# Functional Monodisperse Microparticles from Thiol-Michael Dispersion Polymerizations

Chen Wang and Christopher N. Bowman

Department of Chemical and Biological Engineering, University of Colorado Boulder

Boulder, Colorado, United States

Abstract

Step-growth polymers are ubiquitous in materials, however they have not been generally used for the preparation of polymeric colloids. Herein we report a dispersion polymerization method for the realization of step-growth polymeric microparticles. A "click" reaction, namely thiol-Michael addition reaction, is carried out between multi-thiols and multi-acrylates in methanol. Monodispersed microparticles were successfully prepared with tunable diameters ranging from submicron to five microns. The polymerizations proceeded fast with catalytic amount of organic base and quantitative conversion were achieved at ambient conditions. Simply by applying monomers with varied backbones and functionalities, we have prepared both rubbery and glassy microparticles with well-defined narrow glass transition temperatures. With different backbone structures, both hydrolytically stable and degradable particles were achieved. Moreover, off-stoichiometric polymerizations offer *in situ* functionalities with "clickable" moieties that are ready for further reactions. We have demonstrated that by incorporating particular groups the particles are functionalized with fluorescence, photo-responsiveness, etc. We expect these microparticles will find vast usage in latex materials, composite materials, fluorescent imaging, drug delivery and many other applications.
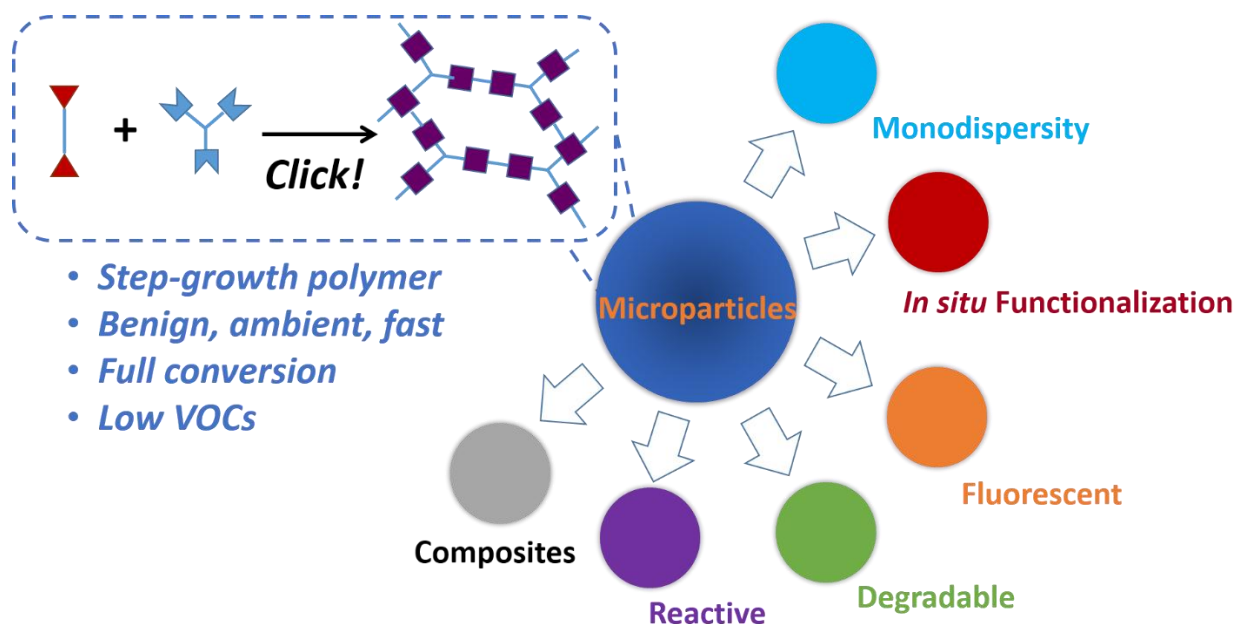
Figure 1. Schematic review of the preparation and the implementation of step-growth thiol-Michael addition dispersion polymerizations.

Introduction

Polymeric microparticles are ubiquitous in many applications such as coatings, composites and drug delivery systems.[1, 2] Particularly, spherical microparticles that are uniform in sizes, or monodisperse microspheres, have unique usages in photonic crystals, biomedical analysis and chromatography applications.[3-5] Free-radical chain-growth polymers including polystyrene and poly(methyl methacrylate) have been generally used for the preparation of such materials.[6, 7] On the other hand, step-growth polymers are seldom used, such as polyamides and polycarbonates. This is mainly because conventional condensation/addition reactions are of low efficiency in dilute conditions, and they are intolerant to disperse media such as water and alcohol. For step-growth polymerizations, the reaction kinetics decelerates sharply as the reaction proceeds with less monomer remaining, which compromise the final conversion and limits the stability of the formed intermediate particles. Uncontrolled amount of the residual complimentary reactive species within the microspheres lead to aggregation and thus colloidal dispersions are unable to be formed. Unlike conventional chain-growth polymers such as polystyrene and poly(meth)acrylates, step-growth mechanism allows the manipulation of polymer backbones simply by altering the monomer structure. In cross-linking polymerizations, structurally uniform crosslinking polymers are generated from step-growth reactions, which offer robust physicochemical properties. Moreover, in step-growth polymerizations, a specific and controlled amount of functional groups remain available for further reactions. With abovementioned advantages, we seek to achieve colloidal polymers from step-growth polymerizations so as to study how those advantages can be utilized.

Recently, the implementations of "click" chemistries in step-growth polymerizations has been seen emerging research interest, including thiol-X reactions[8-11]. The "click" reactions are of exceptional efficiency and proceed with quantitative yields under mild conditions.[12] Furthermore, these reactions including thiol-Michael addition are tolerant to water and alcoholic environments so that they are ideal for being used in polymerization techniques in dispersed systems. Among the techniques for the formation of colloidal polymers, dispersion polymerization is one of the most widely used methods, as firstly reported by Keith Barrett.[13] In such a dispersion polymerization system, particles are generated by a homogeneous to heterogeneous phase transition in the course of proceeding polymerization. Compared with other two common heterogeneous systems (suspension and emulsion polymerizations), no additional energy is required to stabilize the multi-phases dispersions which reduced the associated cost. Many radical-mediated chain-growth polymerizations have been implemented in dispersion systems, including the polymerization of styrenic and (meth)acrylic polymers[14-16], also copolymerizations with numerous functional monomers[17-21]. In recent reports[22, 23] we demonstrated a methodology of carrying out the thiol-Michael addition reactions in dispersion polymerizations, for the first time prepared monodisperse microparticles from step-growth systems. Herein, we report the systematic study of the reaction kinetics, the implementation of various monomer selections, photo-initiation system and the applications including fluorescent labeling, polymeric composites and degradable materials.

Results and Discussion

The reaction scheme for the preparation of microparticles is illustrated in Figure 2. A combination of a tetra-thiol and a tri-acrylate is chosen as a model system, namely pentaerythritol tetra(3-mercaptopropionate) (PETMP, Figure 3-3) and trimethylolpropane triacrylate (TMPTA, Figure

3-4). Since both PETMP and TMPTA are molecules based on aliphatic esters, their structual similarity with methyl methacrylate (MMA) provoked us to adopt a similar recipe with the dispersion polymerization of PMMA. For PMMA, polyvinylpyrrolidone (PVP) is commonly used as the stabilizer and methanol is used as the reaction solvent.[24] For this model system triggered with hexylamine, the morphology of the microparticles are shown in Figure 4A. The microspheres are uniform in size with an average diameter of 3.57 μm and a coefficient of variance (CV) of 5 %. The particles could be readily re-dispersed and remain insoluble in organic solvents, however they flocculated in water because of their inherent hydrophobicity. The sizes of the microparticles can be adjusted with various catalyst loading. Figure 4a, 4b and 4c show polymerizations initiated with 1.6 wt%, 4.0 wt% and 10.0 wt% hexylamine, generating microspheres with diameters of 3.57 μm, 2.10 μm and 1.39 μm, respectively.
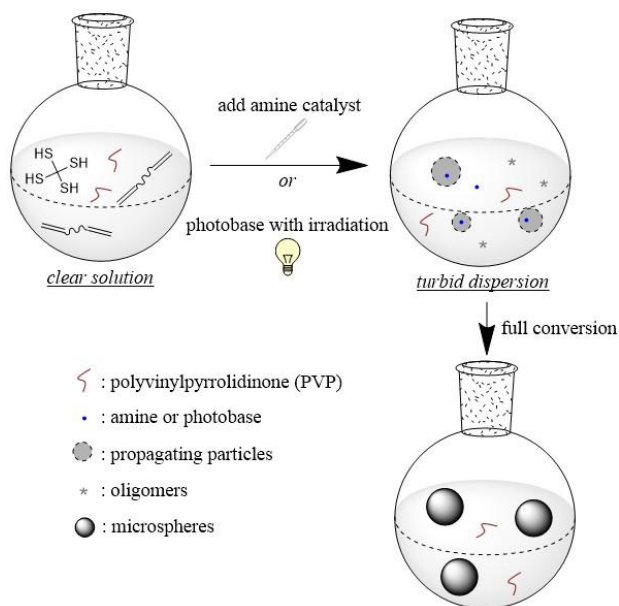
Figure 2. General scheme for the thiol-Michael addition dispersion polymerization. Multi-thiols and multi-acrylates are firstly dissolved in methanol and upon initiation, phase transition occurs rapidly and microparticles are generated. Adapted from literature[23].
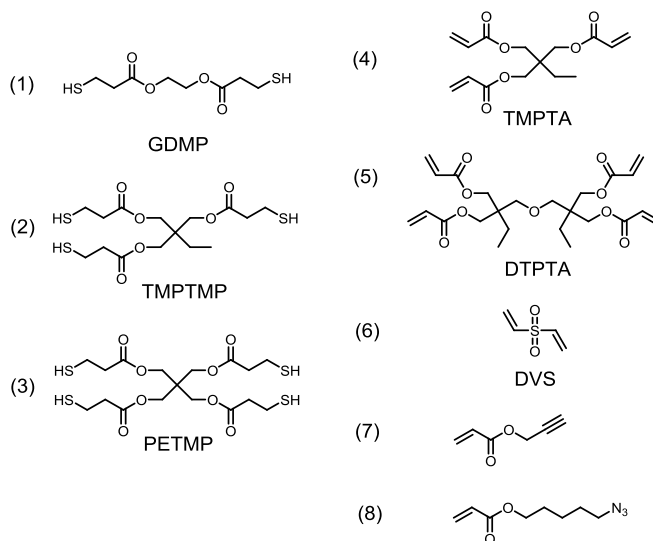
Figure 3. Monomers used in this work: (1) ethylene glycol bis(3-mercaptopropionate) (EGBMP); (2) trimethylolpropane tris(3-mercaptopropionate) (TMPTMP); (3) pentaerythritol tetrakis(3-mercaptopropionate) (PETMP); (4) Trimethylolpropane triacrylate (TMPTA); (5) Di(trimethylolpropane) tetraacrylate (DTPTA); (6)divinyl sulfone (DVS); (7) propargyl acrylate; (8) 6-azidohexyl acrylate. Adapted from literature[22].
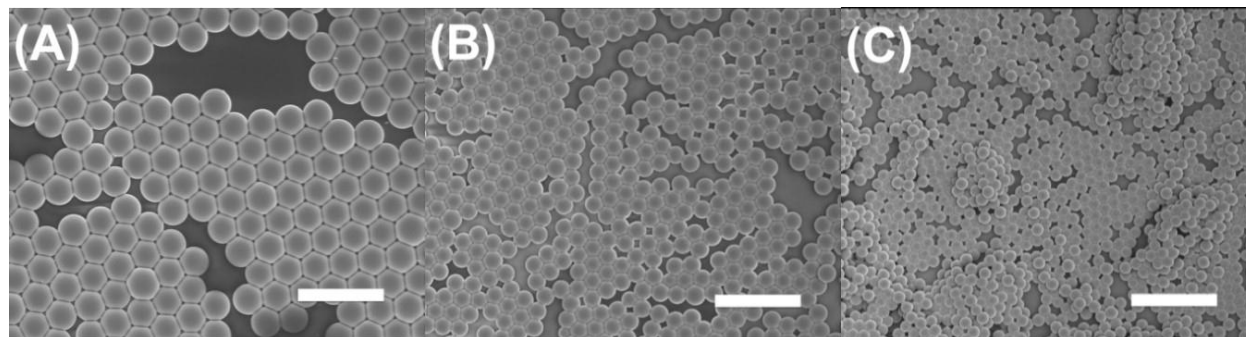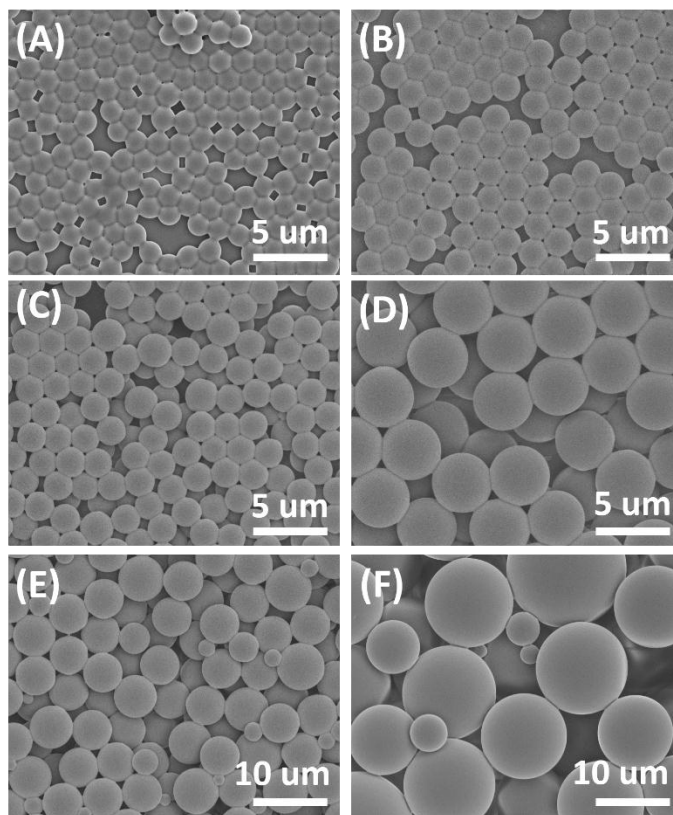

Figure 4. SEM Images of microspheres prepared by thiol-Michael addition dispersion polymerization of stoichiometric PETMP and TMPTA in methanol, with various amount of hexylamine as the initiator: (a) 1.6 wt% (b) 4.0 wt% (c) 10.0 wt% hexylamine with respect to the mass of monomers. Polymerization conditions: PETMP (3.66 g, 7.5 mmol), TMPTA (3.0 g, 10 mmol) and PVP (1.5 g), methanol (150 mL), the mixture was stirred at 400 RPM for 2h after the addition of hexylamine. The scale bar length is 10 μm. Adapted from literature[22].

In chain-growth dispersion polymerizations, the reaction conversion can be measured by determining the amount of remaining unreacted monomer. However for crosslinking step-growth polymerizations this approach is not applicable. In step-growth systems, the amount of reduced monomer does not denote the conversion since a large amount of unreacted species exist on oligomers/polymers. Particularly, the gelation of stoichiometric PETMP-TMPTA system takes place at less than 50% conversion so that the reactants on the particles are not negligible but very significant. As a result, we chose FT-IR spectroscopy to determine the conversion because no bias between solid and liquid phases happens for FT-IR measurement of powder samples. We used diffuse reflectance FT-IR for powder samples that were well mixed with KBr. For the model PETMP-TMPTA system, the reaction scheme and the FT-IR spectra at various reaction extents are shown in Figure 5.

The peak between 2470 and 2600 cm^{-1} was used for measuring the amount of thiol and that between 795 and 810 cm^{-1} was used for the amount of acrylate. An internal reference peak was used which was the broad peak from 2800-3000 cm^{-1} that represents saturated C-H bonds. As shown in Figure 5, the reaction conversions at 1 min, 10 min, 90 min and 330 min were assessed to be 53%, 84%, 98% and 99%, respectively. Quantitative conversion was observed within 6h of reaction at ambient. In comparison with chain-growth dispersion polymerizations, the quantitative conversion of this step-growth system is of great advantage. It is practically impossible for the free-radical polymerization to reach full conversion because of the inefficiency of radical polymerizations at high conversions (diluted monomer concentrations). It is worthy noted that the unreacted monomers in free-radical polymerizations contribute mainly for the volatile organic compounds (VOCs), which are highly disfavored for colloidal materials such as latex, paints and coatings. Not only VOCs are usually toxic but also diminish the mechanical properties as they slowly evaporate and alter the material compositions. By the polymerization mechanism, step-growth polymers intrinsically produce far less VOC which renders them great candidates for engineering better colloidal materials.
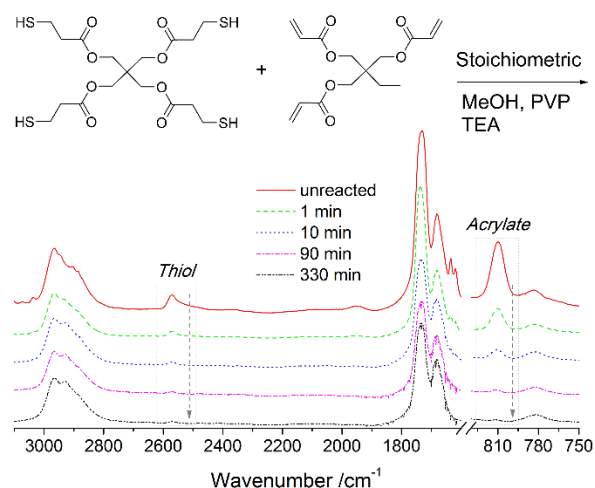
Figure 5. The reaction scheme and FT-IR spectral time evolution series of a thiol-Michael addition polymerization of stoichiometric PETMP-TMPTA at different reaction times. Polymerization conditions: 3 wt% of PETMP and 2.5 wt% of TMPTA were dissolved in methanol (0.2 mol/L of both thiol and acrylate functional groups), with 15 wt% PVP with respect to the total of monomers. The reaction was initiated with 10 wt% TEA (with respect to monomer content). Adapted from literature[23].

Figure 6. SEM images of microspheres prepared from various loadings of stoichiometric PETMP and TMPTA in methanol: (A) 1.4 wt%; (B) 2.8 wt%; (C) 4.2 wt%; (D) 7.0 wt%; (E) 8.4 wt%; (F) 11.2 wt% monomer. Polymerization conditions: monomers were dissolved with 1.5 g PVP in 150 mL methanol; 0.32 g of TEA was used for initiation and the reaction was allowed for 6h. Adapted from literature[23].

The effect of monomer concentration on the particle sizes was also investigated. A series of polymerizations of PETMP and TMPTA were carried out with different concentrations in methanol while keeping all the same other reaction conditions. As the monomer loading enlarged from 1.4 wt% to 11.2 wt%, the particle sizes amplified, as shown in Figure 6. The average diameters for 1.4 wt%, 2.8 wt%, 4.2 wt% and 5.6 wt% monomers loadings turned out to be 1.66 μm, 2.03 μm, 2.14 μm and 2.41 μm, respectively. Further, particle sizes enlarged dramatically with monomer concentrations that were higher than 7 wt%. With 8.4 wt% and 11.2 wt% monomer loadings, the average diameters were measured to be 5.16 μm and 10.9 μm, respectively, both with CVs that were higher than 20%.
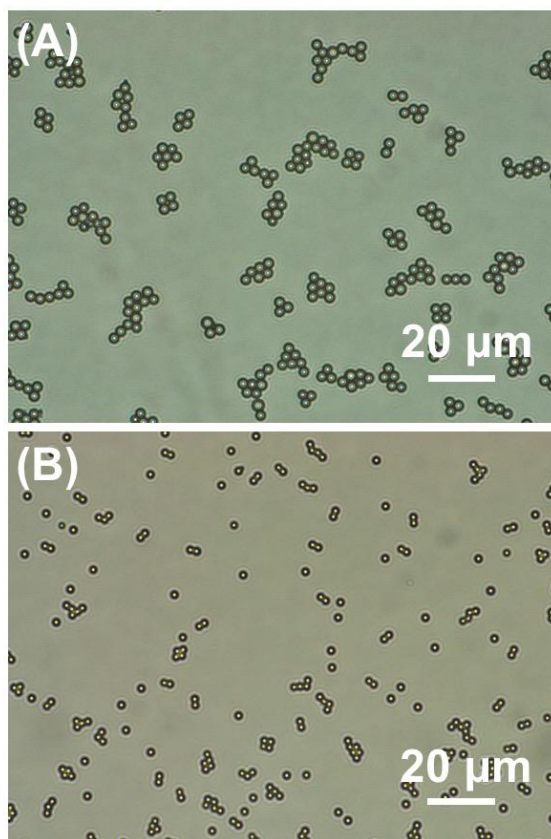
Figure 7. Optical microscope images for PETMP-TMPTA microparticles formed by: (A) NPPOC-hexylamine and UV irradiation under 100 mW/cm2 at 365 nm for 1h. (B) Adding an equimolar amount of hexylamine as compared to NPPOC-hexylamine. Reaction conditions: 3.0 wt% of PETMP and 5.0 wt% of TMPTA in methanol (0.2 mol/L of thiol and 0.4 mol/L of acrylate functional groups), 20 wt% of PVP and 20 wt% of NPPOC-hexylamine or 6.5 wt% of hexylamine were used (all with respect to monomers). Adapted from literature[23].

The spatiotemporal control of photo-induced processes expands the usage of polymerization in many important applications. Moreover, the reaction rate can be facile tuned by adjusting irradiation intensities. In previous reports, a series of 2-(2-nitrophenyl)propyloxycarbonyl (NPPOC) caged amines have been demonstrated to be efficient initiators for thiol-Michael addition reactions.[25, 26] To demonstrate the photo-induced microparticles formation, we used NPPOC-hexylamine coupled with UV irradiation as a replacement of adding the base directly. No phase transition was perceived until applying 320-390 nm UV light (100 mW/cm^2 at 365 nm). The particle morphology is shown in Figure 7A. Optical microscopy images of particles present a diameter of 2.5 μm and monodispersity. In

comparison, particles prepared by directly adding hexylamine of equivalent molar to 20 wt% of NPPOC-hexylamine are shown in Figure 7B. The photo-induced particles were significantly larger than the direct adding counterparts. This is because that the base was released progressively with respect to irradiation. It is well consistent with previous experiments where the particle size reduces with less amount of catalytic base.

Table 1. Dispersion Polymerization of multifunctional thiols and ene's[a]

| Entry	Thiol/ene Monomer Functionality[b]	Dn /μm	CV /%	Yield /%	Tg[c] /°C
1	Di/Tri	9.9	36	72	-24
2	Tri/Tri	6.1	11	90	-6
3	Tetra/Tri	3.6	3.7	94	8
4	Tetra/Tetra	2.8	20	90	16
5[d]	Tetra/Di	1.1	4.0	95	13

[a]Polymerization conditions: 30 mmol of both thiol and acrylate functional groups, 150 mL MeOH, 1.5 g PVP and 60 mg hexylamine; [b]Monomers of varying functionality are shown in scheme 1; [c]Glass transition temperature was measured from DSC; [d]Divinylsulfone is used as ene monomer instead of acrylate. Adapted from literature[22]
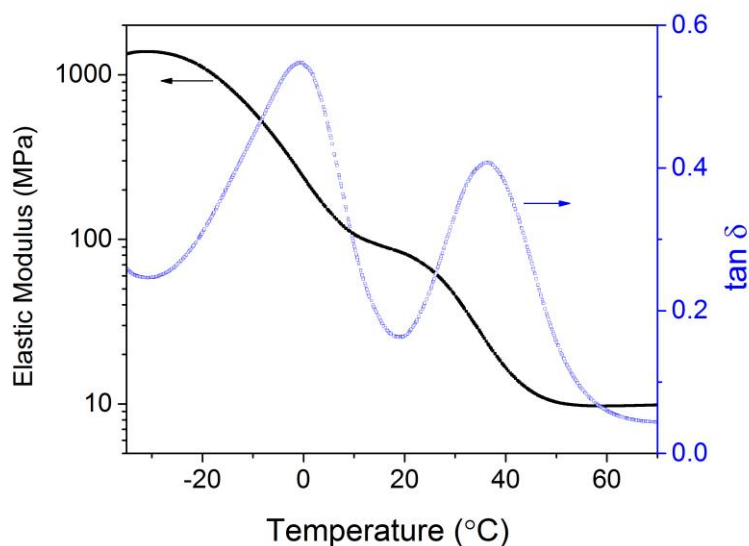
Figure 8. Dynamic mechanical analysis of polymeric composite of PETMP-DVS microspheres in TMPTMP-TMPTA matrix. The composite is composed of 0.5 g of PETMP-DVS microspheres (42 wt%) embedded in 0.7 g of TMPTMP-TMPTA matrix (58 wt%). Adapted from literature[22].

As abovementioned, step-growth polymer networks can be freely adjusted by various crosslinking density and backbone structures. In Table 1, as the crosslink density increases from a dithiol-triene (2-3) system to a tetrathiol-tetraene (4-4) system (entries 1-4), the glass transition temperatures (Tg) increased from -24 °C to 16 °C, as determined from differential scanning calorimetry (DSC). Also, for another tetrathiol-diene (entry 5) system where divinyl sulfone (DVS, Figure 3-6) was used as the Michael acceptor monomer. A significant higher Tg was observed compared with a similarly cross-linked thiol-acrylate microspheres. The low molecular weight DVS moiety provides a stiffer

backbone so that the microparticles possess a higher Tg. This indicates that the dispersion polymerization method is potentially applicable for all combinations of thiol-Michaels monomers and the corresponding properties of polymeric microspheres can be straightforwardly adjusted. With microparticles with well-defined properties, we seek to utilize them in polymeric composites. We prepared a composite material by mixing PETMP-DVS microspheres (40 wt%) well into TMPTMP-TMPTA resins (60 wt%), which were subcequently polymerized. After fully reacted at an elevated temperature the mixture material was an opaque elastomer. Dynamic mechanical analysis (DMA) of such a material is shown in Figure 8. Interestingly, the material presents two distinct Tg's: a Tg at 0°C represents the TMPTMP-TMPTA matrix and a Tg at 37°C comes from the PETMP-DVS microspheres. Further, the storage modulus decreases from 1400 MPa in the glassy state below 0°C to 80 MPa once being heated beyond the first Tg, and then drops to 10 MPa beyond the second Tg at 37°C. It is worth noting that both the matrix and the dispersed particle phases in the composite are of highly cross-linked polymer networks. Two distinct Tg's within a narrow range of 40°C confirm the homogeneity of step-growth networks both for the matrix and the particles. As previous demonstrated, such multiple thermal responses can be engineered into triple shape memory materials.
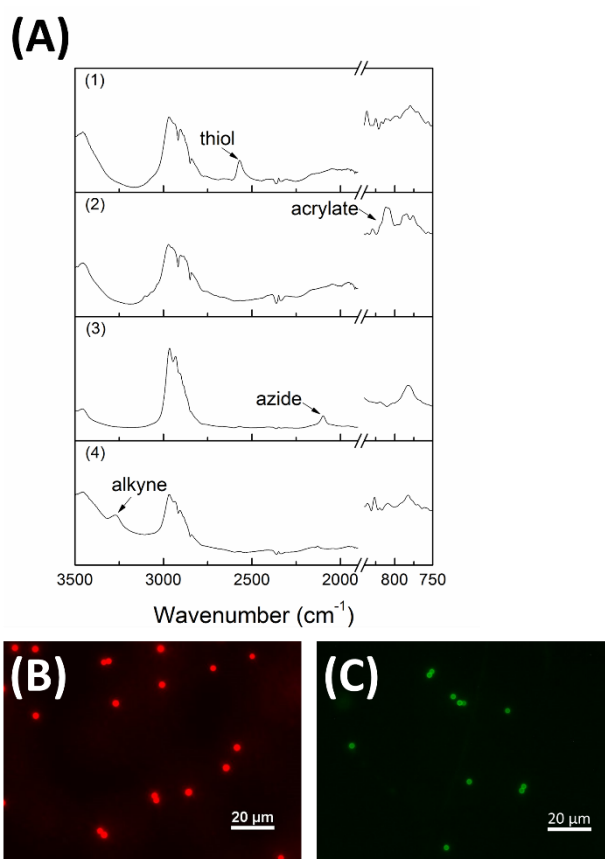
Figure 9. (A) FT-IR spectra of functionalized PETMP-TMPTA microspheres: (1) thiol-excess (33 mol%); (2) acrylate-excess (20 mol%); (3) azide-functionalized(with 10 mol% azide with respect to thiol functionality); (4) alkyne-functionalized(with 15 mol% alkyne with respect to thiol functionality). Images for fluorescently-labeled PETMP-TMPTA microspheres (60X objective): (B) rhodamine B labeled thiol-excess microspheres; (C) rhodamine 110 labeled alkyne-microspheres. Adapted from literature[22].

Another advantage of step-growth polymer networks is off-stoichiometric reaction systems. With either thiol or alkene in excess, microspheres with intrinsic functionalization from the self-limiting reaction were prepared in one step, as confirmed by FT-IR shown in Figure 9A. It is worthy noted that exclusively the excess functionality was observed on FT-IR, indicating the reaction is self-limiting and in full conversion. By copolymerizing functional monomers, a variety of functionalities can be incorporated into the thiol-acrylate microspheres. Both alkyne (propargyl acrylate, Figure 3-7) and azide (azido-hexyl acrylate, Figure 3-8) groups were chosen as examples, since they can undergo the copper catalysed alkyne-azide cycloaddition reaction (CuAAC). Figure 9A (3)-(4) indicates the azide and alkyne moieties on those microparticles. Furthermore, functionalized microspheres were demonstrated as means for fluorescent labelling materials. Thiol-excess microspheres was reacted with a fluorescent acrylic monomer (acryloxyethyl thiocarbamoyl rhodamine B) by a thiol-Michael reaction, as shown in Figure 9B. Also, alkyne-functionalized microspheres were reacted with a fluorescent azide (Rhodamine 110 conjugated PEG azide) via the CuAAC reaction, as shown in Figure 9C.
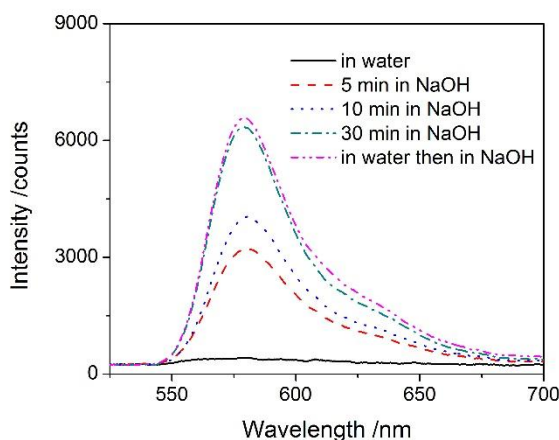
Figure 10. UV-vis spectra of the solution from the degradation of rhodamine B labeled PETMP-TMPTA microspheres made by dispersion polymerizations in various conditions. Adapted from literature[22].

Stimuli-responsive colloids are important to many controlled release systems. In particular, esters are hydrolysable in both acidic and basic conditions. Many polyesters have been studied for biodegradation and controlled release.[27] Interestingly, the thiol-acrylate microspheres contain many thioether esters as building blocks, which are particularly susceptible to hydrolysis. To demonstrate the degradability, such microspheres were dispersed in 1 mol/L NaOH (aq), and the turbid dispersion turned to clear in just 30 min. Upon degradation, the amount of dye that was released into the solution increased gradually with the extent of degradation. This is primitive experiment as NaOH is a very strong base and not practically reasonable for biomedical applications. However as we've shown that the backbone could be easily tuned with monomer structures, the step-growth particles enable a simple design of biomedical applicable drug delivery systems with desired drug loading and release behaviours.

Conclusion

A systematic study on the realization of thiol-Michael addition dispersion polymerizations was performed. Cross-linked polymer microparticles were successfully achieved via thiol-Michael addition

polymerizations between multifunctional thiols and acrylates. With the great adaptability of this dispersion polymerization method and a huge selection of monomer combinations, this work provides a platform for materials engineers for the design of novel polymeric colloidal materials with desired functionality and properties by simple means.

References

1.   Kawaguchi, H. *Progress in Polymer Science* **2000,** 25, (8), 1171-1210.
2.   Jeong, B.; Bae, Y. H.; Lee, D. S.; Kim, S. W. *Nature* **1997,** 388, (6645), 860-862.
3.   Wang, J.; Cormack, P. A.; Sherrington, D. C.; Khoshdel, E. *Angewandte Chemie International Edition* **2003,** 42, (43), 5336-5338.
4.   Deutsch, M.; Vlasov, Y. A.; Norris, D. J. *Advanced Materials* **2000,** 12, (16), 1176-1180.
5.   Terray, A.; Oakey, J.; Marr, D. W. M. *Science* **2002,** 296, (5574), 1841-1844.
6.   Ming, W.; Zhao, J.; Lu, X.; Wang, C.; Fu, S. *Macromolecules* **1996,** 29, (24), 7678-7682.
7.   Sivakumar, M.; Rao, K. P. *Reactive and Functional Polymers* **2000,** 46, (1), 29-37.
8.   Hoyle, C. E.; Bowman, C. N. *Angewandte Chemie International Edition* **2010,** 49, (9), 1540-1573.
9.   Kade, M. J.; Burke, D. J.; Hawker, C. J. *Journal of Polymer Science Part A: Polymer Chemistry* **2010,** 48, (4), 743-750.
10.   Nair, D. P.; Podgórski, M.; Chatani, S.; Gong, T.; Xi, W.; Fenoli, C. R.; Bowman, C. N. *Chemistry of Materials* **2013,** 26, (1), 724-744.
11.   Hoyle, C. E.; Lowe, A. B.; Bowman, C. N. *Chemical Society Reviews* **2010,** 39, (4), 1355-1387.
12.   Xi, W.; Scott, T. F.; Kloxin, C. J.; Bowman, C. N. *Advanced Functional Materials* **2014,** 24, (18), 2572-2590.
13.   Barrett, K. E. *British Polymer Journal* **1973,** 5, (4), 259-271.
14.   Ober, C. K.; Lok, K. P.; Hair, M. L. *Journal of Polymer Science: Polymer Letters Edition* **1985,** 23, (2), 103-108.
15.   Tseng, C. M.; Lu, Y. Y.; El-Aasser, M. S.; Vanderhoff, J. W. *Journal of Polymer Science Part A: Polymer Chemistry* **1986,** 24, (11), 2995-3007.
16.   Li, K.; Stöver, H. D. *Journal of Polymer Science Part A: Polymer Chemistry* **1993,** 31, (13), 3257-3263.
17.   Zhang, F.; Cao, L.; Yang, W. *Macromolecular Chemistry and Physics* **2010,** 211, (7), 744-751.
18.   Xing, C.-M.; Yang, W.-T. *Macromolecular Rapid Communications* **2004,** 25, (17), 1568-1574.
19.   Liu, L.; Ren, M.; Yang, W. *Langmuir* **2009,** 25, (18), 11048-11053.
20.   Žůrková, E.; Bouchal, K.; Zdeňková, D.; Pelzbauer, Z.; Švec, F.; Kálal, J.; Batz, H. G. *Journal of Polymer Science: Polymer Chemistry Edition* **1983,** 21, (10), 2949-2960.
21.   Krishnamoorthy, S.; Haria, M.; Fortier-mcgill, B. E.; Mazumder, J.; Robinson, E. I.; Xia, Y.; Burke, N. A.; Stöver, H. D. *Journal of Polymer Science Part A: Polymer Chemistry* **2011,** 49, (1), 192-202.
22.   Wang, C.; Podgorski, M.; Bowman, C. N. *Materials Horizons* **2014,** 1, (5), 535-539.
23.   Wang, C.; Zhang, X.; Podgórski, M.; Xi, W.; Shah, P.; Stansbury, J.; Bowman, C. N. *Macromolecules* **2015,** 48, (23), 8461-8470.
24.   Shen, S.; Sudol, E.; El-Aasser, M. *Journal of Polymer Science Part A: Polymer Chemistry* **1994,** 32, (6), 1087-1100.
25.   Xi, W.; Krieger, M.; Kloxin, C. J.; Bowman, C. N. *Chemical Communications* **2013,** 49, (40), 4504-4506.
26.   Xi, W.; Peng, H.; Aguirre-Soto, A.; Kloxin, C. J.; Stansbury, J. W.; Bowman, C. N. *Macromolecules* **2014,** 47, (18), 6159-6165.
27.   Rydholm, A. E.; Reddy, S. K.; Anseth, K. S.; Bowman, C. N. *Biomacromolecules* **2006,** 7, (10), 2827-2836.