Published in final edited form as:

React Funct Polym. 2019 January ; 134: 85–92. doi:10.1016/j.reactfunctpolym.2018.11.003.

Step-growth Production of Nanogels for Use as Macromers with Dimethacrylate Monomers

Guangzhe Gao^a, Parag K. Shah^b, Tao Liu^b, and Jeffery W. Stansbury^{a,b,c}

^aMaterials Science and Engineering Program, University of Colorado, Boulder, Colorado 80309-0596, USA

^bDepartment of Chemical and Biological Engineering, University of Colorado, Boulder, Colorado 80309-0596, USA

^cDepartment of Craniofacial Biology, School of Dental Medicine, Anschutz Medical Campus, Aurora, Colorado 80045, USA

Abstract

A series of functional nanogels were synthesized by a step-growth mechanism that involved diisocyanate addition to a modest stoichiometric excess of multi-thiols. Nanogels with sizes less than 10 nm were obtained as room temperature liquids with residual thiol groups used to attach methacrylate functionality. Depending on nanogel structure, bulk nanogel properties varied widely, as did the properties of the nanogel-derived and nanogel-modified polymers. Photopolymerization of the reactive nanogels in combination with a dimethacrylate monomer showed dramatically enhanced reaction rate and conversion compared with the dimethacrylate homopolymer. Polymerization shrinkage/ stress as well as mechanical properties of the polymer networks were controlled by changing the ratio of nanogels and dimethacrylate monomers used in formulations. Thus, this study shows the potential of step-growth nanogels for beneficial changes in resin reactivity and application-based performance.

Keywords

Step-growth polymerization; nanogels; photopolymerization

1. Introduction

Polymeric particles composed of single or multiple physically or covalently interconnected chains can be considered as nanogels if their macromolecular dimensions range from less than ten to a few hundred nanometers and if the discrete particles can be swollen by solvent or monomer.[1–3] Nanogels have drawn substantial attention in applications such as drug

Corresponding authors at: Materials Science and Engineering Program, University of Colorado, Boulder, Colorado 80309-0596, USA, Jeffrey.Stansbury@ucdenver.edu (J.W. Stansbury).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

delivery, tissue engineering and polymer composites due to their versatile structures, tunable size and chemical content, potential for a large number of chain ends and the capacity for both surface and internal modification.[1–2,4–5] Various synthetic methods for the preparation of nanogels have been reported: physical self-assembly of interactive polymers involving controlled aggregation of hydrophilic polymers capable of hydrophobic or electrostatic interactions and/or hydrogen bonding[6]; direct polymerization of monomers in either homogeneous or heterogeneous states [7] including solution polymerization[3,12], emulsion polymerization [8], precipitation polymerization [9]; and template-assisted nanofabrication approaches such as photolithographic techniques and micro-molding methods.[10,11] These processes lead to varied nanoparticle structures and to controlled properties of nanogels that accommodate a broad range of applications.

Although nanogels with high loading capacity and the ability to freely disperse in aqueous solution have emerged as a most versatile platform for biomedical application, functional nanogels as fillers or additives have now become increasingly attractive in the preparation of polymer composites.[5,12,13] Nanogels can be added into dental matrix monomers to reduce polymerization shrinkage and stress of the final polymer composite network.[3,14] Nanogel-modified adhesives have been studied as a way to provide enhanced stability of bonded interfaces in dental materials.[15] Hybrid nanogels have been synthesized by incorporation of nanosized inorganic materials or organic monomers with nanogels, which result in thermally, magnetically, optically or pH responsive composite materials.[5,16–18] Novel hydrogels with very high mechanical strength have also been formed by introducing densely crosslinked nanogels into loosely crosslinked polymer matrices, in which the nanogel component content is not higher than 40–50 % by weight.[19–21] Furthermore, photopolymerizable nanogels as macromolecular precursors can be the primary or even the sole network component to produce covalently crosslinked polymer networks whose macroscopic properties can be controlled from pre-designed nanoscale precursors.[12] These approaches exhibit an extraordinary strategy for the control of polymer network properties by changing the nanogel formulations with dimethacrylate monomers over the entire compositional range, including discretely dispersed nanogel phases, to co-continuous morphologies, to confluent pseudo-interpenetrating polymer networks, to bulk nanogel polymers of which only limited work has been reported recently. The majority of these reactive nanogels have been constructed from chain-growth polymerization processes.

Click reactions have become a robust tool for well-controlled functional polymers, due to their modular nature, high efficiency, quantitative conversion, stereospecificity and generation of few, if any, byproducts.[22,23] In particular, the thiol-isocyanate reaction, as one of the click reactions, has received considerable attention in organic synthesis, functional surfaces, uniformly cross-linked particles, shape memory polymers and extrinsic self-healing materials due to rapid reaction rates under mild conditions, resistance toward oxygen inhibition and substantial libraries of commercially available monomers.[24–28] Furthermore, the addition of thiol to isocyanate yielding thiourethane linkages with hydrogen bonds potentially provides polymers with good mechanical and thermal properties. Through a step-growth mechanism, thiol-isocyanate reactions lead to more homogeneous networks compared with chain-growth polymers such as those made from (meth)acrylate polymerizations, which is due in part to differences in basic network structure and a

significantly delayed gelation point.[29] While thiolisocyanate reactions are widely utilized in many diverse applications, the synthesis of nanogels by thiolisocyanate reactions in solution polymerization has received relatively little attention. Low molecular weight thiol-functionalized thiourethane oligomers have been used in a methacrylate-based dental composite model with significant benefits noted in terms of stress reduction.[30] Distinct from that prior study, our reactive nanogels do not alter network structure through chain transfer reactions but rather create hybrid nanogel/matrix copolymer regimes controlled by the nanogel selection and loading that can extend to monomer-free, bulk nanogel polymerizations.

Although, step-growth polymerization has previously been used to control the topological structures of nano-scale hyperbranched or highly branched polymers, [31] a description of how the intentional variation in these particulate structures relate to their thermomechanical properties as well as how reactive versions of these materials can be used to predictably create or modify macroscopic polymeric networks has been lacking. Herein, our approach for the synthesis of reactive nanogels utilizes the thiol-isocyanate reaction in solution polymerization that achieves well-controlled, high molecular weight nanoparticles despite the macrogelation potential in all cases. Compared with emulsion, precipitation, or solution free radical polymerization, this method was conducted rapidly under ambient condition and the procedure with semi-batch monomer addition is not complicated by requirement of any emulsifier, stabilizer, initiator or chain transfer agent. This semi-batch process technique has been explored to control both macrogelation and loop defects, which has the potential to improve the network properties [32]. A series of nanogels with different monomer formulations were synthesized from base-catalyzed multifunctional thiols and diisocyanates in solution polymerizations. Polymer networks were prepared by photopolymerizing suitably functionalized nanogels with dimethacrylate monomers. Several characterization approaches were conducted including photopolymerization kinetics, shrinkage stress, flexural and tensile strength/modulus, and dynamic mechanical property measurements of these monomer-nanogel polymer composites across the full range of nanogel loading levels.

2 Experimental

2.1 Materials

Hexamethylene diisocyanate (HMDI), dibutyltin dilaurate (DBTDL), butylated hydroxytoluene (BHT), 2,2dimethoxy-2-phenylacetophenone (DMPA), trimethylamine (TEA), dichloromethane (DCM), ethyl ether, chloroform (99.5%) were obtained from Sigma-Aldrich. m-Xylene diisocyanate (XDI), 1,3-bis(isocyanatomethyl)cyclohexane (BIC), 2-isocyanatoethyl methacrylate (IEM), triethylene glycol dimethacrylate (TEGDMA) were purchased from TCI America. Polycaprolactone tetra(3mercaptopropionate) (PCL4MP, $M_n = 1350$), ethoxylated-trimethylolpropan tri(3-mercaptopropionate) (ETTMP, $M_n = 700$) were donated by Evans Chemetics. All materials were used as received.

2.2 Synthesis of thiol functionalized nanogels

Excess thiol monomers were dissolved in 30x volume of DCM, and the solution was purged with nitrogen for 30 min. TEA as the catalyst was added into the solution at 2 wt% based on

the thiol monomer content. The solution was stirred under room temperature with isocyanate monomers infused by syringe pump at the rate of 0.1 mmol/min, and the total ratio of thiol and isocyanate functionalities was 1.5:1. After the 30 min dropwise addition of the diisocyanate, the reaction continued for another 30 min before workup. Isocyanate conversion was determined from Fourier transform infrared (FTIR; Nicolet 6700, Thermo-Fischer Scientific) spectroscopy by monitoring the -NCO peak at 2265 cm^{-1} every 10 min over the course of the reaction. The nanogel product was precipitated into 10× volume of ethyl ether, redispersed in chloroform three times and the isolated nanogels were obtained after residual solvent removal under reduced pressure (yield: ~60%). The resulting nanogels (NG) from the varied comonomer combinations are designated as: PCL4MP-XDI (P-X NG), PCL4MP-BIC (P-B NG), PCL4MP-HMDI (P-H NG) and ETTMP-HMDI (E-H NG).

2.3 Nanogel characterization

Triple-detection gel permeation chromatography (GPC; Viscotek) with differential refractive index (RI, Viscotek VE 3580), viscosity and light scattering detectors (Viscotek 270 dual detector) was used for the analysis of nanogel molecular weight, polydispersity index (PDI) and average hydrodynamic radius (R_h).

Ellman's test was employed to determine the concentration of pendant thiol functionality in the nanogels: nanogels in tetrahydrofuran (THF) solution were mixed with Ellman's reagent solution with N,N-diisopropylethylamine (DIPEA) as catalyst. After stirring for 15 min, ultraviolet–visible spectroscopy (Thermo-Fischer Scientific) was used to obtain the absorption peak at 412 nm, and by comparing with the standard curve, thiol functionality concentration of nanogels can be determined.

A rheometer (TA ARES) was used to measure the viscosity of the bulk liquid nanogels between 20 mm diameter plates from shear rate sweeps. Three replicates were conducted for each nanogel. The solvent swollen particle size of nanogels were determined by dynamic light scattering (DLS) using a Zetasizer NanoZS (ZEN 3600, Malvern). Separate measurements were made in DCM and THF. All measurements were performed three times on 0.5 mg mL^{-1} of solutions in quartz cuvettes.

2.4 Synthesis of polymerizable nanogels

To obtain polymerizable nanogels, thiol functionalized nanogels were dissolved in chloroform with excess IEM relative to the residual thiol functional content and with a catalytic amount of DBTDL. The reaction proceeded overnight at $40\text{ }^{\circ}\text{C}$. The functionalized nanogel product was precipitated into 10× volume of ethyl ether, redispersed in chloroform three times and viscous liquid methacrylated nanogels were obtained after vacuum removal of residual solvent (yield: ~95%). Proton nuclear magnetic resonance (^1H NMR; Bruker Avance-III 300, NMR lab, University of Colorado) was used to aid nanogel structural determination in deuterated chloroform with spectra obtained from 64 scans. All data was analyzed with MestRenova 9.0 software.

2.5 Synthesis of network polymer

For bulk macrogel polymer synthesis, a stoichiometric ratio of the thiol and isocyanate functional monomers were mixed with DBTDL (1 wt%), with the mixtures then heated at 100 °C in an oven overnight to form the PCL4MP-XDI (P-X), PCL4MP-BIC (P-B), PCL4MP-HMDI (P-H), ETTMP-HMDI (E-H) polymeric networks.

For polymer synthesis of resin-modified nanogels, reactive nanogels were mixed with TEGDMA in mass ratio of 0%, 10%, 25%, 50%, 75%, 90%, 100%. DMPA (1 wt%) was added into each sample as photoinitiator. Since the polymerizable nanogels were viscous yet fluid liquids, simple mechanical agitation was sufficient to achieve homogeneous, optically clear solutions. Samples were irradiated for 10 min under 365 nm UV light at 15 mW/cm² in different specimen configurations depending on the characterization technique involved.

2.6 Volumetric shrinkage

Each sample was placed on a thin aluminum disc in a non-contact linear variable differential transducerbased linometer (Academic Center for Dentistry Amsterdam, The Netherlands) for real-time volumetric shrinkage testing. [33] Each specimen disc (3 mm diameter and 1 mm thickness) was irradiated for 10 min through a glass slide with 365 nm UV light at 15 mW/cm². Three replicates were carried out for each sample.

2.7 Shrinkage stress

The dynamic shrinkage stress was measured by a cantilever beam-based tensometer (Volpe Research Center, American Dental Association Foundation, Gaithersburg, MD), which has been described in other publications. [34] Each specimen was sandwiched between two silanized glass rods (silane fusion: George Taub Products & Fusion Co., Inc.) in disc shape (6 mm diameter and 1 mm thickness). Shrinkage stress was evaluated during photocuring, which involved irradiation with 365 nm UV light at 15 mW/cm² for 10 min on the surface of the samples, and continuing for an additional 5 min beyond the irradiation interval. Three replicates were carried out for each sample.

2.8 Photopolymerization kinetics

During the shrinkage stress testing, simultaneous real-time Near-IR spectroscopy was utilized to measure the photopolymerization kinetics profile in direct transmission mode via fiber optic cables. [35] The peak area of the first overtone absorbance of the methacrylate C=CH₂ group at 6165 cm⁻¹ was monitored throughout the polymerization process.

2.9 Mechanical strength testing

A universal testing machine (Mini-Bionix II, MTS) was utilized for gathering mechanical property data. Bar-shaped specimens with dimension of 25 mm×2 mm×2 mm photopolymerized under 365 nm UV light irradiation with intensity of 15 mW/cm² for 10 min and post-cured at 100 °C for 24 h were tested in three-point bending on a 20 mm span at a strain rate 1 mm/min. The ultimate flexural strength and the flexural modulus were determined. Three replicates were carried out for each sample.

For selected nanogel-TEGDMA formulations (50:50, 75:25, 90:10, 100:0 mass ratio), tensile testing was performed to obtain the tensile strength, elastic modulus and the elongation to break. Dogbone samples were prepared under the same conditions as prepared for three-point bending. The specimen dimensions were similar to the ASTM dogbone die D638-V [36], with a 3.15 mm width and 0.25 mm thickness, however the gage length was approximately 15 mm rather than the 7.62 mm specified by ASTM D638-V; according to Saint Venant's Principle, this change should have no significant effect on the data accuracy as the effect of stress intensity effects due to the grip and the dogbone shape would be minimized by this change. The test was under uniaxial tensile loading at a crosshead speed of 1 mm/min. Three replicates were carried out for each sample.

2.10 Dynamic mechanic analysis (DMA) testing

A DMA (Perkin Elmer 8000) was used to measure the T_g of the bulk nanogels by sandwiching 10 mg of nanogels in a thin aluminum pocket, which was then subjected to single cantilever cyclic displacement of 50 μm at 1 Hz. Tan delta data was collected as the sample was cooled from 50°C to -50°C at 2°C/min in air. By this approach, the tan delta magnitude is arbitrary but the position of the tan delta thermal transition peak, with its maximum taken as T_g , accurately reflects the change in the nanogel thermomechanical properties as verified using common polymer standards.

A different DMA (TA Q800) was used to gather the T_g and storage modulus of different nanogel-based photopolymers. Samples with dimensions of 10 mm×4 mm×0.25mm were prepared under the same conditions as for mechanical strength testing. A strain and frequency of 0.01% and 1 Hz, respectively, was applied in tension to the samples during a temperature scan from -50°C to 200°C at 2 °C/min.

Three replicates were carried out for each sample under either DMA testing protocol.

3. Results and discussion

3.1 Nanogel characterization

The mechanism of the nanogel synthesis is simply a spatially-limited network-forming thiol-isocyanate reaction. For step-growth polymerizations, any two compatible functionalities can react with each other with effectively no potential for homopolymerization. To avoid avoid macrogelation and get the desired nanogels, a stoichiometric imbalance is necessary. Dropwise addition of the limiting monomer is used to assure control of nanogel molecular weight. This is critical to avoid the emergence of both larger gel structures and greater degrees of polydispersity. GPC analysis includes molecular weight (M_n), polydispersity index (PDI), hydrodynamic radius (R_h) (Table 1) of P-H NG, P-B NG, P-X NG and E-H NG. The results show that they are all discrete, nanoscale macromolecules instead of a broad aggregation of structures. This is not surprising since according to Flory-Stockmayer theory (considering a reaction of an f -functional monomer RA_f with a difunctional comonomer RB_2)

$$p_c = \sqrt{\frac{r}{f-1}}$$

where r is the molar reactant ratio defined as the initial ratio of A groups to B groups, and we can predict the gel point conversion (p_c). [28] For a dropwise reaction as described in experimental section, isocyanate monomer is infused slowly into the solution containing the excess thiol monomer with respect to the reaction rate, so that from the start and continuing through a significant portion of the reaction, the reactant ratio is adequately large to restrict gel point to conversion levels greater than 100 %. At later stages of the limiting diisocyanate addition, solvent dispersion of the growing nanogel particles is required to reach full isocyanate reaction while avoiding macrogelation. For the 1.5:1 thiol:isocyanate ratio based on a tetrathiol and diisocyanate combination, p_c is calculated as 71%. However, for an analogous reaction in which the catalyst is added to pre-mixed comonomers, these TEA-catalyzed polymerizations macrogelled quickly whether in bulk form or even when diluted with 30x volume of solvent.

The assumption of well-controlled nanogel formation is also demonstrated by the time-series of FTIR spectra (Figure S2) taken throughout the synthesis process, which shows that no apparent isocyanate peak was evident at any stage. The fast reaction of isocyanate with excess of thiol assured that only thiol functionalized oligomers/macromers or unreacted thiol monomers (at early stages) are present in the solution. In a solution polymerization with relatively low monomer concentration, the distance between oligomers/macromers is significant, so the probability of inter-particle connectivity during the timescale of isocyanate persistence is low. This approach provides well controlled thiol-functional, nanoscale macromolecules. From GPC data, the molecular weights of the various nanogels are similar (25–40 kg/mol), as expected because the reactant ratios are all the same and the isocyanate monomers are reacted completely. Based on Carothers theory, which demonstrates that molecular weight of step-growth polymerization depends on reactant ratio and extent of reaction, the similar molecular weights are reasonable. The PDI results are all relatively low (1.2–1.3) for these highly branched polymeric structures because of the dropwise reaction, solvent dilution effects and the potential for selective separation of low molecular weight species during the precipitation step. Hydrodynamic radius results show that the solvent swollen particle size of all the nanogels is around 4 nm, which demonstrates true nanoparticle character. Further swelling tests using dynamic light scattering show that the nanoparticles display significantly larger size in DCM than in THF, which indicates preferential affinity for DCM (Table 1) and highlights that the nanoparticles contain internal free volume. As such, these nanoparticles are accurately described as “nanogels”. By use of an Ellman’s test assay, we calculate that the average residual thiol functional group distribution is more than 15 per nanogel due to the excess of thiol monomers, which subsequently can be exploited to allow further functionalization of these nanogels.

Rheology measurements were applied to determine the bulk viscosity of these nanogels (Figure 1). When shear rate is increased, bulk P-H NGs, P-B NGs and P-X NGs show shear thinning behavior and display relatively high viscosity, but E-H NGs behave as a Newtonian fluid with relatively low viscosity. This is likely because the PCL4MP-based nanogels have

longer chains and branches, and there may be more inter-particle chain entanglements in the network structure as compared with the ETTMP-based nanogel, which also has more flexible PEG-type linkages. P-X NGs display the highest viscosity likely due to greater network rigidity and pi-pi stacking between benzene rings.

The T_g of each of the nanogels (Figure 2 & Table 1) was tested by DMA, which demonstrated that the relatively narrow tan delta peaks are entirely below room temperature. As such, the nanogels are all viscous liquids under ambient condition. E-H NGs show the highest T_g due to the ETTMP-based structure that introduces a denser nanogel network. PCL4MP-based nanogels display a progressive increase in T_g as the diisocyanate monomer is changed from HMDI to BIC and then to XDI as the resulting thiourethane spacer segment advances from linear to cycloaliphatic to aromatic.

3.2 Bulk polymerization of nanogels

The initially synthesized nanogels retain residual thiol terminal groups both on the surface and within the nanoparticles. In order to achieve bulk polymerization, the thiol functionalized nanogels were modified by addition of methacrylate groups through reaction with IEM and DBTDL in DCM. From ¹H-NMR analysis (Figure S3), residual mercapto-groups from thiol monomers have chemical shift at 2.8 ppm, and after modification, this peak disappears and is replaced by peaks at 6.2, 5.6 and 2.0 ppm that originate from the methacrylate groups. During this process, beta hydrogen to the sulfur has chemical shift at 2.7 which is not changing. The ¹H NMR results indicate quantitative transition of the thiol groups to thiourethane methacrylates. As such, it is reasonable to assume that the methacrylate group concentrations are equivalent to the prior thiol group concentrations determined by Ellman's test. These reactive nanogels are suitable for photopolymerization under monomer-free and solvent-free conditions as well as for copolymerization with monomer matrices.

Figure 3 shows the ambient bulk photopolymerization kinetics of each nanogel. All the nanogels produced rapid polymerization with final conversion above 95 %. The reason these nanogels display different reaction rates is probably due to differences in initial viscosity, with E-H NGs showing the lowest viscosity and highest reaction rate.

The bulk nanogel photopolymers were tested by DMA. The T_g of the final nanogel-derived network polymers (Figure 4) are all considerably higher than those of the original nanogels. The higher T_g observed for the polymer formed from PCL4MP-based nanogels is likely due in part to the slightly higher reactive group concentrations compared with the ETTMP-containing nanogel, which leads to more covalent inter-particle connections that reinforce the physically overlapping, confluent nanogel network structures. Compared with bulk polymer obtained from the same thiol and isocyanate monomer components at a 1:1 ratio of thiol to isocyanate (with minimal pendant group presence), the bulk nanogel photopolymer can reach higher T_g than the analogous bulk polymer (Figure S4) with the same components. The higher nanogel-based polymer T_g is likely because of the intra- and inter-particle polymerization of the methacrylate-functionalized nanogels, which result in interlaced chain-growth and step-growth network components along with the "loop-defect" control effect promoted by the semi-batch monomer addition during synthesis of nanogels

that can improve network connectivity and mechanical properties. [32] The P-B NGs produced the highest T_g and the greatest T_g during bulk nanogel polymerization with nearly the entire tan δ peak positioned above room temperature. These nanogels offer an option to create high conversion, dense polymer network structures from without reliance on a diluent comonomer.

3.3 Photopolymerization of nanogels and monomers mixture

To further examine the properties of the polymers, co-reactive nanogel formulations with TEGDMA over the entire compositional range provided resins that were analyzed for reaction kinetics, polymer thermomechanical properties and stress. Three PCL4MP-based nanogels were studied here.

3.3.1 Photopolymerization kinetics—When using methacrylated NGs with varying proportions of TEGDMA as a matrix monomer, at low nanogel loading levels, there are two phases in the system – monomer-infiltrated nanogel regions and bulk monomer; however, at moderate and high loadings, co-continuous or confluent hybrid structure due to near contact or overlap of the monomer-swollen nanogel regions can be formed.[14] It is evident that as NGs loading level is increased, the final conversion of the polymerization is increased and reaches at least 90 % when nanogel loading is 50 % or higher no matter which NGs were used (Figure 5). The reasons why the P-H NG can reach higher conversion than the other nanogel composites at the same loading level are probably due to its lower T_g and viscosity, which allows for greater mobility and delayed vitrification during photopolymerization. Also of interest is the significantly increased reaction rate obtained for the monomer-swollen nanogels compared with the independent polymerization of either the monomer or the bulk nanogel (Figure 5). The local increased viscosity experienced by TEGDMA monomer in and around nanogels irrespective of the nanogel concentration promotes early-stage auto-acceleration behavior during photopolymerization. There is significant synergistic effect of small amounts of diluent monomer added to the confluent nanogel formulations in terms of the reaction kinetics and at the other extreme, relatively small amounts of the reactive nanogels added to TEGDMA greatly enhance reaction rate and final conversion, particularly with P-H NG.

3.3.2 Volumetric shrinkage tests—Volume change during polymerization is the result of the reduced distance between covalently linked monomers relative to the free monomer state as well as the reduced mobility in the polymer that allows closer packing. The volumetric shrinkage in nanogel-modified materials is expected to scale inversely with nanogel loading, because the great majority of polymerization involving nanogels is performed prior to its introduction into a secondary monomer. This controllably reduces the initial reactive group concentration and leads to lower volumetric shrinkage. P-X NGs was selected to undergo shrinkage testing at varying weight percentages in TEGDMA. Despite the higher degree of conversion obtained with the nanogel additives, there is a 26.8 % reduction in volumetric shrinkage when 10 wt% of this nanogel is added to TEGDMA as compared with the homopolymer (Figure 6). With the further addition of reactive nanogel, shrinkage was reduced in a linear manner until reaching the 75 wt% loading level. At the highest nanogel loading levels, shrinkage decreases dramatically and eventually reaches an

essentially volume neutral state for bulk nanogel polymerization. This significant reduction in shrinkage at the highest loading levels may be due to a modest decrease in the degree of overlap between the confluent nanogel particles, which provides a physical accommodation of the densification effects associated with the chemical reaction.

3.3.3 Shrinkage stress tests—For vinyl-based glassy networks, shrinkage stress generated during the polymerization process due to the decrease of free volume during the transition from a mobile liquid monomer to a constrained polymer remains a critical problem. For homopolymerization of TEGDMA, it is not surprising to find relatively high shrinkage stress of about 2 MPa (Figure 7). With the addition of nanogels, the shrinkage stress was reduced regardless of nanogel type. This is because as the primary component of the final network structure transitions from TEGDMA to the step-growth NGs as the loading level is increased, both the reduced volumetric shrinkage and the lower modulus of the NG-based network relative to that of the TEGDMA homopolymer results in stress moderation. As with the shrinkage results, reduced stress is achieved in a more or less proportional manner even with the very high polymerization conversion promoted by the nanogel additives. For example, at 25 wt% nanogel loading, shrinkage stress values were reduced by 26.7%, 19.4%, 24.5% for P-H NG, P-B NG and P-X NG, respectively, compared with TEGDMA homopolymer. The P-H NG formulations may be more effective in stress reduction since these nanogels present the lowest T_g and viscosity, which leads to higher mobility of monomers and a delay in vitrification as well as internal physical compliance between nanogel domains as a stress relaxation mechanism. It is noteworthy that polymers with high nanogel loading (>75 wt%) present very low shrinkage stress (less than 0.5 MPa), which offer an opportunity to form polymer network without defects induced by polymerization shrinkage.

3.3.4 Mechanical characterization—DMA was used to obtain the tan δ curves of the fully polymerized samples at various nanogel loadings in TEGDMA following a thermal post-cure treatment since limiting conversion under ambient cure varies considerably for the different compositions. The results (Figure 8) show the TEGDMA homopolymer presents a broad thermal transition that reflects the heterogeneous network structure expected from dimethacrylate polymerizations. The bulk nanogel polymers have relatively low T_g compared with TEGDMA homopolymer. When P-H NGs were used, for the compositions with nanogel loading increasing up to 50 wt%, the polymers yield broad bimodal tan δ plots with a progressively lower T_g maximum for the TEGDMA domain along with a T_g that represents the TEGDMA/nanogel hybrid domain. Above 50 wt% nanogel content, the polymer provides a single T_g that becomes narrower in breadth and occurs at lower temperature with increasing nanogel content. This indicates that nanogel confluence is achieved above loading levels of 50 wt% to give homogeneous networks that only differ in network density based on the proportion of infiltrated TEGDMA and the degree of nanogel overlap. Similar tan δ profiles were obtained for the other nanogel compositions with the confluence threshold also occurring above 50 wt% nanogels loading.

The mechanical properties of P-H NG, P-B NG and P-X NG systems at different nanogel loadings are shown in Table 2. All photocured polymers were optically clear, which means

there was no phase separation or nanogel aggregation occurring during the photopolymerization process. From the 3-point bending results, TEGDMA homopolymer had a flexural strength of 101.4 MPa and a flexural modulus of 2.22 GPa. For P-X NG, the retention of polymer mechanical strength and stiffness at nanogel loading levels up to 35 wt % is attributed to the nanoscale multiphase network structure that allows for a continuous TEGDMA phase that is more rigid. For the P-H NG and P-B NG series, the maximum loading of nanogels that maintains a statistically similar flexural strength and modulus relative to TEGDMA homopolymer is not higher than 25 wt% nanogel loading. As demonstrated with the DMA results, the threshold for nanogel confluence is near the 50 wt% loading level and so approaching or exceeding this nanogel content provides a continuous or confluent nanogel domain morphology that progressively softens as the TEGDMA proportion of the network decreases. So, if using these NGs as reactive additives in applications where lower polymerization shrinkage and stress photopolymers are desired along with requirements for high mechanical strength, the loading level for the nanogels described here cannot be higher than ~25 wt%. On the other hand, based on tensile testing, bulk P-H NG polymers show relatively high elongation although very low strength in tension. However, when adding only 10 wt% TEGDMA monomer into this nanogel, the polymers still shows similar elongation but the tensile strength is increased about three-fold. P-X NG displays a similar phenomenon. As a result, the properties of the polymer networks can be controlled by changing the ratio of nanogels and dimethacrylate monomers used in formulations. Moreover, bulk polymer obtained from the same thiol and isocyanate monomers at a 1:1 ratio of thiol to isocyanate functionality was also subjected to tensile testing (Table S1) with the results showing that the tensile strength is equivalent or greater for polymers based on bulk polymerized nanogels relative to the corresponding polymers produced by direct stoichiometric polymerization of the component monomers, which correlates with the previously mentioned T_g results. The elongation to failure for the bulk nanogel photopolymers and complementary monomer-based polymers varies depending on the nanogel used. However, the bulk P-H NG polymer shows better ductility than its corresponding directly photocured polymer. Therefore, the functionalized nanogels can produce macroscopic polymer networks with better mechanical performance than the directly formed bulk polymer. In addition, the mechanical properties of nanogel-based polymers can readily be tuned based on the selection and proportioning of nanogel-monomer mixtures.

4. Conclusion

High molecular weight functional nanogels can be synthesized efficiently through a “clickable” step-growth approach where internal network densities and reactive group concentrations can be well controlled. Bulk nanogels can be photocured rapidly and efficiently with the final polymer properties dependent on the structure of the nanogels. By mixing the reactive nanogels with dimethacrylate monomers, the photopolymerization process showed significantly enhanced reaction rates and limiting conversion compared with TEGDMA homopolymer. The volumetric shrinkage and shrinkage stress of the nanogel containing polymers can be reduced in a more or less linear manner based on addition of nanogels. It is demonstrated that nanogel confluence can be achieved above loading levels

above 50 wt%. Mechanical properties can be maintained as high as TEGDMA homopolymer up to about 25 wt% nanogel addition depending on the nanogel type. As elastomers, for P-H NG and P-X NG systems, bulk nanogel polymers strength can be improved dramatically by addition of just 10 wt% of a dimethacrylate monomer without affecting its good ductility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This work was supported by NIH/NIDCR R01DE023197 and the Industry/University Cooperative Research Center for the Fundamentals and Applications of Photopolymerization. The authors gratefully thank Matthew Barros for the GPC characterization of the nanogel materials as well as Dr. Bruna Fronza for her assistance with the DMA testing.

References

- [1]. Oh JK, Drumright R, Siegwart DJ, Matyjaszewski K The development of microgels/nanogels for drug delivery applications. *Prog. Polym. Sci* 33 (4) (2008) 448–477.
- [2]. Hamzah YB, Hashim S, Rahman WA Synthesis of polymeric nano/microgels: a review. *J. Polym. Res* 24 (9) (2017) 134.
- [3]. Moraes RR, Garcia JW, Barros MD, Lewis SH, Pfeifer CS, Liu J, Stansbury JW Control of polymerization shrinkage and stress in nanogel-modified monomer and composite materials. *Dent. Mater* 27 (6) (2011) 509–519. [PubMed: 21388669]
- [4]. Jiang Y, Chen J, Deng C, Suuronen EJ, Zhong Z Click hydrogels, microgels and nanogels: emerging platforms for drug delivery and tissue engineering. *Biomaterials*. 35 (18) (2014) 4969–4985. [PubMed: 24674460]
- [5]. Molina M, Asadian-Birjand M, Balach J, Bergueiro J, Miceli E, Calderón M Stimuli-responsive nanogel composites and their application in nanomedicine. *Chem. Soc. Rev* 44 (17) (2015) 6161–6186. [PubMed: 26505057]
- [6]. Kabanov AV, Vinogradov SV Nanogels as pharmaceutical carriers: finite networks of infinite capabilities. *Angew. Chem. Int. Ed* 48 (30) (2009) 5418–5429.
- [7]. Akiyoshi K, Kobayashi S, Shichibe S, Mix D, Baudys M, Kim SW, Sunamoto J Self-assembled hydrogel nanoparticle of cholesterol-bearing pullulan as a carrier of protein drugs: complexation and stabilization of insulin. *Journal of Controlled Release*. 54 (3) (1998) 313–320. [PubMed: 9766251]
- [8]. An Z, Shi Q, Tang W, Tsung CK, Hawker CJ, Stucky GD Facile RAFT precipitation polymerization for the microwave-assisted synthesis of well-defined, double hydrophilic block copolymers and nanostructured hydrogels. *J. Am. Chem. Soc* 129 (46) (2007) 14493–14499. [PubMed: 17967023]
- [9]. Lu A, Moatsou D, Longbottom DA, O'Reilly RK Tuning the catalytic activity of L-proline functionalized hydrophobic nanogel particles in water. *Chem. Sci* 4 (3) (2013) 965–969.
- [10]. Rolland JP, Hagberg EC, Denison GM, Carter KR, De Simone JM High-resolution soft lithography: Enabling materials for nanotechnologies. *Angew. Chem. Int. Ed* 43 (43) (2004) 5796–5799.
- [11]. Tang MD, Golden AP, Tien J Molding of three-dimensional microstructures of gels. *J. Am. Chem. Soc* 125 (43) (2003) 12988–12989. [PubMed: 14570447]
- [12]. Dailing EA, Setterberg WK, Shah PK, Stansbury JW Photopolymerizable nanogels as macromolecular precursors to covalently crosslinked water-based networks. *Soft Matter*. 11 (28) (2015) 5647–5655. [PubMed: 26075300]

- [13]. Funke W, Okay O, Joos-Muller B Microgels-intramolecularly crosslinked macromolecules with a globular structure. *Adv. Polym. Sci* 136 (1998) 139–234.
- [14]. Liu J, Howard GD, Lewis SH, Barros MD, Stansbury JW A study of shrinkage stress reduction and mechanical properties of nanogel-modified resin systems. *European Polymer Journal*. 48 (11) (2012) 1819–1828. [PubMed: 23109731]
- [15]. Morães RR, Garcia JW, Wilson ND, Lewis SH, Barros MD, Yang B, Pfeifer CS, Stansbury JW Improved dental adhesive formulations based on reactive nanogel additives. *J. Dent. Res* 91 (2) (2012) 179–184. [PubMed: 22019910]
- [16]. Hoare T, Timko BP, Santamaria J, Goya GF, Irusta S, Lau S, Stefanescu CF, Lin D, Langer R, Kohane DS Magnetically triggered nanocomposite membranes: a versatile platform for triggered drug release. *Nano Lett.* 11 (3) (2011) 1395–1400. [PubMed: 21344911]
- [17]. Strong LE, West JL Thermally responsive polymer–nanoparticle composites for biomedical applications. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*. 3 (3) (2011) 307317.
- [18]. Zhang X, Pint CL, Lee MH, Schubert BE, Jamshidi A, Takei K, Ko H, Gillies A, Bardhan R, Urban JJ, Wu M Optically-and thermally-responsive programmable materials based on carbon nanotube/hydrogel polymer composites. *Nano Lett.* 11 (8) (2011) 3239–3244. [PubMed: 21736337]
- [19]. Huang T, Xu HG, Jiao KX, Zhu LP, Brown HR, Wang HL A novel hydrogel with high mechanical strength: a macromolecular microsphere composite hydrogel. *Adv. Mater* 19 (12) (2007) 1622–1626.
- [20]. Hu J, Kurokawa T, Hiwatashi K, Nakajima T, Wu ZL, Liang SM, Gong JP Structure optimization and mechanical model for microgel-reinforced hydrogels with high strength and toughness. *Macromolecules*. 45 (12) (2012) 5218–5228.
- [21]. Stansbury JW Water compatible nanogel compositions. US Patent 9845415-B2. December 19, 2017.
- [22]. Kolb HC, Finn MG, Sharpless KB Click chemistry: diverse chemical function from a few good reactions. *Angew. Chem. Int. Ed* 40 (11) (2001) 2004–2021.
- [23]. Nair DP, Podgórski M, Chatani S, Gong T, Xi W, Fenoli CR, Bowman CN The thiol-Michael addition click reaction: a powerful and widely used tool in materials chemistry. *Chem. Mater* 26 (1) (2013) 724–744.
- [24]. Li H, Yu B, Matsushima H, Hoyle CE, Lowe AB The thiol– isocyanate click reaction: facile and quantitative access to ω -end-functional poly (N, N-diethylacrylamide) synthesized by RAFT radical polymerization. *Macromolecules*. 42 (17) (2009) 6537–6542.
- [25]. Hensarling RM, Rahane SB, LeBlanc AP, Sparks BJ, White EM, Locklin J, Patton DL Thiol–isocyanate “click” reactions: rapid development of functional polymeric surfaces. *Polym. Chem* 2 (1) (2011) 88–90.
- [26]. Tan J, Li C, Dan S, Li H, Gu J, Zhang B, Zhang H, Zhang Q One-step thiol-isocyanate dispersion polymerization: Preparation of uniform, cross-linked and functional particles. *Chemical Engineering Journal*. 304 (2016) 461–468.
- [27]. Dailing EA, Nair DP, Setterberg WK, Kyburz KA, Yang C, D’Ovidio T, Anseth KS, Stansbury JW Combined, independent small molecule release and shape memory via nanogel-coated thiourethane polymer networks. *Polym. Chem* 7 (4) (2016) 816–825. [PubMed: 27066114]
- [28]. Hillewaere XK, Teixeira RF, Nguyen LT, Ramos JA, Rahier H, Du Prez FE Autonomous Self-Healing of Epoxy Thermosets with Thiol-Isocyanate Chemistry. *Adv. Funct. Mater* 24 (35) (2014) 5575–5583.
- [29]. Young RJ, Lovell PA Introduction to Polymers. CRC press Third edition (2011) 21–60.
- [30]. Bacchi A, Yih JA, Platta J, Knight J, Pfeifer CS Shrinkage/stress reduction and mechanical properties improvement in restorative composites formulated with thio-urethane oligomers. *J. Mech. Behav. Biomed. Mater* 78 (2018) 235–240. [PubMed: 29175492]
- [31]. Chen H, Kong J Hyperbranched polymers from A2+ B3 strategy: recent advances in description and control of fine topology. *Polym. Chem* 7 (22) (2016) 3643–3663.
- [32]. Gu Y, Kawamoto K, hong MZ, Chen M, Hore MJ, Jordan AM, Korley LT, Olsen BD, Johnson JA Semibatch monomer addition as a general method to tune and enhance the mechanics of polymer

networks via loop-defect control. *Proc. Natl. Acad. Sci* 114 (2017) 4875–4880. [PubMed: 28439017]

- [33]. De Gee AJ, Feilzer AJ, Davidson CL True linear polymerization shrinkage of unfilled resins and composites determined with a linometer. *Dent. Mater* 9 (1) (1993) 11–14. [PubMed: 8299861]
- [34]. Lu H, Stansbury JW, Dickens SH, Eichmiller FC, Bowman CN Probing the origins and control of shrinkage stress in dental resin composites. II. Novel method of simultaneous measurement of polymerization shrinkage stress and conversion. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*. 71 (1) (2004) 206–213.
- [35]. Stansbury JW, Dickens SH Determination of double bond conversion in dental resins by near infrared spectroscopy. *Dent. Mater* 17 (1) (2001) 71–79. [PubMed: 11124416]
- [36]. American Society for testing and Materials. Standard test method for tensile properties of plastics. D638–02a. Philadelphia, Pa: ASTM, 2002.

Figure 1.
Viscosity data of different NGs.

Figure 2. DMA thermograms of bulk nanogels. Tg of each NGs is: -21.7°C (PCL4MP-HMDI NGs), -18.2°C (PCL4P-BIC NGs), -16.8°C (PCL4MP-XDI NGs) and -10.3°C (ETTMP-HMDI NGs).

Figure 3. Photopolymerization kinetic of methacrylate-functionalized nanogels system. (DMPA loading: 1 wt%. Irradiation condition: 365 nm UV-light, 15 mW/cm²)

Figure 4.

Tan delta curves of networks formed from different NGs. Tg of each polymer is: 32.6°C (P-H NG polymer), 44.1°C (P-B NG polymer), 30.9°C (P-X NG polymer), 23.1°C (E-H NG polymer).

Figure 5.

Polymerization kinetics of systems with different NGs loading (From left to right, P-H NG, P-B NG, P-X NG was incorporated into the systems separately. DMPA loading: 1 wt%. Irradiation condition: 365 nm UV-light, 15 mW/cm², light on for 10 min).

Figure 6.
Volumetric shrinkage results for P-X NG systems at different loading level.

Figure 7.

Polymerization shrinkage stress of systems with different NGs loading. (From left to right, P-H NG, P-B NG, P-X NG was incorporated into the systems separately. DMPA loading: 1 wt%. Irradiation condition: 365 nm UV-light, 15 mW/cm², light on for 10 min).

Figure 8.

DMA test (second heating runs) of polymers with different NG loading levels. (From left to right, P-H NG, P-B NG, P-X NG incorporated into TEGDMA.)

Table 1.

Nanogel characterization by triple-detection GPC, DMA and thiol concentration (per NG) obtained from Ellman's test.

Sample	M _n	R _h (nm)	PDI	Size in DCM(nm)	Size in THF(nm)	Thiol con.(per NG)	Tg(°C)
PCL4MP+HMDI NGs	3.8E+4	4.34	1.22	7.40±1.07	5.09±0.72	23.5±0.7	−21.7
PCL4MP+BIC NGs	2.4E+4	4.02	1.32	13.04±0.93	6.72±1.42	23.1±1.4	−18.2
PCL4MP+XDI NGs	2.5E+4	3.89	1.23	6.37±1.02	3.98±0.78	20.8±0.6	−16.8
ETTMP+HMDI NGs	3.0E+4	4.08	1.20	9.04±2.92	4.12±0.62	18±0.4	−10.3

Table 2.

Flexural strength, flexural modulus, tensile strength and elongation ratio of polymers with different NG loading level. (polymers with NG loading from 0–25% are glassy, and were not tested in tension)

Composite formula	Wt.% of nanogels	Flexural Strength (MPa)	Flexural Modulus (GPa)	Tensile Strength(MPa)	Elongation ratio %
TEGDMA	0	101.4±4.2	2.22±0.09	/	/
P-H NG/TEGDMA	10	103.9±3.7	2.25±0.17	/	/
	25	83.4±3.5	1.97±0.03	/	/
	50	60.0±1.8	1.25±0.05	25.5±1.3	3.4±0.4
	75	17.5±0.1	0.42±0.05	18.9±2.3	35.7±3.6
	90	2.40±0.07	0.090±0.002	5.65±0.05	53.1±3.4
	100	2.15±0.09	0.032±0.004	1.72±0.04	59.6±5.6
P-B NG/TEGDMA	10	103.2±11.1	2.27±0.09	/	/
	25	98.7±2.4	2.16±0.07	/	/
	50	61.1±2.8	1.06±0.05	46.6±3.2	8.6±0.9
	75	34.9±2.4	0.38±0.02	26.7±1.7	33.8±2.4
	90	13.2±3.8	0.15±0.05	25.8±1.5	53.8±3.3
	100	2.6±1.4	0.10±0.04	3.98±0.01	106.3±4.1
P-X NG/TEGDMA	10	101.2±3.1	2.21±0.04	/	/
	25	101.4±5.0	1.91±0.05	/	/
	35	90±8.2	1.92±0.01	/	/
	50	58.6±2.1	1.16±0.02	69.9±1.5	12.6±3.3
	75	25.0±3.1	0.64±0.03	30.5±2.5	17.0±3.3
	90	5.0±0.5	0.11±0.01	11.8±1.2	52.7±5.1
	100	1.1±0.2	0.11±0.01	2.35±0.2	55.2±7.5