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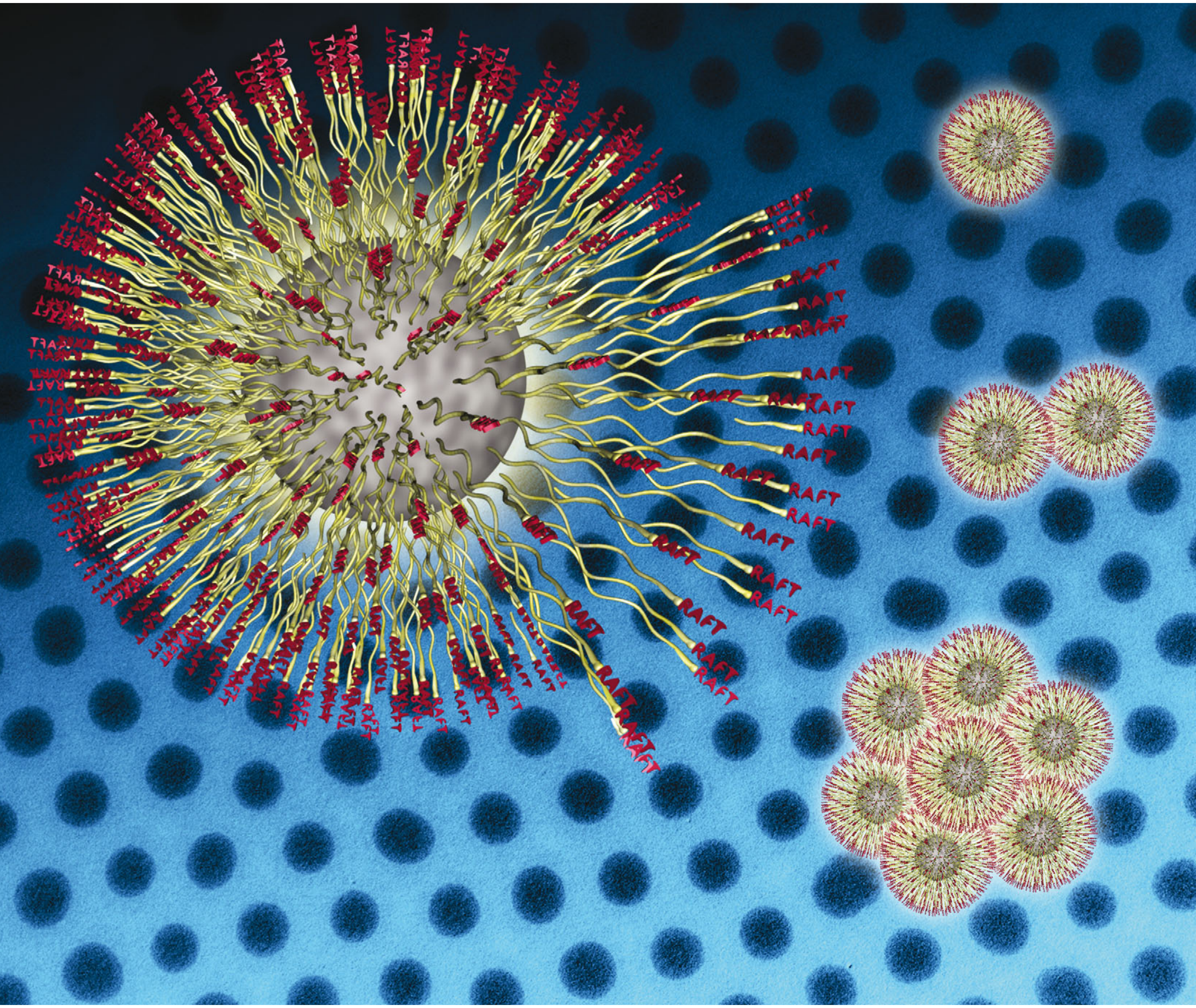

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FEATURE ARTICLE

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Hybrid nanoparticles hold great promise for a range of applications such as drug-delivery vectors or colloidal crystal self-assemblies. The challenge of preparing highly monodisperse particles for these applications has recently been overcome by using living radical polymerization techniques. In particular, the use of reversible addition–fragmentation chain transfer (RAFT), initiated from silica surfaces, yields well-defined particles from a range of precursor monomers resulting in nanoparticles of tailored sizes that are accessible *via* the rational selection of polymerization conditions. Furthermore, using RAFT allows post-polymerization modification to afford multifunctional, monodisperse, nanostructures under mild and non-stringent reaction conditions.

Introduction

Inorganic nanoparticles such as quantum dots,[1] (multi)metallic nanoparticles[2–4] and metal oxide[3,5] nanoparticles in particular have been well-studied in the literature due to their therapeutic,[5] diagnostic[6] and catalytic[4] properties. These types of nanoparticles have well-defined properties that often have to be narrowly tailored to a particular type of application. Thus, they lack the versatility necessary for usage over a broad range of applications without significant redesign of their core properties. To overcome these drawbacks researchers often coat the particles with a polymer layer either *via* adsorption, covalent attachment or layer-by-layer techniques. Additionally, the incorporation of polymers onto the nanoparticle surface can confer properties such as responsiveness to pH,[7–10] temperature[7,10] and light;[7,11] resistance to oxidation;[3,12] biocompatibility;[6,12] and stability in a range of solvents[3,6] that would not be possible with a re-design of the particle core. This versatility of polymers has allowed their highly successful use as coatings for a range of inorganic nanoparticles to yield 'core–shell' nanoparticles with a polymer shell surrounding an inorganic core (or template).[7–9,12–14]

While the focus of polymeric and polymer-coated nanoparticles has been in the area of drug delivery, several authors have also reported the use of polymer-based nanoparticles for material science applications. Four such examples are shown in Fig. 1: (Fig. 1A–C) Ohno *et al.* demonstrate the formation of colloidal crystals by tuning the refractive index of a solvent to match that of a core–shell nanoparticle;[15] (Fig. 1D and E) Park *et al.* form a cell-scaffold from which cells detach when the temperature of the system is lowered;[16] (Fig. 1F) Li *et al.* show the effect of an external magnetic field on silica–polymer core–shell nanoparticles with a magnetic core dispersed in water;[17] (Fig. 1G–I) Inoue *et al.* demonstrate the formation and pH-responsiveness of 'liquid marbles' from silica nanoparticles grafted with polymer.[18]

For the vast majority of these applications in which an advanced, functional material is targeted, a high degree of control over the size and uniformity of the polymer chain is crucial. For example, it has been shown that the length of the polymer chain has serious implications for circulation lifetimes of intravenously administered nanoparticles,[19] while the density and molecular weight of grafted chains influence the mechanical properties of composite materials.[20] Thus, significant research has been directed at growing polymers of predictable molecular weights and narrow molecular weight distributions. To this end, much research into techniques such as ring-opening, radical and anionic polymerization has been undertaken such that polymers can be grown in a controlled fashion.[21,22]

Living polymerization refers to the fact that within this subset of reactions, the formal termination step is eliminated. The products of the reaction are 'dormant' polymer chains as opposed to 'dead' polymer chains. These dormant chains can then further propagate in the presence of additional monomer and, therefore, a measure of control over the length of the final polymer can be exerted.

Of the various types of polymerization in common use, radical polymerization offers ready access to a wide range of

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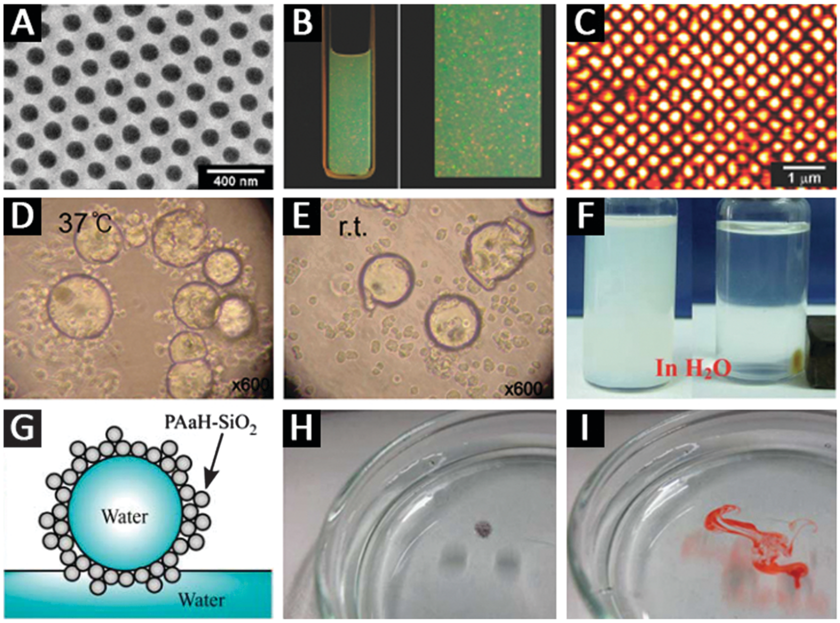


Fig. 1 (A) Silica nanoparticles grafted with polystyrene; (B) colloidal crystal formed from the particles in A; (C) confocal laser scanning microscopic image of the colloidal crystal in B; (D) silica microparticles grafted with *N*-isopropylacrylamide used as a scaffold for Chinese hamster ovary cells; (E) the scaffold in D with temperature lowered to room temperature; (F) silica particles with an iron-oxide core and *N*-isopropylacrylamide shell dispersed in water; (G) schematic of water-in-gas Pickering emulsion (liquid marble); (H) the liquid marble in G containing a dye in a dish of water; (I) the system in H on addition of a NaOH solution. A–C adapted from Ohno *et al.*;[15] D–E adapted from Park *et al.*;[16] F adapted from Li *et al.*;[17] G–I adapted from Inoue *et al.*[18]

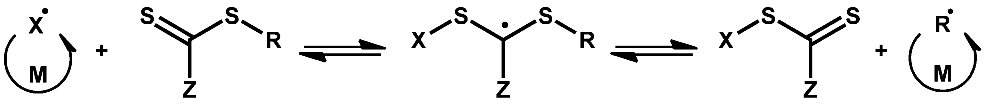
acrylate, methacrylate and styrenic polymers without the requirement for highly specific reaction conditions. Although in radical polymerization, the termination step can never be truly eliminated, it is still possible to minimise termination events and establish some degree of control using a variety of controlled radical techniques. These reactions can be described as pseudo-living as they proceed in a controlled manner and are capable of being re-initiated in the presence of additional monomer.

Controlled radical techniques such as nitroxide-mediated radical polymerization (NMP),[23] (transition) metal-mediated living radical polymerization,[24–26] reversible addition–fragmentation chain transfer (RAFT),[27] tellurium-mediated polymerization (TERP),[28] macromolecular design *via* the interchange of xanthates (MADIX),[29] reversible chain transfer catalysed polymerization (RTCP),[30] reversible complexation-mediated living radical polymerization (RCMP)[31] and cobalt-mediated radical polymerization (CMRP)[32] offer scientists a range of tools for controlling the material properties of a variety of monomers. Amongst these, RAFT has emerged as a technique of choice due to its mild reaction conditions and tolerance to a wide array of monomers and functional groups.[33–35]

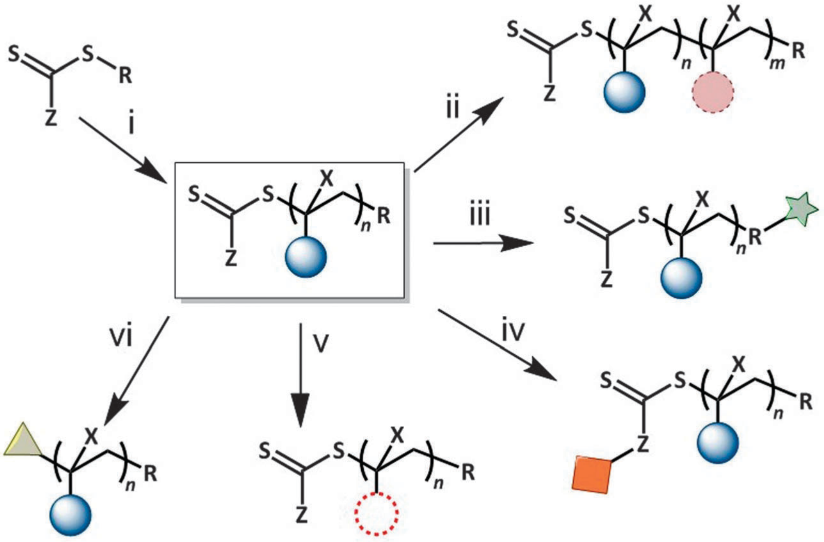
RAFT is based on degenerative chain transfer reactions, where a conventional radical polymerization system is mediated by a thiocarbonylthio-based chain transfer agent (CTA). The CTA typically contains a C=S double bond, which is susceptible to radical addition in combination with a stabilising Z-group and a re-initiating R-group. The CTA allows the polymerization to be controlled *via* the continuous reversible deactivation of growing chains as shown in Scheme 1. This reversible deactivation process means that as one chain enters the dormant state, another (macro)radical is generated, which is capable of further propagation. This rapid exchange of propagating radicals between the CTA and the growing chain serves to mediate the polymerization.[34,36]

As with other controlled radical systems, RAFT allows access to complex polymeric architectures such as block copolymers, gradient copolymers, star-shaped polymers *etc.*, which can further be modified to introduce functionality post-polymerization. Additionally, several researchers have exploited the fact that both the 'R' and the 'Z' group of the CTA can be functionalised with groups orthogonal to the radical process in order to impart chain-end functionalities to the RAFT-mediated polymers. Finally, the thiocarbonylthio of the RAFT group itself can easily be modified either by conversion into a thiol, by radical-induced reduction, or a range of other modifications.[37] A summary of these modifications is shown in Scheme 2.

The adaptability of RAFT has seen it being used to functionalise a variety of surfaces including carbon nanotubes,[38] gold



Scheme 1 General RAFT mechanism where M is the monomer, X is either an initiator, initiator-derived polymeric adduct, the R-group of the CTA or R-group-derived polymeric adduct and R is either the R-group or R-group-derived polymeric adduct.



Scheme 2 (i) RAFT polymerization of a vinyl-bearing monomer; (ii) chain-extension of the first block; (iii) modification of the R-group; (iv) modification of the Z-group; (v) modification of the polymer chain; (vi) modification of the thiocarbonylthio group. X represents H or Me, *n* and *m* represent the number of monomer repeat units of the first and second block respectively.

nanoparticles,[39] gold nanorods,[40] cellulose,[41] cotton,[42] iron oxide nanoparticles[43] and CdSe nanoparticles.[44] One of the most versatile solid substrates, however, is silica which, due to the Stöber method of synthesis, is readily available in a variety of particle sizes with high uniformity and narrow size distributions.[45]

In recent years, several researchers have incorporated silica particles into controlled radical techniques in order to have greater control over the nanoparticles synthesised.[46] NMP,[47,48] ATRP[13,49–52] and RAFT[43,53–61] have all been investigated in this regard. RAFT is of particular interest as it allows the polymerization of the broadest range of monomers and allows ready post-polymerization modification. Until recently, RAFT was traditionally not the technique of choice for silica-supported polymerization due to the difficulty in obtaining a high density of RAFT agents on silica surfaces.[46] There have been, however, several recent innovative and promising investigations into the use for RAFT for this purpose. This review focuses on these recent findings and new developments on the synthesis and use of hybrid nanoparticles with a silica 'core' and a polymer 'shell' formed *via* RAFT polymerization.

Two approaches to silica–polymer core–shell nanoparticles

The literature on RAFT-mediated polymerizations, in general, focusses on two main approaches to achieve silica–polymer core–shell nanoparticles: the "*grafting from*" and the "*grafting to*" methods. The *grafting from* approach relies on the localisation of initiators on the surface of silica particles. Polymerization then takes place in a solution containing the monomer wherein the initiators can react with monomer units to grow polymer chains from the surface of the particles. On the other hand, the *grafting to* method involves the attachment of pre-formed polymer chains to the surface of the silica particles. This can either be accomplished by reacting an appropriate moiety on the polymer chain with the hydroxyl groups on the silica particles or by pre-functionalising the silica particle with a functional group capable of reacting with a complementary group on the polymer chain. A third method, "*grafting through*" may also be considered where a polymerizable group is anchored on a silica surface, which is subsequently added to a solution RAFT polymerization. The process, therefore, relies on the diffusion of oligomers (or macromonomers) bearing RAFT functional groups to the surface of the particle such that the surface-bound monomer can react and be under RAFT control. There are a few examples of this system reported in the literature, each using a variation of a methacryloxypropyl alkoxysilyl precursor.[62–65] While the final materials obtained by this route are discussed in the applications section (*vide infra*), the bulk of this review will instead focus on the more widely employed *grafting from* and *grafting to* approaches.

In the particular case of RAFT polymerization, there are additional nuances to the *grafting from* and *grafting to* approaches discussed above. The *grafting from* approach can be used to describe a system where either the initiator or the R-group of the RAFT agent is attached to the silica surface prior to polymerization mediated by the modified silica particle. Whereas the *grafting to* approach can mean either the attachment of pre-formed polymer chains to the silica surface *via* complementary functional groups, or the attachment of the Z-group to the surface of a silica particle followed by RAFT polymerization. Each approach has previously been investigated by researchers using a range of monomers (Fig. 2) and their findings are discussed in detail below.

Grafting from

Grafting from a surface traditionally involves anchoring an initiator molecule onto the surface before beginning polymerization. In the

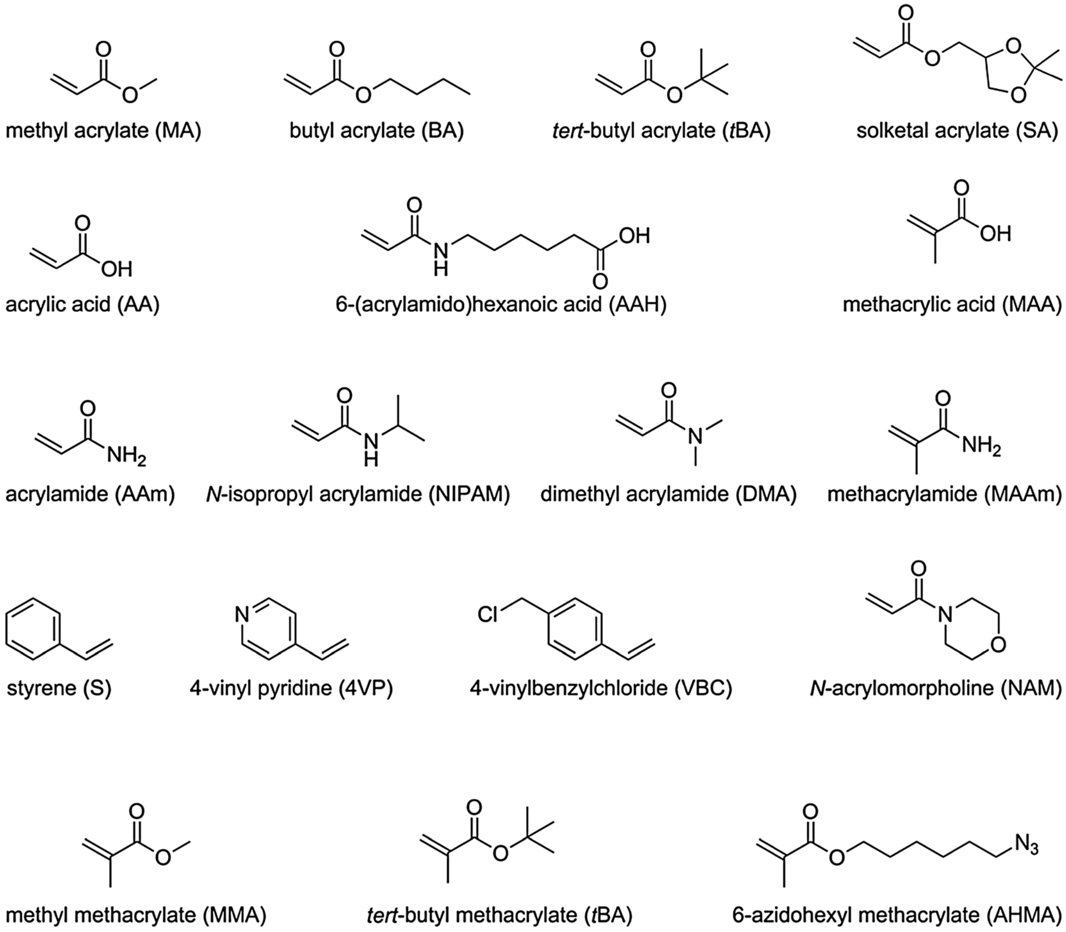


Fig. 2 Monomers grafted to silica surfaces using RAFT.

case of the controlled radical techniques NMP and ATRP, this means that the CTA is anchored to the surface and that polymer chains produced by the CTA are thereby tethered to the surface. However in RAFT, since the initiator is a separate moiety from the CTA, *grafting from* can either also refer to a system where the R-group of the initiator is bound to the surface of the silica particle and the polymerization initiated by a free initiator in solution. Since the initiator (or the re-initiating R-group) is bound to the surface of the particles, grafting of polymer chains takes place when the monomer molecule makes its way to the surface of the particle and encounters an active radical. Thus, there is very minimal steric hindrance of large polymer chains as propagation takes place at the terminus of the grafted chains.

The first report of grafting an initiator to the surface of silica particles was by Baum and Brittain who used azoundecylchlorosilane as their tethered initiator. The polymerization was then initiated in the presence of cumyldithiobenzoate (a commonly used RAFT CTA) and monomer. The result of the polymerization were 'free' chains, mediated by the cumyldithiobenzoate in solution, as well as grafted chains possessing the dithiobenzoate Z-group of the RAFT agent.[66] A similar technique was used by Titirici and Sellergren to form molecularly imprinted thin films.[67] Rotzoll and Vana proposed an original approach by immobilizing both 'looped' initiator and RAFT agent onto the surface of particles; remarkably, they noted that under certain conditions, the polymerization could occur without the formation of free chains in solution.[68] The majority of work on *grafting from* silica particles in the context of RAFT has used an anchored R-group to obtain the desired materials. A summary of the RAFT agents used for this type of *grafting from* approach is presented in Table 1 below.

The first report of a silica-supported R-group RAFT agent was accomplished by the transformation of a surface-bound ATRP initiator by Tsujii *et al.* who initially polymerized styrene (S) from a secondary bromide ATRP initiator bound to a silica surface. Cleavage of the carbon–bromide bond in the presence of a dithiobenzoate RAFT agent yielded particles with a RAFT agent tethered *via* the R-group. This RAFT-functionalised particle was then used to further mediate the RAFT-polymerization of styrene under standard RAFT conditions.[72] The authors noted that the introduction of a free RAFT agent (in addition to the surface-bound RAFT agent) significantly increased the control over the polymerization. This is because increasing the concentration of free RAFT agent in solution allows an efficient exchange between surface-bound radicals and free (Z-group-terminated) chains resulting in excellent control over the grafted chains even at high conversions. An added benefit of the free RAFT agent is that it results in the formation of free polymers. These polymers were shown, both by Tsujii *et al.* and

Table 1 Silica-supported RAFT agents used for polymer grafting from silica surfaces. X indicates either –H, –OMe, –OEt or –OSi

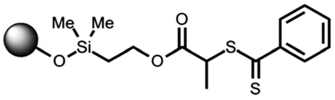
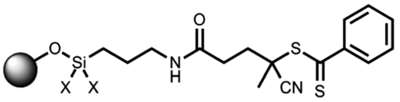
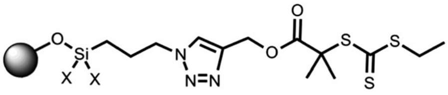
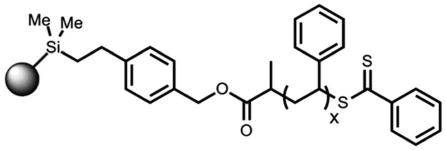
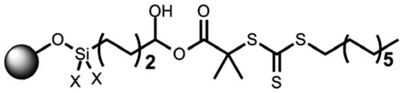
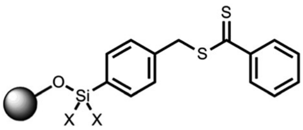
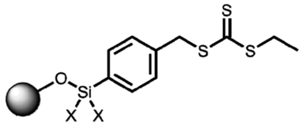
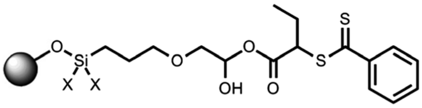
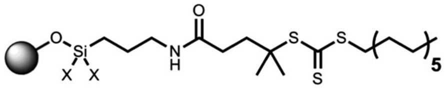
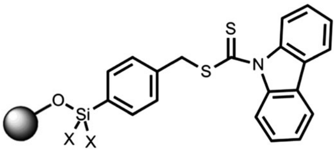
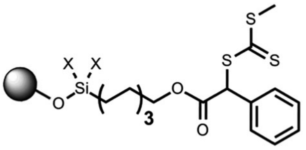
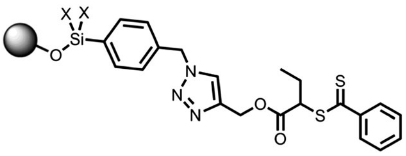
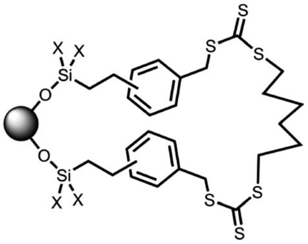
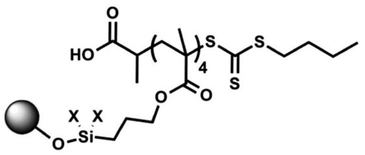
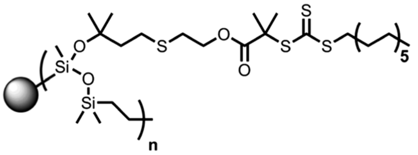
Ref.	RAFT agent	Monomer(s)
53		BA, S
18, 54, 69–71		MMA, S, AHMA, *t*BMA, MAA
58		S, MA
72		S
56, 73		S, AA
74, 75		4VP, AAm
76		AA
55		S
77		MA
17, 78		4VP, NIPAM
43, 79, 80		MMA, S, NIPAM, BA, VBC
81		MAAm
82, 83		MA

Table 1 (*continued*)

Ref.	RAFT agent	Monomer(s)
84		S
16		NIPAM

Monomer abbreviations: AA, acrylic acid; AAm, acrylamide; AHMA, 6-azidohexyl methacrylate; BA, butyl acrylate; MA, methyl acrylate; MAA, methacrylic acid; MAAm, methacrylamide; MMA, methyl methacrylate; NIPAM, *N*-isopropyl acrylamide; S, styrene; *t*BMA, *tert*-butyl methacrylate; 4VP, 4-vinyl pyridine; VBC, 4-vinylbenzyl chloride.

by subsequent researchers, to reflect the molecular weights and dispersities of the grafted chains.[43,72] Thus, analysis of the free chains in solution can be used as a means of determining the nature of the grafted chains.

Li and Benicewicz used the R-group approach and circumvented the ATRP polymerization step by synthesising a methoxysilane RAFT agent, which was subsequently attached to silica particles. The RAFT-functionalised particles were then used to mediate the polymerization of styrene and butyl acrylate (BA) as well as di-block copolymers of the two monomers.[53] Excellent control over the polymerization was achieved, although reactions were kept at low monomer conversion (10–18%). Benicewicz and co-workers followed this work with an extensive study in which an alternate method of attaching RAFT agents to silica particles was described: the silica particles were first pre-functionalised with an amine that was subsequently reacted with a RAFT agent, bearing an activated ester to form an amide bond through which the RAFT agent was tethered to the surface at a density of 0.093 to 0.54 chains per nm^2.[54,69,70] Using this elegant approach, the authors reported the formation of silica particles grafted with a wide range of polymers, namely styrene,[54] methyl methacrylate (MMA),[54,69] 6-azidohexyl methacrylate (AHMA),[69] and *t*-butyl methacrylate (*t*BMA).[70]

Other research groups have also used the reaction between pre-functionalised silica particles in order to graft RAFT agents in an efficient manner. Hua *et al.* used an amine functionalised particle and an amide coupling reaction with a RAFT agent to obtain RAFT agent-grafted silica particles that were used to mediate the polymerization of methyl methacrylate.[77] Pan and co-workers attached epoxides on the surface of mesoporous silica and converted the epoxides into alcohols that were subsequently reacted with the carboxylic acid groups of RAFT agents to yield RAFT-functionalised silica on which the R-group is anchored to the surface.[55,56] These silica particles were either mesoporous[56] or solid[55] with graft densities as high as 0.6 RAFT agents per nm^2 being reported for the later.

Ranjan and Brittain 'clicked' an alkyne-functionalised RAFT agent onto azide-functionalised silica particles to achieve R-group-functionalised silica particles capable of mediating the polymerization of styrene and methyl methacrylate.[58] This study is particularly insightful as the researchers also used a *grafting to* approach with the same RAFT agent and pre-functionalised silica demonstrated that a much higher grafting density of polymer chains per nm^2 was accessible *via* the *grafting from* approach when compared to that of the *grafting to* method. The papers focusing on the latter approach are discussed in the *grafting to* section below.[57,85] The results of this comparison were mirrored by the findings of Rotzoll and Vana who grafted MA loops to silica surfaces using bifunctional RAFT agents anchored *via* either the R-group or the Z-group.[82] The authors however noted that the molecular weights of polymers grafted with the Z-group attached to the silica were higher than those in cases when the R-group was attached, which can be rationalised by the fact that in the Z-group approach, larger, radical-terminated polymer chains in solution are capable of reacting with surface bound RAFT agents due to the lower steric hindrance caused by low grafting densities.

The capacity of the *grafting from* approach to enable formation of well-defined particles with a silica core and a polymer shell was demonstrated by Lu *et al.*[74] and Liu *et al.*[17,78] who functionalised silica particles with benzylchloride groups to transform them into RAFT-grafted silica particles, which were subsequently used to mediate the polymerization of 4-vinylpyridine and *N*-isopropyl acrylamide. Core–shell nanoparticles were also formed by Yang *et al.* in a hybrid *grafting from–grafting to* approach wherein a trimethoxysilane-bearing monomer (3-methacryloxypropyltrimethoxysilane) was first oligomerised under standard RAFT conditions and subsequently grafted to silica nanoparticles. These nanoparticles bearing the oligo-RAFT agent, tethered *via* the R-group, were then used to mediate the polymerization of styrene in a *grafting from* approach.[84]

Recently Ohno *et al.*[43] have used the R-group approach to form core–shell particles that are so well-defined and monodisperse that they are capable of self-assembling into two-dimensional films with long-range order. A problem that often plagues the grafting of RAFT agents on the surface of silica particles is the use of basic conditions to catalyse the coupling of trimethoxysilanes onto silica: Since the basic conditions would lead to degradation of the RAFT agent, this approach is not practical. Hence, the various approaches described above involving the use of pre-functionalised silica particles to attach RAFT agents add significant synthetic complexity to the preparation of RAFT agent-grafted silica particles. To avoid such difficulties, Ohno *et al.* used azeotropic distillation to localise a triethoxysilane-bearing RAFT agent onto the surface of silica nanoparticles. Thus, high grafting densities of RAFT agents were achieved on the silica surfaces (0.8 RAFT agents per nm^2) and the resultant nanoparticles were shown by transmission electron microscopy and confocal laser scanning microscopy to self-assemble into a two- and three-dimensional crystalline lattice with the polymer shells keeping the silica cores equidistant from each other (Fig. 1A–C).

In general, the R-group approach has been shown to yield well-defined particles with a silica core and polymer shell.[43,53,55,74,78] Due to the fact that this *grafting from* approach does not rely on the diffusion of large polymer chains to the surface, high grafting densities can be achieved with this approach, thereby offering a route to highly functionalised silica particles.[43,58,70]

Grafting to (sequential and tandem approaches)

The *grafting to* approach is a synthetically more straightforward route towards polymer-functionalised nanoparticles. Since the polymer chain can be grown in solution under full RAFT-control and subsequently can be attached to the silica particles, it is possible to graft well-defined chains onto the particle surface. This can either be done by reacting functionalized silica particles with the backbone of the polymer or *via* the end groups of the polymer. In terms of using the end-group to functionalise a solid surface with a macromolecule, a highly efficient reaction is required to overcome the steric hindrance inherent in solvated polymer chains. To this end copper-catalysed azide–alkyne cycloaddition (CuAAC) has been the technique of choice for researchers.

Ranjan and Brittain used 3-bromopropyltrichlorosilane to functionalise silica particles with a bromide group that was subsequently transformed into an azide using sodium azide. Polystyrene and polyacrylamide polymers, which had been produced previously by an alkyne functionalised RAFT agent, were then attached to this functionalised surface. Upon completion of the CuAAC reaction, silica particles were isolated that were grafted with 0.37 chains per nm^2 of polystyrene and 0.31 chains per nm^2 of polyacrylamide.[57] To increase the grafting densities obtained, the authors employed a *tandem* approach in which they performed the RAFT polymerization of styrene and the CuAAC reaction concurrently.[85] This approach resulted in higher grafting densities of 0.54 chains per nm^2, which is an improvement over the *grafting to* method, yet not as high as what can be obtained using the *grafting from* method under identical conditions.[58] This is understandable since, unlike the *grafting from* method, the *grafting to* method relies on the diffusion of large polymeric chains to the silica surface for successful grafting to take place and, thus, substantial steric hindrance of the reaction is to be expected. Nonetheless, there are distinct approaches to the *grafting to* approach that have been exploited by several researchers (*vide infra*) and the field of research is an active one. The structures of the solid-supported RAFT agents used in the various *grafting to* approaches discussed in this manuscript are shown in Table 2.

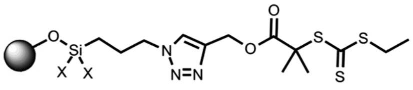
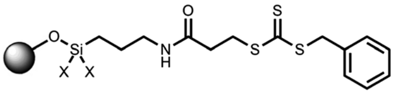
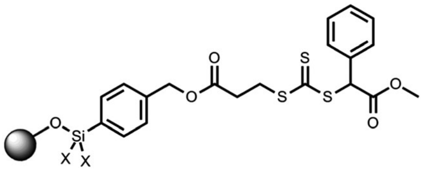
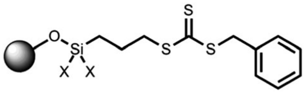
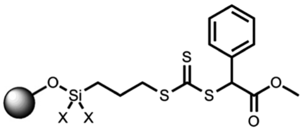
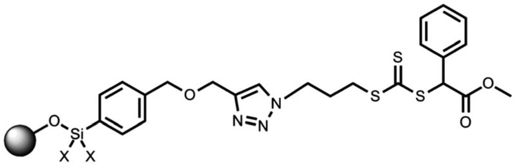
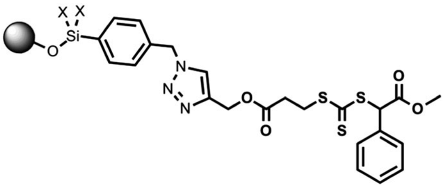
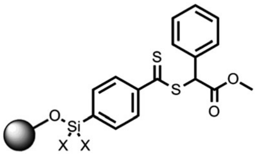
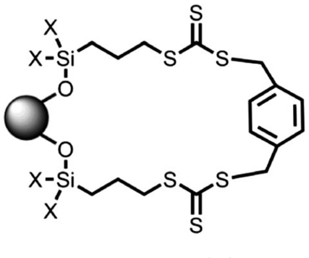
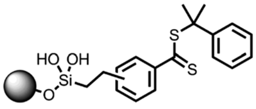
Zhao and co-workers minimized the complexity of the *grafting to* approach by using a RAFT agent functionalised with a trimethoxysilane group, which was then grafted onto silica particles. This step avoided pre-functionalising the silica surface and resulted in grafting densities of 0.018 chains per nm^2 to 0.076 chains per nm^2 for a range of monomers including methyl methacrylate, methyl acrylate, butyl acrylate, *t*-butyl acrylate, solketal acrylate (SA), styrene, dimethyl acrylamide (DMA), *N*-isopropylacrylamide (NIPAM) and *N*-acryoyl morpholine (NAM).[61] The group also used CuAAC to couple polymers derived from an azide-functionalised RAFT agent to silica particles pre-functionalised with alkyne moieties (*i.e.* the opposite approach as that employed by Ranjan and Brittain[57,58,85]). This method led to grafting densities varying from 0.017 to 0.085 chains per nm^2 and on performing the reaction concurrently, the authors noted similar (0.025 to 0.078 chains per nm^2) grafting densities.[88] This is contrary to the improvement noted by Ranjan and Brittain when using a tandem approach over a sequential approach.[85] Zhao and co-workers' lower grafting densities may be explained by the fact that they chose to attach the polymers to the silica surface *via* the Z-group and, thus, propagating radicals would have to overcome steric hindrance of grafted chains to migrate to the surface of particles. Ranjan and Brittain, however, attached the RAFT agent to the silica particles *via* the R-group and, thus, the propagating radical was always on the surface of the particles, minimizing steric hindrance of monomers diffusing to the surface resulting in higher grafting densities.

Grafting to (Z-group approach)

RAFT polymerization is a degenerative process; if a RAFT agent is anchored to the surface *via* the Z-group, then a chain is grafted to the surface when a propagating chain (with an active radical) migrates to the surface-bound RAFT, reacts with the dithioester and releases the R-group as an active radical. Thus, despite the fact that the RAFT agent is attached to the surface, the Z-group approach is more akin to the *grafting to* approach as it relies on the diffusion of pre-formed polymer chains to the surface in order to obtain a grafted silica particle.

The first example of RAFT agents being attached to silica surfaces *via* the Z-group was reported by Perrier and co-workers who functionalised silica particles with 4-(chloromethyl)-phenyltrimethoxysilane and subsequently converted the pendant chloride into a dithiobenzoate. The silica-supported RAFT agent was then used to mediate the polymerization of methyl acrylate without the addition of a free CTA.[90] In later publications the authors expanded on this work by extending the range of monomers to include *n*-butyl acrylate, styrene, dimethyl acrylamide, *N*-isopropylacrylamide and methyl methacrylate.[59,60,87] The later work also involved the localisation of

Table 2 Silica-supported RAFT agents used for grafting polymers to silica surfaces. X indicates either –H, –OMe, –OEt or –OSi

Ref.	RAFT agent	Monomers
57, 85		AAm, S
86		NIPAM
59		MA, MMA, S
60, 68, 87		MA, BA, DMA, S, MMA, NIPAM
60, 61, 87		MMA, MA, BA, *t*BA, S, DMA, NIPAM, NAM
88		MMA, S, NIPAM, DMA, *t*BA, NAM, SA
89		MMA, S, NAM, DMA, *t*BA, SA, MA, NIPAM
90		MA
68, 82, 83		MA
91		S, MMA

Monomer abbreviations: AAm, acrylamide; BA, butyl acrylate; DMA, dimethyl acrylamide; MA, methyl acrylate; MMA, methyl methacrylate; NAM, *N*-acryloyl morpholine; NIPAM, *N*-isopropyl acrylamide; SA, solketal acrylate; S, styrene; *t*BA, *tert*-butyl acrylate; *t*BMA, *tert*-butyl methacrylate.

4-(chloromethyl)phenyltrimethoxysilane onto silica surfaces, although in this case the pendant chloride was transformed into one of two trithiocarbonate-based RAFT agents. The solid-supported RAFT agents were also used to form di-block copolymers from various combinations of the monomers. To improve the control of the reaction the authors added a free CTA to the polymerization mixture confirming the findings of Tsujii *et al.*[72]

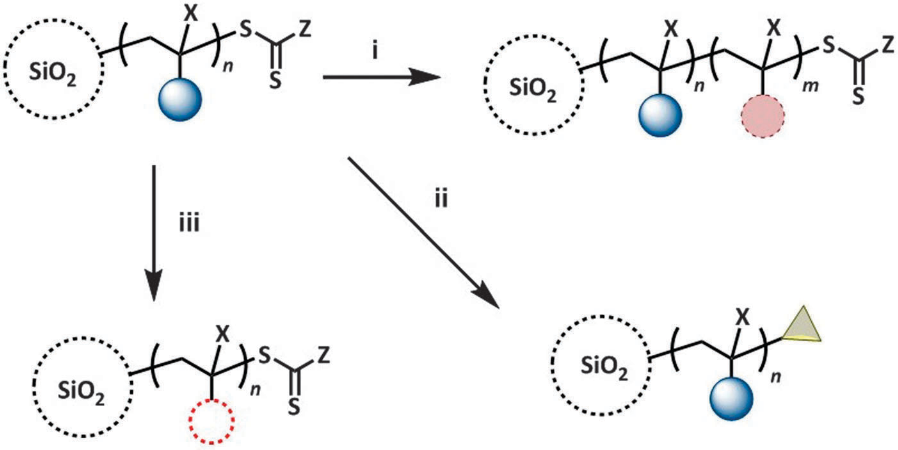
Thus, the Z-group approach is a reliable method of producing well-controlled, 'pure' polymers as every polymer chain bound to the particle contains the Z-group of the RAFT agent and is considered 'living.' The challenge with the Z-group approach is that with each attached chain the steric hindrance is increased to subsequent chains diffusing to the surface and thus being grafted. As a result, the Z-group approach typically leads to a lower density of chains grafted onto the silica support. This drawback of the approach was exploited by Zhao *et al.* who used azide-functionalised silica particles and an alkyne-functionalised RAFT agent in a tandem CuAAC–RAFT approach to generate silica-polymer core–shell composites wherein only a certain proportion of the silica-bound azide groups were grafted with polymer chains. The polymer could then be cleaved from the composite material and the remaining azide groups used for subsequent RAFT–CuAAC reactions. Thus, the azido-silica particles served as a (albeit limited) reusable solid support to generate highly pure, well controlled polymers using RAFT polymerization.[89]

Beyond polymerization: post-polymerization modification and applications

A distinct advantage of using a controlled radical technique such as RAFT is the variety of modifications that can be performed on the polymer chain post-polymerization. Post-polymerization modification of polymer chains is an attractive way of introducing functionality onto the particles that may be incompatible with the polymerization conditions. Indeed, as the RAFT group is intact at the end of the polymerization, it should be possible to chain-extend the grafted polymer – forming silica particles functionalised with a di-block copolymer shell (Scheme 3i). The RAFT group is also an attractive moiety in terms of post-polymerization functionalisation, since it can be easily reduced to a thiol, which lends itself to highly efficient modifications *via* reactions such as thiol–ene,[92] thiol–yne,[93] or thiol–isocyanate[94] (Scheme 3ii). Lastly, it should be possible to carry out post-polymerization functionalisation of the polymer shell in order to change its properties and, thus, the properties of the hybrid nanoparticle (Scheme 3iii). Although the literature on these types of post-polymerization modifications is still not yet mature, the few examples that have been demonstrated so far offer a tantalising glimpse into the future of this field.

The ability to extend a polymer chain with additional monomers is a powerful tool to introduce additional functionality to polymer-grafted nanoparticles. Grafted di-block copolymers by RAFT were first reported by Benicewicz and co-workers who successfully extended grafted poly(butyl acrylate) with styrene[53] and, subsequently, grafted poly(6-azidohexyl methacrylate) with methyl methacrylate.[69] Similarly Ranjan and Brittain reported grafted di-blocks of polystyrene extended with MA using the R-group approach,[58] while Rotzoll *et al.* extended grafted MA blocks with styrene using the Z-group approach.[68]

The work on di-block copolymers was significantly expanded upon by Zhao and co-workers. Initially, di-blocks of various combinations of S, MMA, MA, and BA were prepared using a grafted Z-group.[59] Eventually the range of monomers was expanded to include *t*BA, SMA, NiPAm and NAM while the synthesis of grafted di-, tri- and tetra-block copolymers was demonstrated.[61,88] The work demonstrates the versatility of the Z-group approach in producing well-defined polymers. As an illustration, the dispersity of a de-grafted block of poly(S-*b*-NAM-*b*-NIPAM) was shown to be 1.19[88] while that of poly(NIPAM-*b*-NAM-*b*-S-*b*-MA) was shown to be 1.24.[61] A dispersity of 1.00 would indicate a perfectly controlled polymerization (unobtainable experimentally), while that of 1.05 is typical of a well-controlled RAFT system. Given these values, the de-grafted tri- and tetra-block show remarkable uniformity.



Scheme 3 Post-polymerization modification of hybrid nanoparticles: (i) chain extension of RAFT-grafted polymer chain; (ii) modification of thiocarbonylthio end-group; (iii) modification of grafted polymer chain. X represents H or Me, *n* and *m* represent the number of monomer repeat units of the first and second block respectively.

Post-polymerization functionalisation of the grafted polymer chains themselves has been demonstrated by Benicewicz and co-workers who modified azide groups grafted onto silica particles with alkyne-bearing small-molecules and macromolecules using CuAAC.[69] Recently, Qu *et al.* used post-polymerization modification of grafted AA chains to graft streptavidin onto silica particles to form hybrid particles capable of being loaded with biotin or biotinylated molecules.[76] Benicewicz and co-workers also demonstrated the cleavage of the ester bond in grafted *tert*-butyl methacrylate polymers to yield particles with grafted carboxylic acid functionalities[70,71] and the removal of the trithiocarbonate end-group.[70,95] Recently, our group showed the use of post-polymerization modifications to engineer particles for bioapplications, by quaternizing poly(4-vinylbenzyl chloride) chains grafted onto silica nanoparticles to yield hydrophilic core–shell particles for use in cell-imaging applications.[80]

Indeed, RAFT-mediated polymer-grafted silica nanoparticles have recently been demonstrated as likely candidates in a variety of applications. For example, silica-polymer core–shell particles have been shown to be able to from colloidal crystals.[43] They have also been used as a precursor to noble metal-bearing organic–inorganic hybrid nanoparticles.[78] There are also several reports of molecularly imprinted core–shell particles that can be used in the selective extraction of contaminants from aqueous solutions.[17,65,74,75,81]

From a materials standpoint, incorporation of the hybrid nanoparticles into polymer matrices has allowed the tuning of the mechanical and thermal properties of the composite material.[20,62,95] Furthermore, the versatility of RAFT polymerization allows the bimodal grafting of polymer brushes of different lengths to the same particle to improve dispersibility and to further tune its mechanical properties.[95] Alternatively, fluorescent moieties can be grafted to the silica particles alongside polymer brushes to form a platform for potential drug loading and imaging applications.[71] A particularly striking example has been demonstrated by Li *et al.* who used RAFT polymerization in conjunction with Stöber synthesis to produce magnetic, thermoresponsive, fluorescent nanoparticles (Fig. 1F).[17]

Using RAFT to polymerize pH-responsive acrylic acid allowed Hong *et al.* to produce nanocontainers that could release fluorescent payloads from silica mesopores in response to environmental stimuli.[73] Similarly, RAFT in conjunction with ATRP has been used to graft *N*-(2-hydroxypropyl)methacrylamide (HPMA) and 2-diethylaminoethyl methacrylate (DMAEMA) to the surfaces of mesoporic silica particle. The hybrid nanoparticles, thus formed, show improved biocompatibility (due to the HPMA) and pH-triggered release of Doxorubicin from the pores (due to the pH-responsiveness of DMAEMA).[96] Inoue *et al.* have also demonstrated the use of polymer-grafted silica particles to form pH-responsive millimetre-sized liquid-in-gas Pickering emulsions known as 'liquid-marbles' (Fig. 1G–I).[18]

Thermoresponsive polymers have also been grafted onto silica particles yielding promising structures such as three-dimensional cell scaffolds or stationary phases for HPLC columns. In the former example, the authors grafted NIPAM onto silica nanoparticles, which allowed cells to grow on the scaffold when above the lower critical solution temperature (Fig. 1D) and detach when the temperature was lowered (Fig. 1E).[16] In the latter example, NIPAM was also used, in this case exploiting its thermo-responsiveness to separate proteins on an HPLC column packed with the hybrid nanoparticles.[97]

The field of core–shell particles *via* RAFT is one that does promise several avenues of investigation. Some future challenges for researchers in the area may be to design systems that use the core–shell particles as building blocks for tailored materials such as photonic crystals or three-dimensional patterns. Indeed, the exploitation of the unique properties of these 'semisoft' particles containing a 'soft' corona surrounding a 'hard' core is promising for long range ordering.[98] From a chemical viewpoint, a key challenge is the exploitation of the terminal RAFT group to introduce additional functionality onto the particles. In particular the field of efficient thiol-based coupling chemistries with such core–shell particles has not fully been explored as it has with RAFT-derived free-polymer chains.[92–94]

Summary

Polymerization of a wide range of monomers has been demonstrated using the RAFT process mediated by chain transfer agents grafted to the surface of silica nanoparticles. The two distinct approaches towards these silica–polymer core–shell nanoparticles, *grafting from* and *grafting to*, respectively yield particles with a high density of grafted chains or with grafted polymers free of dead chains.

Post-polymerization of grafted polymer chains can be effected using block extension or chemical modification of the functionalities of the polymers. The Z-group approach with its ability to produce highly pure block copolymers is an attractive route to the formation of multi-functional silica–polymer core–shell composites. The R-group approach on the other hand offers the incentive of placing the highly functionalisable RAFT end-group on the periphery of the particles. This may offer a novel method of modifying the corona of the core–shell particles, but has not yet been fully exploited in literature. There, however, have been numerous reports of the use of nanoparticles generated with the use of RAFT polymerization in applications as diverse as bulk-property modification of polymer matrices to stimuli-responsive drug-delivery vehicles. With the chemistries described in the papers within this review, it is clear that the area of RAFT-mediated silica-polymer core–shell nanoparticles is a promising area of research that is likely to lead to highly versatile materials for a range of cutting edge applications.

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