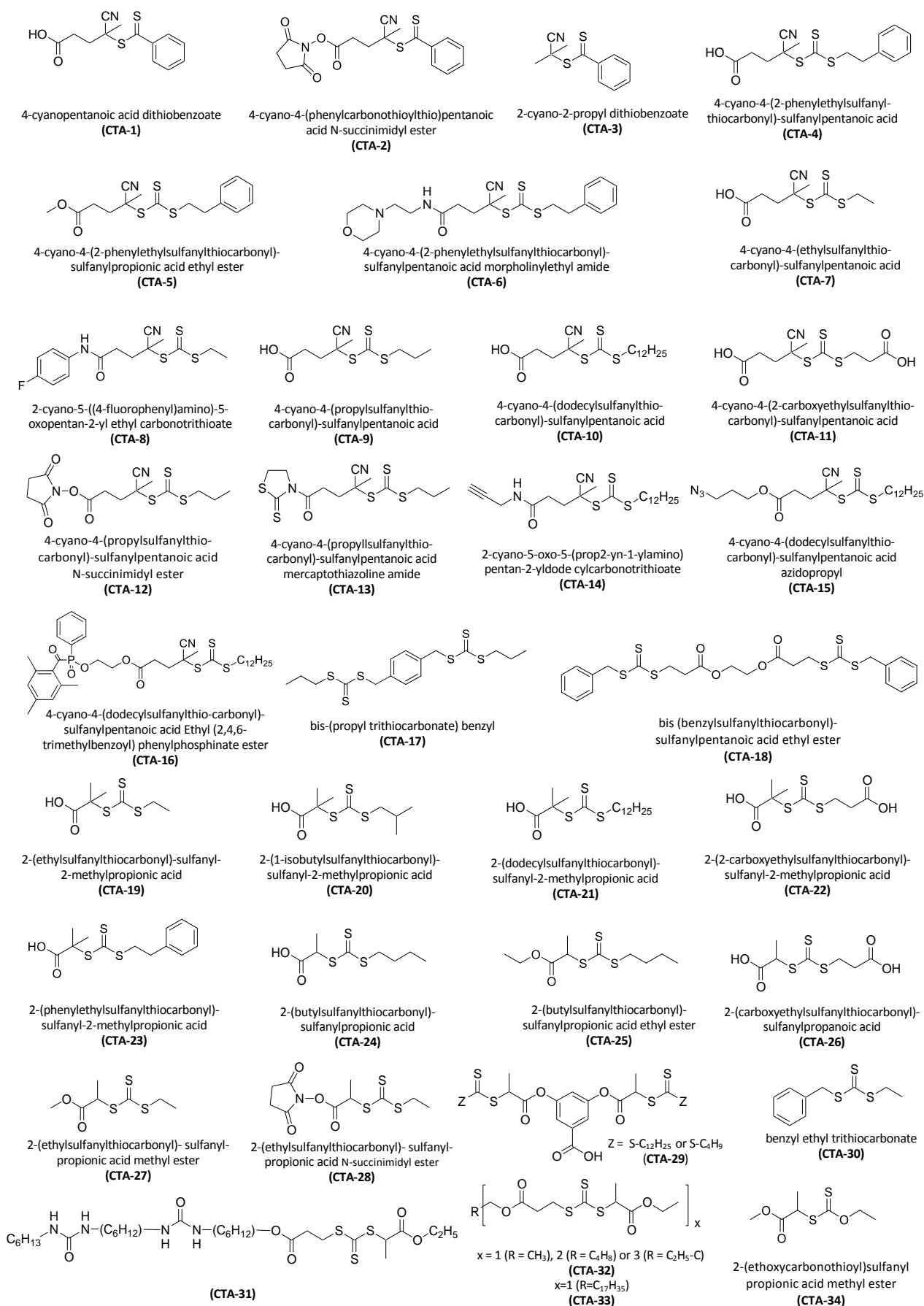
HPMA + RBMA	PPEGMA	PET	CTA-10, CTA-15, RB (595nm, 0.2 mW/cm <sup>2</sup> , RT)	S	[237]
MEA + PEGA	PDMA	TI	CTA-30, V-50 (70°C)	NG	[238]
AAM + AN			CTA-20, VA-044 (45°C)	S, WLM	[239]
DAAM + PEGMA		PET	CTA-11, ZnTMPyP (595nm, RT).	S, WLM	[240]
HBA + DAAM	PDMA	RI	CTA-21, KPS/NaAs, pH=3 (30°C)	S, WLM, ULV	[241]

109

## 110 2.1. Chain transfer agent (CTA).

111 A judicious selection of the appropriate CTA depending on the nature of the monomer to polymerize is  
112 crucial to ensure a good control of the RAFT polymerization.[242] **It was reported recently that the control**  
113 **degree of the RAFT polymerization can impact the nano-objects morphology in aqueous dispersion RAFT**  
114 **PISA.[243, 244]** CTAs are organosulfur compounds containing thiocarbonylthio function and carrying an  
115 activating/stabilizing Z-group that influences the addition step, and a fragmenting R-group that influences  
116 the fragmentation and re-initiation steps. Among the four types of CTAs, dithioesters and trithiocarbonates  
117 have been mainly used in aqueous dispersion RAFT PISA (**Fig. 2**). This may be explained by the nature of  
118 the monomers, more activated monomers (MAM) such as (meth)acrylate and (meth)acrylamide that are  
119 compatible with those CTAs. To the best of our knowledge, 2-(ethoxycarbonothioyl)sulfanyl propionic  
120 acid methyl ester (CTA-34) is the only thiocarbonate-type CTA reported in the literature to mediate the  
121 polymerization of a low activated monomer (vinylpyrrolidone, VP) in aqueous dispersion RAFT  
122 PISA.[201] Dithiocarbamates have been never reported yet. **Fig. 2** shows the wide range of functionalized  
123 CTAs reported in the context of aqueous dispersion RAFT PISA. Some of these CTAs have been  
124 extensively used, thanks to their commercial availability such as 4-cyanopentanoic acid dithiobenzoate  
125 (CTA-1), 2-cyano-2-propyl dithiobenzoate (CTA-3), and 4-cyano-4-(dodecylsulfanylthio-carbonyl)-  
126 sulfanylpentanoic acid (CTA-10), or to their facile synthesis route such as 4-cyano-4-(2-phenylethanesul-  
127 fanylthiocarbonyl)-sulfanylpentanoic acid (CTA-4), 4-cyano-4-(ethylsulfanylthio-carbonyl)-  
128 sulfanylpentanoic acid (CTA-7). Note that CTA-10 could be considered as a universal CTA model due to  
129 its compatibility with all RAFT-initiation systems (**Table 1**). It is well known that the rate of production of  
130 radicals affects both the control and the rate of polymerization.[99] Although temperature has been widely  
131 used as stimulus since the early works on aqueous dispersion RAFT PISA,[102] other activation ways  
132 have been successfully investigated such as light, ultrasound, redox, and enzymatic. As shown in **Fig. 3**,  
133 the activation of aqueous dispersion RAFT PISA has been achieved *via* two pathways: i) using an external  
134 radical source, and ii) taking advantage of the CTA dissociation.





135

136

**Fig. 2** Chain transfer agents (CTA) used in aqueous dispersion RAFT PISA.

## 2.2. RAFT activation via exogeneous radical sources.

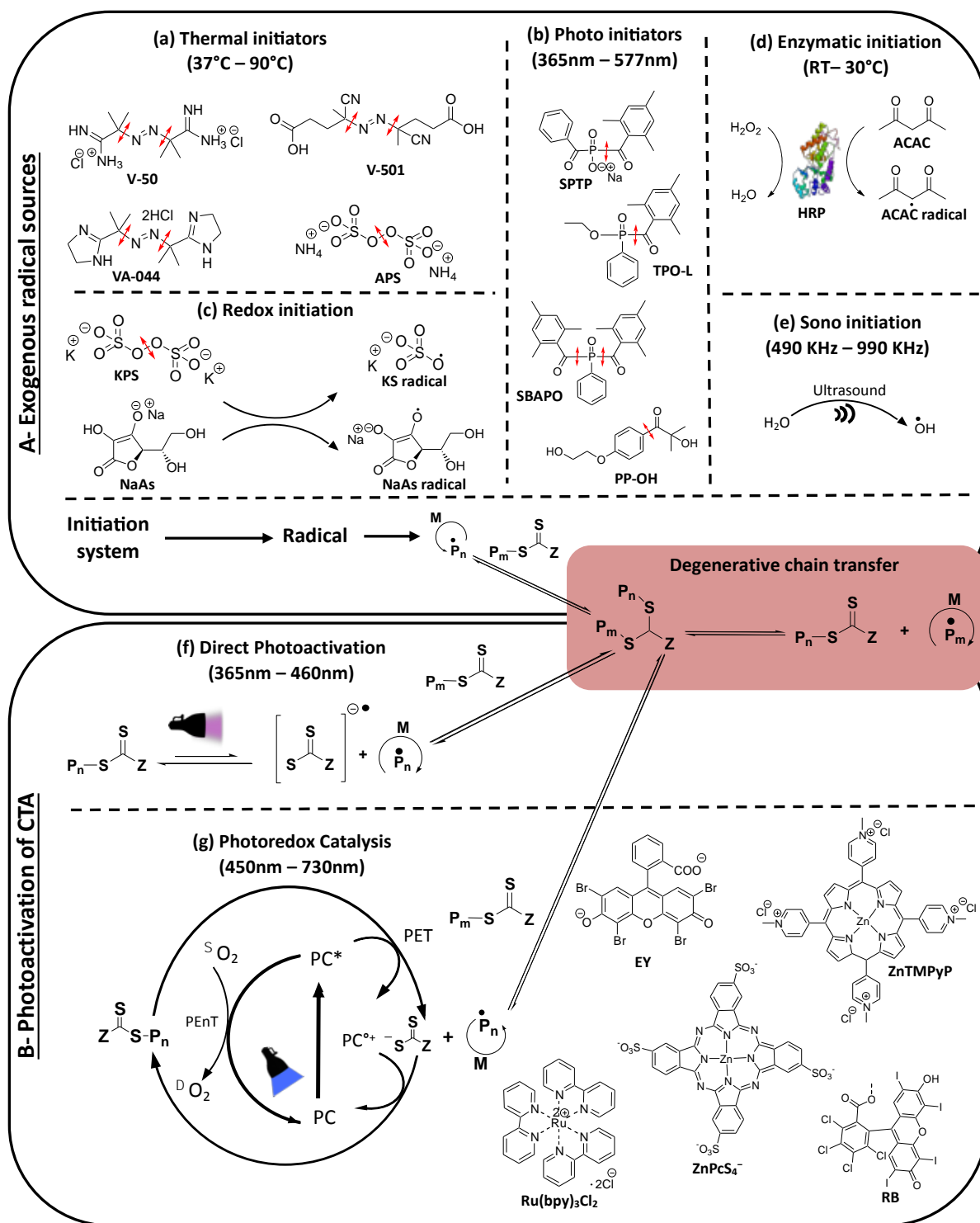
This method requires external initiation systems that forms radical to initiate RAFT polymerization. **Fig. 3A** summarizes the different initiation systems reported in the literature in the context of aqueous dispersion RAFT PISA.

*Thermally initiated (TI) RAFT PISA* involves the formation of radicals by decomposition upon heating of water-soluble azo compounds such as 4,4'-azobiscyanovaleric acid (V-501), 2,2'-azobis(2-(2-imidazolin-2-yl)propane) dihydrochloride (VA-044), and 2,2'-azobis(2-methylpropionamidine) dihydrochloride (V-50) that are the commonly thermal initiators employed in aqueous dispersion RAFT PISA (**Fig. 3a**). PISA involving V-501 and V-50 initiators are generally conducted above 60°C regarding their high 10-hour half-life temperature of 69°C and 56°C, respectively. However, VA-044 is suitable to perform PISA at relatively lower temperature (in the range of 37°C – 50°C) thanks to its 10-hour half-life temperature of 44°C. Due to the facile experimental protocol requested, TI-RAFT polymerization, which is by far the most reported technique in PISA, was used in various aqueous dispersion RAFT PISA formulations to produce large set of nano-objects morphologies (**Table 1**). However, the relatively high temperature requested could unable performing TI-RAFT PISA of monomers forming thermo-sensitive polymers or in the presence of biomolecules.[103, 245]

*Photo-initiated (PI) RAFT PISA*: during the last decade, light has grasped great interest of researchers as a potential alternative to temperature, due to its ability to carry out polymerization under mild reaction conditions (at ambient or below) and for its temporal (by turning on/off the light) and spatial (partial or total irradiation of the reaction medium) control of polymerization.[101, 103, 246-248] In a similar way as for TI-RAFT, PI-RAFT involves formation of radicals by decomposition of photoinitiators that absorb light at UV-visible (mostly around 405nm). Phosphine oxides-based compounds, including sodium phenyl-2,4,6-trimethyl-benzoylphosphinate (SPTP), phenylbis(2,4,6-trimethylbenzoyl) phosphine oxide (SBAPO), and ethyl phenyl(2,4,6-trimethylbenzoyl)phosphinate (TPO-L) as well as 2-hydroxy-4-(2-(hydroxyethyl)ethoxy)-2 methylpropio-phenone (PP-OH) are successfully used in aqueous dispersion PI-RAFT PISA (**Table 1**). Ultra-fast RAFT polymerization rate was observed, few minutes are needed to achieve full monomers conversion,[132, 158, 192] which is an additional advantage for PI-RAFT PISA compared to TI-RAFT PISA.

*Other radical sources*: alternative initiation approaches have been investigated to activate aqueous dispersion RAFT PISA under mild conditions. Briefly, due to the relatively low activation energy, Redox-initiated (RI) RAFT polymerization[151, 210, 212-214, 241] involving redox reaction between potassium persulfate (KPS) and L-ascorbic acid sodium salt (NaAs) to form radicals has been investigated in the context of aqueous dispersion RAFT PISA at room temperature. In Enzymatic-initiated (EI) RAFT polymerization, horseradish peroxidase (HRP) enzyme has been used to catalyse the oxidation of acetylacetone (ACAC) to ACAC radical by hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). [129, 147, 209] Recently,

172 ultrasound was used as stimulus to activate RAFT polymerization in aqueous dispersion RAFT PISA  
 173 (Sono-RAFT). In Sono-RAFT, no exogenous initiator is required, because radicals are generated *in-situ* by  
 174 the homolysis of water. [148, 205]. Although the potential of these approaches for aqueous dispersion  
 175 RAFT PISA, only few works have been reported in this context. The absence of a stimulus to drive the  
 176 spatiotemporal control of RI and EI RAFT polymerizations and the specific equipment required for Sono  
 177 RAFT polymerization are the main drawbacks of these initiation methods compared to the PI-RAFT.[102]  
 178



179

180 **Fig. 3** Initiation systems used in aqueous dispersion RAFT PISA. The double-headed red arrows represent where  
181 the species break down to form the radicals.

### 182 2.3. RAFT activation via a photoactivation of CTA.

183 Alternative pathways for RAFT activation under mild conditions using light as stimulus have been recently  
184 investigated in aqueous dispersion RAFT PISA, thanks to the well-known thiocarbonylthio  
185 photoactivity.[249]

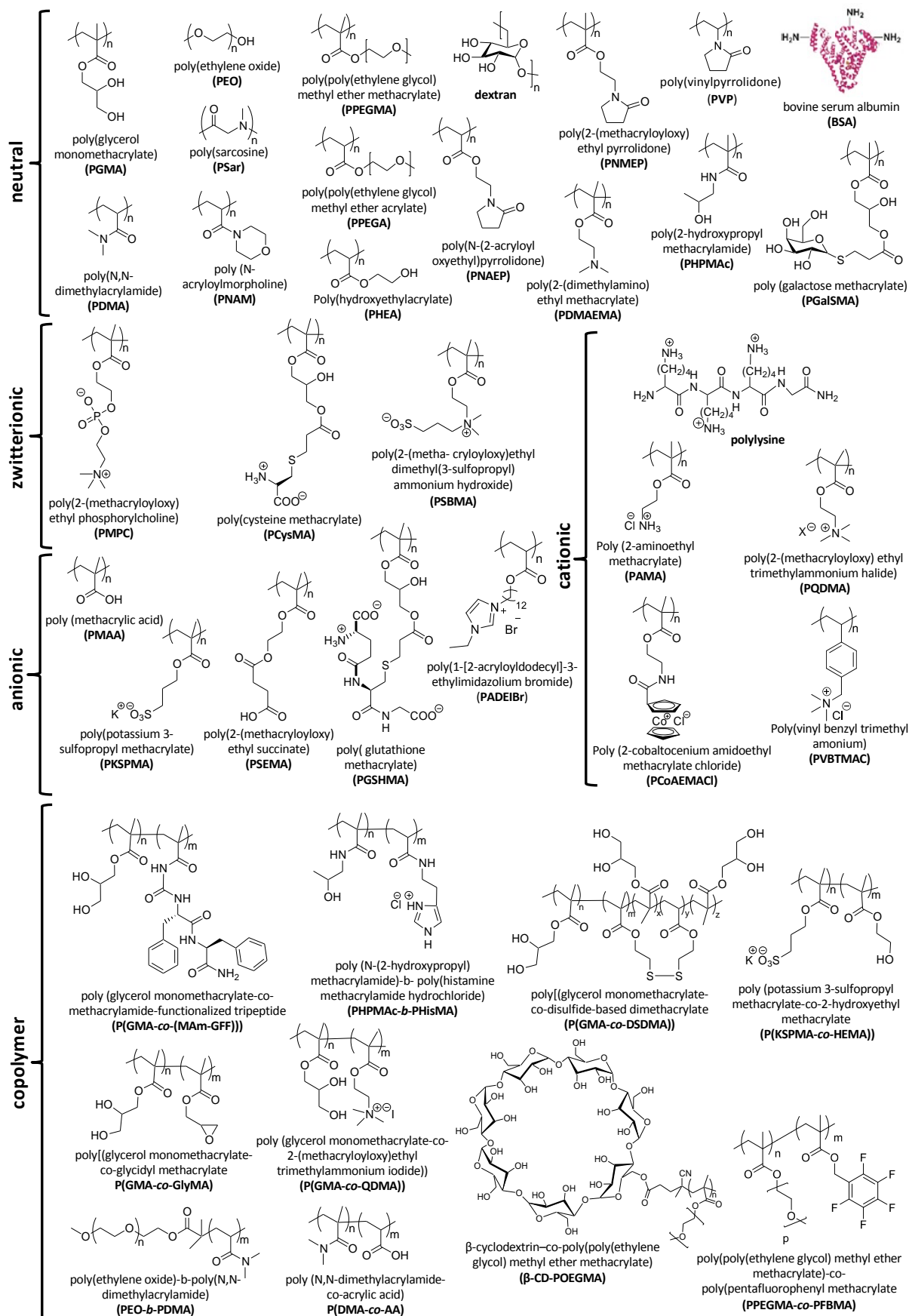
186 The first method involves a direct dissociation (DD) of CTA under irradiation, thanks to the high  
187 absorption of CTA at UV region ( $\sim 320$  nm,  $\pi \rightarrow \pi^*$  electronic transition) and at visible region ( $\sim 430$  nm  $n$   
188  $\rightarrow \pi^*$ ), resulting in the fragmentation of the weakest C–S bond generating a thiyl radical and an active  
189 carbon radical able to initiate and control the chain propagation (**Fig. 3f**). In this case, the CTA acts as  
190 iniferter (initiator-transfer-terminator). This approach was successfully used in many aqueous dispersion  
191 RAFT PISA[132, 140-142, 155, 156] as summarized in **Table-1**. DD of CTA under UV-visible irradiation  
192 is an attractive technique since no exogeneous initiator is required to initiate the polymerization. However,  
193 a slow RAFT polymerization is communally observed under visible light due to the slow C-S dissociation.  
194 Under UV irradiation, CTA can undergo a photolytic degradation resulting in a loose of polymerization  
195 control.[250]

196 An efficient RAFT activation under visible light radiation has recently been developed by photoredox  
197 catalysis to minimize the unwanted photolysis of CTAs. In this approach (**Fig. 3g**), called photo-electron  
198 transfer RAFT polymerization (PET-RAFT),[251-254] the polymerization is carried out by irradiating a  
199 photocatalyst (PC) under an appropriate wavelength to generate an excited species (PC\*) enables reducing  
200 the CTA by an electron transfer into an anion radical and a radical that propagates the polymerization.  
201 After a few successive additions of monomers, the catalytic cycle is completed by regenerating the  
202 dormant polymer chain and the PC in its ground state.[255, 256] Various water-soluble PC such as zinc  
203 meso-tetra(N-methyl-4-pyridyl) porphine tetrachloride (ZnTMPyP),[144, 240]  
204 tris(bipyridine)ruthenium(II) chloride (Ru(bpy)<sub>3</sub>Cl<sub>2</sub>),[143, 145, 161, 233] Eosin Y (EY),[194]  
205 tetrasulfonated zinc phthalocyanine (ZnPcS<sub>4</sub><sup>-</sup>),[146] and Rose Bengal [237] have been successfully used to  
206 catalyse aqueous dispersion RAFT PISA (**Table-1**).

### 208 3. Hydrophilic steric stabilizer block.

209 A wide variety of functional hydrophilic polymers has been used to conduct aqueous dispersion RAFT  
210 PISA and ultimately to stabilize the formulated nano-objects. **Fig. 4** summarizes the chemical structures of  
211 the steric stabilizers reported to date in the literature. The most commonly are: i) neutral such as  
212 poly(glycerol methacrylate) (PGMA),[114, 124] poly(ethylene oxide) (PEO),[131, 132, 135, 147, 148] and  
213 poly(2-hydroxypropyl methacrylamide) (PHPMAc),[154, 197, 227] ii) cationic such as poly(2-  
214 dimethylamino)ethyl methacrylate)) (PQDMA),[43, 168] iii) anionic such as poly(3-sulfopropyl potassium  
215 methacrylate) (PKSPMA),[43, 171] and iv) zwitterionics such as poly(2-methacryloyloxyethyl

216 phosphorylcholine) (PMPC),[130, 164, 165] poly(potassium 3-sulfopropyl methacrylate) cysteine)  
217 (PcysMA),[166] and poly(sulfobetaine methacrylate) (PSBMA).[167] Mixture of homopolymers[130, 166,  
218 173-177, 231] or copolymers[168, 171, 180, 182, 206, 207, 217] were also used.



219

220 Fig. 4. Steric stabilizer blocks used for aqueous dispersion PISA.

221 Although the scope of aqueous dispersion PISA is widely focused on steric stabilizer blocks based on  
222 synthetic polymers, some reports describe the successful preparation of nanostructures from natural  
223 polymers such as dextran[155-159] and  $\beta$ -cyclodextrin,[181] bovine serum albumin (BSA) [161] as well as  
224 polylysine as bio-inspired peptide.[170] Recently, we demonstrated for the first time the suitability of the  
225 aqueous dispersion PISA process to prepare polysaccharides-based nano-objects of advanced  
226 morphologies, in contrast to solvent-switch methods that led mainly to spheres.[29, 32] To do so, graft  
227 copolymers composed of dextran as a hydrophilic backbone bearing poly(2-hydroxypropyl methacrylate)  
228 grafts, were prepared *via* PI-RAFT PISA at room temperature.[155, 157-159] Our investigations revealed  
229 that this model system can form well-defined vesicles of modulable membrane thickness over a wide range  
230 of solid content.[158]

231 Two strategies have been reported in the literature to prepare reactive steric stabilizers used in PISA  
232 process. The first one, and probably the most used, involves TI-RAFT polymerization of vinyl derivatives  
233 monomers to produce the corresponding macromolecular chain transfer agent (macroCTA) such as PGMA  
234 and PHPMAc. The second is based on the functionalization of a pre-synthesized polymers by CTA. For  
235 instance, CTA group is introduced on PEO by esterification of its terminal hydroxyl function, while for  
236 dextran, BSA and polylysine, the CTA group is introduced through an amidation coupling.

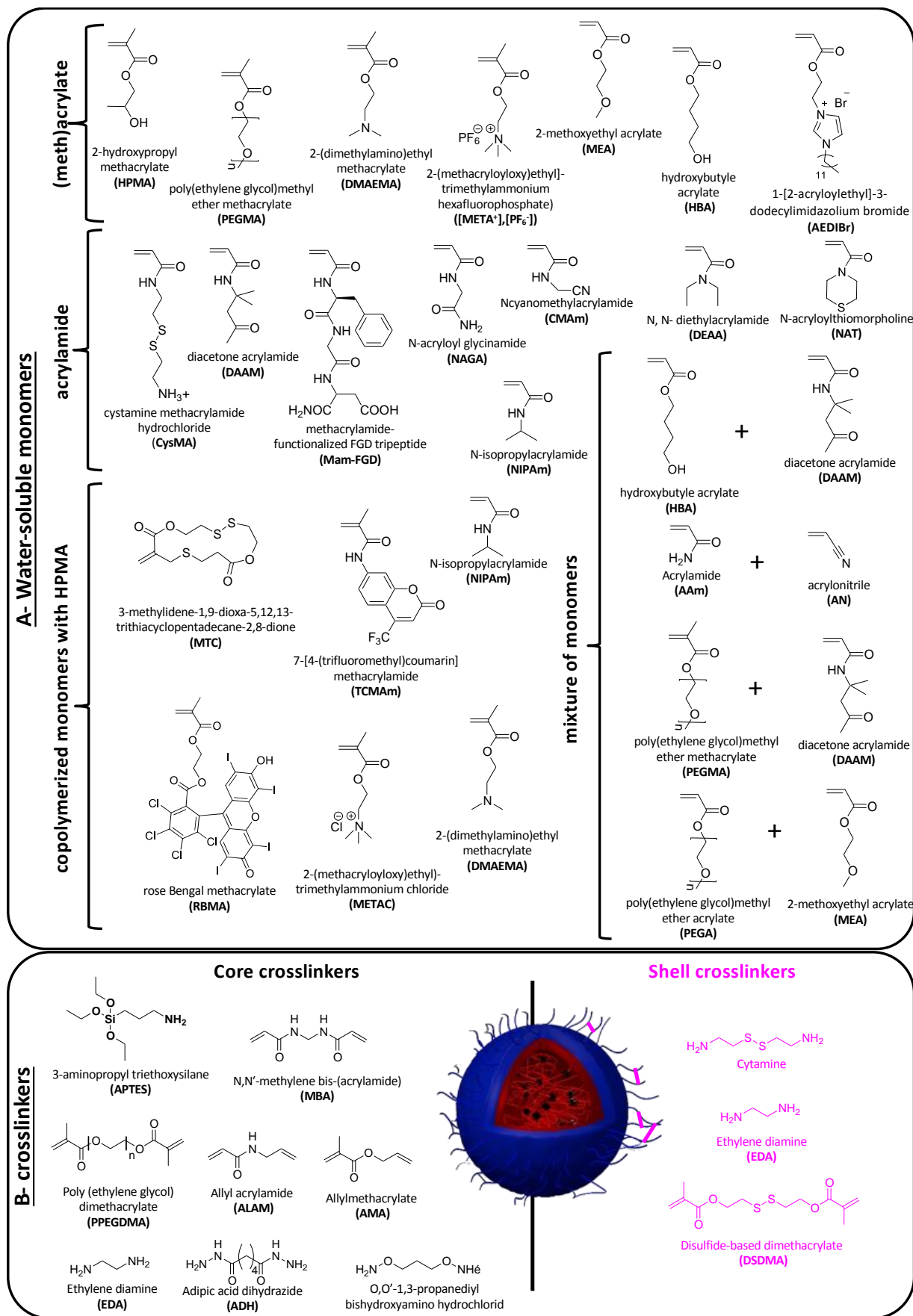
237

## 238 **4. Water-soluble monomers**

### 239 **4.1. Overview**

240 The essential criterion to well conduct an aqueous dispersion PISA is the initial water-solubility of the  
241 monomer used that leads to a water-insoluble polymer. Thus, a limited number of monomers respecting  
242 this condition was known in 2014 when Warren and Armes reported the first review on aqueous dispersion  
243 RAFT PISA.[71] At this time, the literature examples included N-isopropylacrylamide (NIPAM),[42]  
244 N,N'-diethylacrylamide (DEEA),[41, 217, 218] 2-methoxyethyl acrylate (MEA),[210] 2-hydroxypropyl  
245 methacrylate (HPMA), [43, 114-117, 121, 123, 131, 165, 168, 171, 177, 180] and di(ethylene glycol)  
246 methyl ether methacrylate (DEGMA).[223] Moreover, regardless of the polymerization methods used to  
247 grow the core-forming block, only HPMA enables a direct access to advanced nano-objects morphologies  
248 (worms and vesicles).[114-117, 121, 123, 131, 165, 177, 180] During the last ten years, great efforts have  
249 been made to overcome these limitations either by playing on the experimental conditions or by  
250 developing new monomers. The monomers currently reported for aqueous dispersion RAFT PISA are  
251 summarized in the **Fig. 5A** and the experimental conditions used for their polymerization are summarized  
252 in the **Table-1**. In the following paragraphs, recent progress made for previous monomers (NIPAM, MEA,  
253 DEEA and DEGMA) as well as newly developed ones for aqueous dispersion RAFT PISA will be  
254 described. A particular attention will be given to HPMA, the monomer of reference and diacetone  
255 acrylamide (DAAM) the emerging water-soluble monomer.

256



257

258 Fig. 5. Water-soluble monomers and (B) crosslinkers used in aqueous dispersion RAFT PISA.



## 4.2. Water-soluble (meth)acrylates

*N,N'*-dimethylaminoethyl methacrylate (DMAEMA) is a water soluble monomer forming a cationic polymer with thermo- and pH-responsive behavior.[257] DMAEMA is probably the first methacrylate monomer used in aqueous dispersion RAFT PISA. Yan and Tao[219] reported the chain extension of PEO macro-RAFT agent with DMAEMA at 65°C, above the lower critical solubility temperature (LCST) of poly(*N,N'*-dimethylaminoethyl methacrylate) - PDMAEMA,[258] in the presence of a diacrylamide symmetric crosslinker (*N,N'*-methylene bis-(acrylamide), MBA). However, only spherical nanogel (NG) has been formed when cooling down the formulation to RT, probably due to the action of MBA that prevents chain reorganization into higher order morphology. By introducing a permanent cationic charge in DMAEMA resulting in 2-(methacryloyloxy)ethyltrimethyl-ammonium hexafluorophosphate ([META<sup>+</sup>],[PF<sub>6</sub><sup>-</sup>]) An and coworkers[220] have modulated the water-solubility of ([META<sup>+</sup>],[PF<sub>6</sub><sup>-</sup>]) and the water-insolubility of its corresponding homopolymer. Thus, in an elegant way, the authors succeeded in producing stable spheres, worms and high-density network structure by chain extending poly(ethylene glycol)methyl ether methacrylate (PEGMA) macro-RAFT agent with ([META<sup>+</sup>],[PF<sub>6</sub><sup>-</sup>]) in water and without adding any crosslinker. By taking advantage from the facile self-assembly of HPMA-based diblock amphiphilic copolymers into advanced morphologies, as it will be discussed below, several research groups have been interested in studying the DMAEMA/HPMA binary system to drive the formation of higher-order morphologies.[137, 232-234] In a first study, Tan and coworkers[232] observed various morphologies, such as worms and vesicles, by chain extension of poly(poly(ethylene glycol) methyl ether methacrylate), PPEGMA, macro-CTA with HPMA/DMAEMA co-monomers at RT using PI-RAFT polymerization. In a second study, Guragain and Perez-Mercader[233] extended PEO-*b*-PDMAEMA diblock copolymer spheres with HPMA to produce worms that can undergo a morphological transition to vesicles by switching the pH of the medium.

*2-Methoxyethyl acrylate* (MEA) is a highly water-soluble monomer forming a water-insoluble poly(2-methoxyethyl acrylate) - PMEAA. Such a feature has appealed the attention of researchers for developing novel system for aqueous dispersion PISA.<sup>[209-211]</sup> An and co-workers<sup>[210]</sup> reported formulation of crosslinked spherical nanoparticles (NPs) by chain extending PPEGMA with MEA, in the presence of a poly(ethylene glycol) diacrylate (PEGDA) crosslinker at 30°C by using a low temperature initiation system (RI-RAFT polymerization in the presence of KPS/NaAs). As we previously mentioned, crosslinking the core of nano-objects during the PISA using a symmetric crosslinker leads to a frozen spherical morphology.[223, 238] In this context, Maeda and coworkers[211] have successfully observed vesicles at high solid content (20% to 30%), while worms were observed only at 15% w/w, by performing PISA of MEA from PEO macro-CTA at 70°C without adding any crosslinker. To increase the experimental window of worms, and more particularly fiber morphology, Rieger and coworkers[208] used an end-

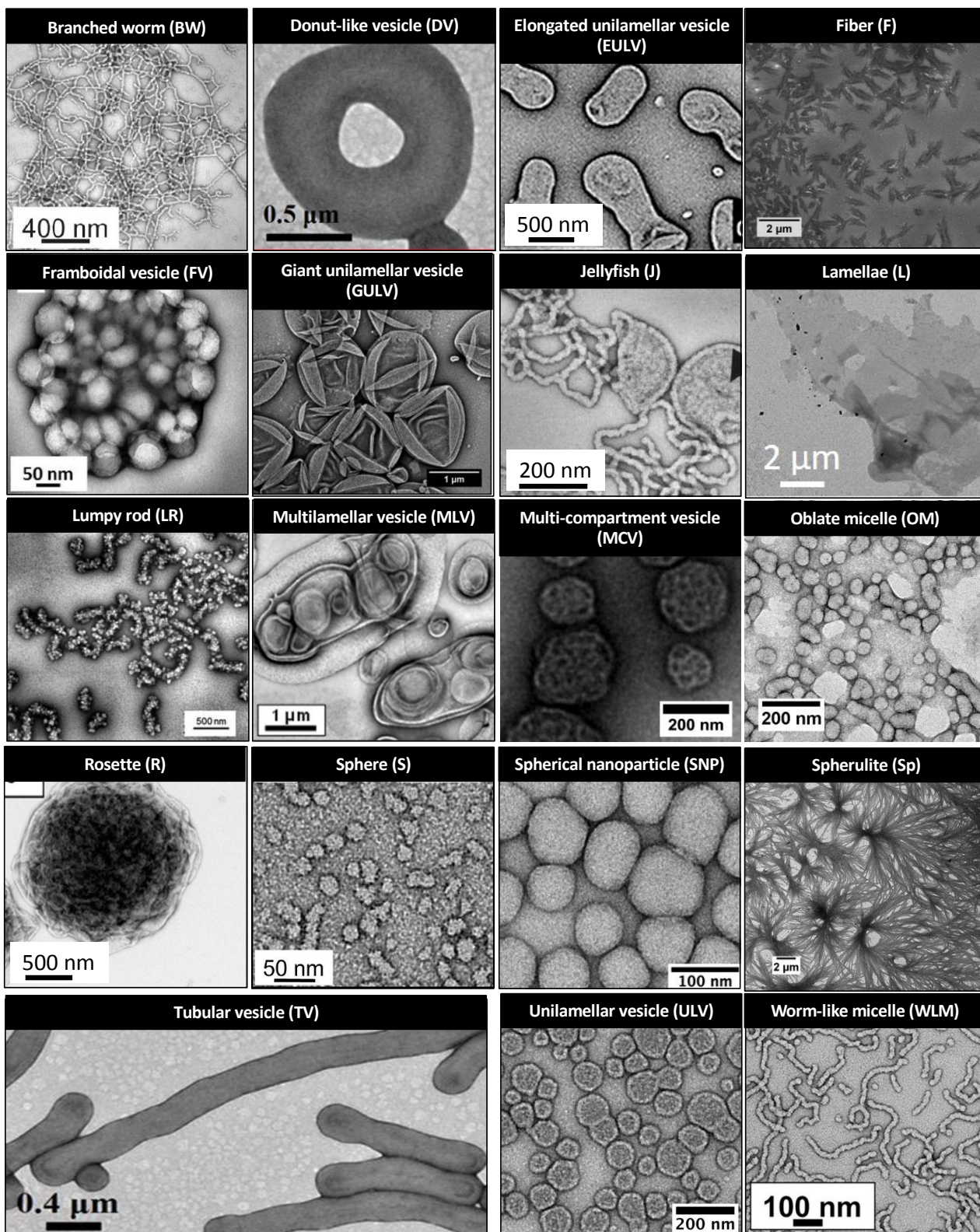
293 functionalized poly(N,N- dimethylacrylamide) (PDMA) macro-CTA with a hydrogen- bonded bis-urea to  
294 drive PISA of MEA in water towards fiber.

295 *Hydroxypropyl methacrylate (HPMA)* is a water-miscible[259] monomer, up to 13% at 25°C, forming a  
296 water-insoluble homopolymer (poly(hydroxypropyl methacrylate) - PHPMA) from an average degree of  
297 polymerization of ~15. PHPMA exhibits glass transition temperature ( $T_g$ ) of 95°C in bulk which decreases  
298 to 47°C by plasticization in water (values determined for PHPMA of an average molar mass of 30000  
299 g/mol).[114] HPMA is a commercially available monomer prepared by reacting propylene oxide with  
300 methacrylic acid resulting in HPMA (75 mol%) and 25 mol% of its isomer (2-hydroxyisopropyl  
301 methacrylate - HIPMA) due to the poor regioselectivity of the epoxide ring opening reaction.[259] To the  
302 best of our knowledge, the contribution of each isomer in the self-assembly has not yet been studied.  
303 Employed for the first time in 2010,[43] HPMA has become arguably the most studied monomer in the  
304 context of aqueous dispersion PISA. As summarized in **Table 1**, more than 60 publications have been  
305 reported to date on the formulation of nano-objects composed of PHPMA as core-forming block. The  
306 particularity of HPMA that makes it a highly attractive monomer for PISA comes probably from its  
307 capacity to form large set of morphologies including common morphologies (micelle or sphere (S) worm-  
308 like micelles (WLM) and unilamellar vesicle (ULV)) as well as complex ones (framboidal vesicle (FV),  
309 jellyfish (J), tubular vesicle (TV), multi-compartment vesicle (MCV) and donut-like vesicle (DV)). **Fig. 6**  
310 summarizes some images of such various morphologies. In the following paragraphs, the discussion will  
311 be limited to a few key works on HPMA in the context of aqueous dispersion RAFT PISA.

312 HPMA was successfully polymerized from a variety of functional steric stabilizers in aqueous dispersion  
313 RAFT PISA to prepare nano-objects with variable surface chemistry. Nano-objects with neutral stabilizers,  
314 including PGMA[116, 121, 123, 125, 129] and PEO,[131, 134, 135, 140, 260] were designed for  
315 biomedical applications,[116, 131, 134, 135, 260] for stabilization of oil-in-water pickering  
316 emulsions,[121, 123, 125] and to improve the resistance against surfactants.[129, 140] On the other hand,  
317 polyelectrolyte-based stabilizers block including cationic[168-170, 175] and anionic[166, 171, 172] ones  
318 were used to enhance the electrostatically stabilization of nanoparticles[166, 169-172] and for  
319 antimicrobial activity.[170] However, only spheres are observed when using polyelectrolytes, due to the  
320 strong electrostatic repulsion between the charged chains forming the steric stabilizer. Various strategies  
321 have been used to reduce the charges around such nano-objects and thus to reach higher morphologies,  
322 such as the use of statistical copolymer-based stabilizers by copolymerization of the ionic monomer with a  
323 nonionic comonomer,[168] or the use of binary mixtures of polyelectrolytic stabilizer and nonionic  
324 one.[166, 174, 176, 231] HPMA has also been used as a model monomer to study the mechanism of PISA  
325 in aqueous dispersion from natural stabilizers such as BSA [161] and dextran.[155-159] Note that aqueous  
326 dispersion RAFT PISA was beneficial in achieving advanced morphology (including vesicles) using  
327 dextran as polysaccharide stabilizer[155-159] in contrast to nanoprecipitation, [157] which only led to

328 spherical nanoparticles. On the other hand, HPMA has been used to study the impact of the ACPs  
329 architecture on the resulted nano-objects morphology. Comparing with linear ACPs, it was demonstrated  
330 that branched ACPs[139] did not facilitate the formation of higher-order morphologies, while the  
331 bottlebrush[153] or graft[158, 159] ACPs can promote the formation of higher-order morphologies when  
332 targeting similar degrees of polymerization. Further studies are needed to generalize these observations.

333



334

335 **Fig. 6** A selection of some TEM images of PHPMA core-forming block nano-objects prepared by aqueous  
 336 dispersion RAFT PISA. Images reproduced and adapted with permission: BW (ref [114]. Copyright 2011,  
 337 American Chemical Society), DV (ref [126]. Copyright 2020, American Chemical Society), EULV (ref [160].  
 338 Copyright 2018, American Chemical Society), F (ref [178]. Copyright 2020, American Chemical Society), FV (ref

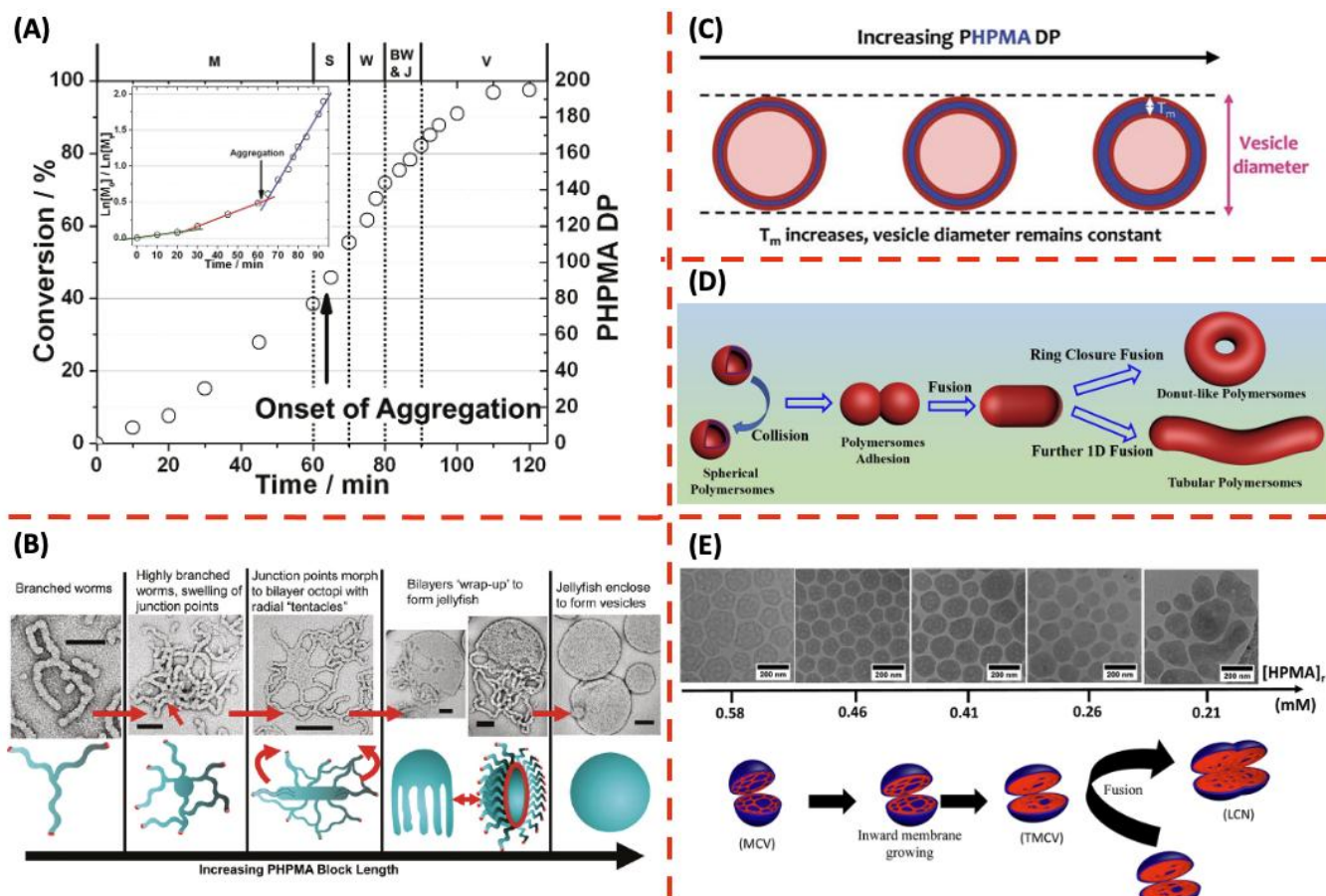
339 [117]. Copyright 2012, American Chemical Society), GULV (ref [132]. Copyright 2017, Royal Society of  
340 Chemistry), J (ref [114]. Copyright 2011, American Chemical Society), L (ref [138]. Copyright 2019, Royal  
341 Society of Chemistry), LR (ref [165]. Copyright 2011, Royal Society of Chemistry), MLV (ref [131]. Copyright  
342 2014, American Chemical Society), MCV (ref [159]. Copyright 2022, American Chemical Society), OM (ref [155].  
343 Copyright 2018, Royal Society of Chemistry), R (ref [134]. Copyright 2019, American Chemical Society), S (ref  
344 [114]. Copyright 2011, American Chemical Society), SNP (ref [156]), Sp (ref [178]. Copyright 2020, American  
345 Chemical Society), TV (ref [126]. Copyright 2020, American Chemical Society), ULV (ref [158]. Copyright 2021,  
346 American Chemical Society), and WLM (ref [116]. Copyright 2012, American Chemical Society).

347

348 PGMA-*b*-PHPMA was used as model to investigate the polymerization behavior in aqueous dispersion TI-  
349 RAFT PISA (**Fig. 7A**). [114] A non-linear evolution of the semilogarithmic plot, displaying mainly two  
350 distinct regimes was observed for the first time. To sum up, the reaction medium remained homogeneous  
351 in the first regime, revealing a modest growth of PHPMA that resulted in the formation of water-soluble  
352 diblock copolymers. The medium became turbid at a specific time called onset of nucleation, indicating  
353 that PHPMA block has reached its water-soluble critical size. At this time, monodisperse micelles were  
354 observed by DLS and TEM. In the second regime, the dispersion became progressively heterogeneous and  
355 opaque, involving an increase in the slope of the semilogarithmic plot. This unusual kinetic profile is  
356 attributed to the diffusion of the unreacted HPMA monomers into nascent micelles, resulting in an increase  
357 in the local monomer concentration and thus an enhancement of the polymerization rate. TEM images of  
358 aliquots extracted in the second regime enabled authors to establish a remarkable mechanistic of the *in situ*  
359 structural evolution from micellar nucleation to the final vesicular morphology. These images reveal that  
360 “jellyfish-like” structure is the key intermediate in the transition WLM to ULV as shown in **Fig. 7B**.

361 Morphology transition beyond the vesicular one has been studied by many research groups. By using *in*  
362 *situ* SAXS studies, Armes and coll. [119] demonstrated that the overall vesicle diameter remained constant  
363 while the vesicle membranes continue to thicken, suggesting an ‘inward growth’ mechanism of  
364 polymersomes during the final stages of the HPMA polymerization from PGMA at 70°C (**Fig. 7C**). Using  
365 the same PISA system but at room temperature under 405nm irradiation, Tan and coll. [126] observed that  
366 polymersomes fused to form tubular and donut-like polymersomes (**Fig. 7D**). By polymerizing HPMA  
367 from dextran backbone *via* PI-RAFT PISA, our group [159] observed the formation of large compound  
368 nano-objects (LCNs) resulting from a fusion of multicompart ment vesicles as intermediate structures,  
369 when targeting long PHPMA grafts degrees of polymerization (**Fig. 7E**). We attributed the formation of  
370 this unprecedented intermediate structure to a local phase separation of dextran and PHMPA/HPMA,  
371 which leads to aqueous phase domains.

372



373  
 374 **Fig. 7** (A) HPMA polymerization kinetics obtained for the targeted PGMA<sub>47</sub>-b-PHPMA<sub>200</sub> diblock copolymer  
 375 nano-objects prepared via aqueous dispersion TI-RAFT PISA at 70 °C and 10% w/w solids. The inset shows a  
 376 semilogarithmic plot. Reproduced with permission from ref [114] Copyright 2011, American Chemical Society. (B)  
 377 Suggested mechanism for the WLM-to-V transformation during the synthesis of PGMA<sub>47</sub>-b-PHPMA<sub>200</sub> by aqueous  
 378 dispersion TI-RAFT PISA at 70 °C. Reproduced with permission from ref [114] Copyright 2011, American  
 379 Chemical Society (C) Schematic representation of the 'vesicle inward growth' mechanism when targeting PGMA<sub>45</sub>-  
 380 b-PHPMA<sub>200</sub> vesicles via aqueous dispersion TI-RAFT PISA at 70 °C. Reproduced with permission from ref [119]  
 381 Copyright 2020, Royal Society of Chemistry. (D) Schematic Illustration for the growth of polymersomes during the  
 382 synthesis of PGMA<sub>62</sub>-b-PHPMA<sub>1000</sub> by aqueous dispersion PI-RAFT PISA at 25 °C and 20% w/w. Reproduced with  
 383 permission from ref [126] Copyright 2020, American Chemical Society (E) CryEM images of HPMA and  
 384 schematic Illustration for the transformation of MCV intermediate structure to LCN morphology during the  
 385 synthesis of Dex-g<sup>12</sup>-PHPMA<sub>500</sub> by aqueous dispersion PI-RAFT PISA at 25 °C and 10% w/w. Reproduced with  
 386 permission from ref [159] Copyright 2022, American Chemical Society.

### 388 4.3. Water-soluble acrylamides

389 *N*-isopropylacrylamide (NIPAm) is a water-soluble monomer forming a thermoresponsive polymer,  
 390 poly(*N*-isopropyl-acrylamide) (PNIPAm), that undergoes a coil-to-globule transition in water at  
 391 temperature higher than its lower critical solution temperature (LCST) (≈32 °C).[261] Inspired from the

392 work of Jo and coll.[262] that exploited the particular thermosensitive characteristics of PNIPAm to  
393 produce crosslinked nanogels *via* aqueous dispersion ATRP mediated PISA, Stucky and coll.[42] were the  
394 first preparing PNIPAm-based nanogels (NG) by aqueous dispersion RAFT PISA. In this pioneering work,  
395 NIPAm was grown in water from a preformed PDMA macromolecular RAFT agent at 70°C. 2 mol% of  
396 MBA crosslinker (relative to NIPAm) was voluntarily added at the beginning of the polymerization to  
397 progressively crosslink the core of nano-objects and avoid the dissolution of nano-objects after cooling  
398 down to room temperature (RT). NGs have been also observed by others when NIPAm was copolymerized  
399 with MBA even by modifying both the chemical nature of the hydrophilic steric stabilizer  
400 (poly(oligo(ethylene glycol) methyl ether acrylate), PPEGMA, instead of PDMA)[205] and the architecture  
401 of copolymer (tribloc instead of dibloc).[203] Different strategies were employed to prepare higher-order  
402 morphologies of PNIPAm-based block copolymers nanoparticles. Sumerlin and coll.[206] have selectively  
403 crosslinked the corona of the nanoparticles instead of the core. To do this, authors prepared nano-objects at  
404 70°C by polymerizing NIPAm from a water-soluble copolymer composed of acrylic acid (AA) and DMA,  
405 followed by an immediate crosslinking of the corona at 70°C prior cooling *via* the reaction of the  
406 carboxylic acid groups of AA with ethylene diamine (EDA) in the presence of a carbodiimide. Tan and  
407 coll.[263] have successfully prepared advanced nano-objects morphology by copolymerizing NIPAm and  
408 a small amount of asymmetric allyl acrylamide (ALAM), containing two vinyl groups of different  
409 reactivities (**Fig. 5B**), from PDMA under purple irradiation (405nm) at 70°C. Unlike MBA, which reacts  
410 and crosslinks the nanoparticles-core from the beginning of the polymerization, ALAM delays the  
411 crosslinking step at the end of the polymerization, thanks to the difference of reactivity between the  
412 acrylamide function that reacts at the early stage of polymerization and the allyl function that reacts at the  
413 late polymerization stage.[186] We suspect that the development of this second strategies can improve the  
414 attractivity of NIPAm for aqueous dispersion PISA.

415 *N,N*-diethylacrylamide (DEAA) is another water-soluble monomer forming thermosensitive poly(*N,N*-  
416 diethyl-acrylamide) homopolymer (PDEAA) exhibiting LCST at 32 °C.[264] DEAA is one of the first  
417 monomer carried out in aqueous dispersion PISA. In 2007, Charleux and coll.[41] reported preparation of  
418 crosslinked core PDEAA-based NG directly in water. In this seminal work, a hydrophilic poly(sodium  
419 acrylate) alkoxyamine macroinitiator was chain extended by DEAA *via* NMP. Few years later, the same  
420 team carried TI-RAFT polymerization of DEAA in the presence of MBA, at 60°C-70°C in water from  
421 PEO-*b*-PDAM copolymer as hydrophilic steric stabilizer.[217, 218] Only spherical NGs have been  
422 observed as judged by transmission electron microscopy images. Ten years later, Boyer and coll.[264]  
423 used PDEAA NGs as model to prepare *in situ* doxorubicin (DOX)-loaded nanoparticles for drug delivery  
424 by aqueous dispersion PI-RAFT PISA under mild conditions (37°C). In addition to being an efficient  
425 antitumor drug, the authors discover that DOX plays an unexpected role of photocatalyst in the presence of  
426 triethylamine, leading to an acceleration of the rate of polymerization. Despite the potential of DEAA, this

427 monomer is still underexploited in aqueous dispersion PISA, and that more effort is needed to find the  
428 adequate experimental conditions allowing access to advanced morphologies.

429 *Diacetone acrylamide (DAAM)* is an emerging commercially available water-soluble monomer that forms  
430 a water-insoluble polymer (PDAAM) from an average degree of polymerization of 50.[265] During the  
431 last seven years, DAAM has grasped attention of scientists due to its potential to produce polymeric nano-  
432 objects of advanced morphology in aqueous dispersion PISA. DAAM was used for the first time in 2015,  
433 simultaneously but separately, by An's group[188] and Cai's group[197] in aqueous dispersion RAFT  
434 PISA to produce vesicles and micelles, respectively. DAAM is undoubtedly the second most studied  
435 monomer in the context of aqueous dispersion PISA. DAAM was chain extended by RAFT polymerization  
436 using light[194, 197] and temperature[188] as stimulus from various hydrophilic macro-RAFT agents  
437 including neutrals (PDMA,[188] PHPMAc,[197] PEO[196] and poly(N-vinylpyrrolidone) (PVP)[201])  
438 and cationic ones (Poly((vinylbenzyl) trimethylammonium chloride) (PVBTMAC)[200] and poly(N-(2-  
439 hydroxypropyl) methacrylamide)-block-poly(histamine methacrylamide hydrochloride) (PHPMAc-*b*-  
440 PHisMA)[202] to produce nano-objects of various advanced morphology and surface functionality. To the  
441 best of our knowledge, DAAM is the only monomer that has been chain extended in aqueous dispersion  
442 PISA from PVP, a hydrophilic steric stabilizer prepared by the polymerization of N-vinylpyrrolidone (VP),  
443 a less activated monomer.[201] To do so, VP was polymerized using xanthate chain transfer (CTA-34, **Fig.**  
444 **2)** *via* PI-RAFT. Subsequently, PVP was chain extended with DAAM in water at 60°C *via* TI-RAFT  
445 polymerization. Spheres and vesicles were observed in this case, although the uncontrolled RAFT  
446 polymerization behavior during PISA due to the undesirable side reactions that PVP can undergoes in  
447 aqueous media. Crosslinking approaches have been exploited (**Fig. 5B**) both *in-situ* [186, 187, 189] and  
448 post-polymerization[183, 193], to increase the stability of PDAAM-core forming nano-objects. An. and  
449 coll.[187] have reported another original approach to improve the colloidal stability of vesicles against  
450 harsh conditions such as solvent dilution, freeze-drying and surfactants competitors. To do so, the  
451 crosslinked PDAM-*b*-PDAAM diblock copolymer vesicles were served as a platform from which third  
452 hydrophilic blocks, neutral PDAM, anionic poly(2-acrylamido-2-methyl-1-propanesulfonic acid sodium  
453 salt), or cationic poly(3-acrylamidopropyl trimethylammonium chloride), were initiated to generate  
454 crosslinked triblock copolymer vesicles without any morphological transitions whatever the size of the  
455 third hydrophilic block.

456 Bilayer-based morphologies (lamellae or vesicle) are relatively easily obtained with DAAM *via* PISA,  
457 which is a considerable advantage compared to other monomers. However, anisotropic morphologies  
458 (worms) are rarely observed with DAAM. In this context, Cai and coll.[199] reported the formation of  
459 pore-switchable nanotubes at high solid content (>35%) derived by hydrogen bound interactions. **Armes**  
460 and coll.[183] demonstrated that the chain extension of PDMA with DAAM can produce pure worms in an  
461 extremely narrow window in the phase diagram composed of large domains of both vesicles and  
462 sphere/worm mixtures. In this case, the PDAAM-core forming nano-objects was stabilized by post-



463 polymerization using adipic acid dihydrazide (ADH), which reacts selectively with the pendent ketone  
464 groups on the hydrophobic PDAAM chains to form hydrazone moieties. Simultaneously, Sumerlin and  
465 coworkers.[193] demonstrated that tuning the hydrophilicity/hydrophobicity of PDAAM-core forming  
466 block nano-objects during the PISA process, through the copolymerization of DAAM with a DAM  
467 hydrophilic monomer, favored the formation of worms of controlled length. Due to the thermoresponsive  
468 behavior of PDAAM-based amphiphilic copolymers, the nano-objects were crosslinked immediately  
469 before cooling by reacting a difunctional alkoxyamine (O,O'-1,3-propanediyl bishydroxyamino  
470 hydrochlorid) with ketone functional groups of the DAAM units to produce hydrolytically stable oxime  
471 linkages. This allowed to lock the morphology prepared during PISA at high temperature and to prevent  
472 the system from any morphology transition. Recently, it was found that the morphology of nano-objects  
473 resulted from the PISA of DAAM can be impacted by the experimental conditions[192, 198] and the  
474 copolymer architecture.[184, 190, 196] Cai and coll.[198] studied the aqueous dispersion PI-RAFT PISA  
475 of DAAM monomer using PHPMAc macro-CTA and SPTP initiator in water at 25 – 60 °C. The authors  
476 observed lamellae (L) when conducting PISA at RT, while WLM or ULV were observed at higher  
477 temperatures. Moreover, reversible thermoresponsive ULV-to-L-to-ULV and ULV-to-V-to-ULV  
478 transitions were observed upon a cooling-heating cycle. By taking advantage of the difference in  
479 polymerization rates between TI-PISA and PI-PISA, Tan and coll.[192] demonstrated that the  
480 polymerization kinetics has a strong impact on the self-assembled structures formed in PISA of DAAM.  
481 By performing PISA at the same temperature (70°C), they found that the relatively low polymerization rate  
482 of TI-RAFT PISA provides sufficient time for block copolymers to relax and reorganize from spheres to  
483 worms and vesicles, while kinetically trapped spheres were formed by PI-RAFT PISA due to its ultrafast  
484 rate.

485 *Novel synthetic acrylamides.* The limited number of monomers that meet requirements of aqueous  
486 dispersion PISA has prompted many research groups to develop new synthetic monomers. In this context,  
487 Pascual and coll.[266] have explored for the first time the well-known synthetic water-soluble monomer *N*-  
488 *acryloyl glycinamide* (NAGA) that forms poly(*N*-acryloyl glycinamide), PNAGA, a homopolymer  
489 exhibiting an upper critical solution temperature (UCST) behavior. Thermosensitive NGs was prepared by  
490 the chain extension of PPEGA hydrophilic stabilizer with NAGA at 3°C *via* PI-RAFT PISA under UV  
491 irradiation ( $\lambda = 365$  nm) in the presence of PP-OH photoinitiator. NGs were crosslinked *in situ* by MBA  
492 crosslinker during polymerization at 3°C to prevent NGs from dissolution at high temperature.  
493 Simultaneously, Rieger and coll.[239] reported another UCST thermosensitive nano-objects prepared by  
494 chain extension of PDMA *via* RAFT copolymerization of *acrylamide* (AAm) and *acrylonitrile* (AN) in  
495 water at 45°C, without adding a crosslinker. WLM and S that underwent either reversible  
496 aggregation/dissociation (S to individual chains) or reversible morphological transition (WLM to S) have  
497 been observed upon heating, depending on the length and the molar fraction of AN in the poly(AAm-*co*-  
498 AN) core forming block. Inspired by this work, the same team has recently developed a novel water-

499 soluble monomer *N*-cyanomethylacrylamide (CMAM)[267] by merging both AN and AAm in a single  
500 monomer. Various nano-objects including S, WLM and ULV were successfully prepared *via* chain  
501 extension of PDMA with CMAM in water at 45°C.[268] Semasarihar and coll.[224] have developed a  
502 novel *tripeptide-containing methacrylamide (MAM-FGD)* based on the phenylalanine-glycine-aspartic acid  
503 sequence. Chain extension of PGMA used as macromolecular chain agent with MAM-FGD in water at  
504 70°C resulted in the formation of unprecedented morphology of large dendritic and bow-tie shaped fibrous  
505 spherulitic (Sp) structures. *N*-acryloylthiomorpholine (NAT)[269] is another novel hydrophilic monomer  
506 forming hydrophobic homopolymer even at very short length ( $X=25$ ) recently used by Brendel and  
507 coll.[221] A wide range of nano-objects morphologies behavior has been formed by chain extension of  
508 poly(*N*-acryloylmorpholine) (PNAM), a hydrophilic macro-CTA prepared by polymerizing *N*-  
509 acryloylmorpholine (NAM) that exhibits a chemical structure similar to NAT. Moreover, the nano-objects  
510 morphology can be tuned from S to ULV by increasing the polymerization temperature used during the  
511 PISA process. Cai and coworkers. [227, 270] reported successful aqueous dispersion RAFT PISA of  
512 cationic core-forming monomers, 2-aminoethylacrylamide hydrochloride (AEAM)[270] and cystamine  
513 methacrylamide hydrochloride (CysMA),[227] using a nonionic PHPMAc macro-CTA in the presence of  
514 an anionic poly(2-acrylamido-2- methylpropanesulfonic acid) (PAMPS) which induces *in situ* polyion  
515 complexation and morphology transition depending on the size of core-forming block.

## 516 **Conclusions**

517 In summary, aqueous dispersion RAFT PISA process has reached some maturity in terms of production of  
518 highly ordered nano-objects. Activation of the polymerization in this process was demonstrated using  
519 different stimuli and in the presence of various steric stabilizers. Extensive investigations have been carried  
520 out using traditional water-soluble monomers forming water-insoluble polymers, and novel monomer for  
521 advanced polymer properties. Diagrams of morphology are now known for some specific model systems.  
522 It was established that the morphology could be modulated, for some system, by varying the core-forming  
523 block size or the solid content. Aqueous dispersion RAFT PISA process remains currently empirical, and it  
524 is important now to carry out deeper studies to rationalize the large data generated during the past decade  
525 or so. Many fundamental questions remain unanswered: *is it possible to predict the morphology of nano-*  
526 *objects according to the chemical nature of the hydrophilic stabilizing block and/or to the monomers used*  
527 *? How can we modulate the morphology of nano-objects by playing on the architecture of the final*  
528 *copolymer ?*

## 529 **Conflicts of interest**

530 There are no conflicts to declare.

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