UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

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MODIFICAÇÃO DA INTERFACE DE UNIÃO ENTRE PARTÍCULAS DE CARGA E MATRIZ RESINOSA DE COMPÓSITOS RESTAURADORES

MODIFICATION OF FILLER PARTICLE AND RESIN MATRIX INTERFACIAL DESIGN OF RESTORATIVE COMPOSITES

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Tese apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Doutora em Materiais Dentários.

Thesis presented to the Piracicaba Dental School of the University of Campinas as partial fulfillment of the requirements for the degree of Doctor in Dental Materials.

Orientador: Prof. Dr. Marcelo Giannini

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RESUMO

O objetivo deste estudo foi desenvolver uma nova interface entre partículas de carga e matriz resinosa de compósitos resinosos. Nanogéis foram sintetizados e reagidos na superfície das partículas de carga em combinação com agentes silanos alternativos, com a finalidade de utilizar essa interface não apenas como sítio de ligação entre as fases inorgânica e orgânica, mas como um mecanismo de redução das tensões desenvolvida durante a reação de polimerização. Inicialmente, nanogéis com funcionalidades isocianato-metacrilato foram adicionados à superfície das partículas via ligações de ureia associados a silanos a base de amina. Em uma segunda abordagem, nanogéis com funcionalidades tiol foram reagidos com partículas tratadas com um silano vinil via reação tiol-ene. Partículas tratadas com silano convencional γ-metacrilioxipropiltrimetoxi foram utilizadas como controle. Os procedimentos de silanização foram realizados por deposição hidrolítica. Os nanogéis foram caracterizados por cromatografia de permeação em gel (GPC) e análise mecânica dinâmica (DMA). A proporção de 1:3 em peso de partícula:nanogel foi utilizada nas reações. Os tratamentos de superfície foram avaliados por análise termogravimétrica (TGA) e espectroscopia de refletância difusa (DR-IR). Compósitos foram formulados com uma blenda de BisGMA/TEGDMA com adição de 60% em peso de partículas silanizadas ou modificadas por nanogel. Os materiais foram avaliados quanto à cinética de polimerização, tensão de polimerização (PS), contração volumétrica, propriedades mecânicas e reologia. Análise estatística foi realizada pelos testes ANOVA e Tukey a nível de significância de 5%. Os tratamentos de superfície foram confirmados por TGA e DR-IR. As partículas modificadas por nanogéis foram capazes de reduzir significativamente a PS, para ambas estratégias de interface, sem comprometer o grau de conversão e módulo de elasticidade. Um desenvolvimento similar do módulo foi observado para os diferentes grupos nas análises de reologia concomitantemente com a polimerização. O mesmo efeito não foi observado quando quantidades semelhantes de nanogéis foram adicionados livres na matriz resinosa, no qual foi necessário 15% em peso de nanogéis para promover uma redução da PS na mesma magnitude. Para tanto, também foram

avaliados os efeitos da adição de nanogel livre na matriz resinosa, combinados ou não com partículas modificadas por nanogel. Quando ambas as estratégias foram associadas, houve uma redução de 50% da PS. As taxas de polimerização e contração volumétrica foram significativamente reduzidas para esses sistemas com aditivos de nanogel livre na resina. Notavelmente, o módulo de elasticidade nesses sistemas não foi comprometido. Já para a resistência à flexão, observou-se redução significativa para grupos de silanos amina, no entanto, não houve diferença significativa do grupo controle quando os nanogéis de isocianato-metacrilato foram adicionados. Em contrapartida, uma redução significativa na resistência à flexão associada à interface modificada com nanogel de tiol foi observada. Dessa forma, conclui-se que modificação da interface entre partícula de carga e matriz resinosa com nanogéis apresenta um potencial de redução da tensão de polimerização, sem comprometer o módulo de elasticidade. Essa estratégia pode ser combinada com quantidades relativamente baixas de aditivos de nanogel livres na fase de resina, reduzindo assim drasticamente a PS de compósitos.

Palavras-chave: Resinas compostas. Metacrilatos. Silanos. Polimerização. Estresse mecânico.

ABSTRACT

The objective of this study was to develop a novel filler particle and resin matrix interfacial design in resin composites. Polymeric nanogels were synthesized and attached to the filler surface in combination with alternative silane coupling agents, in order to use this interphase not only as a linkage between inorganic and organic components but also as a source of compliance to minimize stress development during polymerization. At first, isocyanate-methacrylate functional nanogels were end-threated to the fillers surface via urea linkages using amine functional silanes. In a different approach, nanogels with thiol functionalities were reacted to vinyl silane treated fillers via free-radical thiol-ene 'click' reaction. Fillers treated with the conventional γ-methacryloxypropyl-trimethoxy silane were used as control. Silanization procedures were carried out through hydrolytic deposition. Polymeric nanogels were characterized by triple-detector gel permeation chromatography (GPC) and dynamic mechanical analysis (DMA). Nanogels were reacted to the silanated surfaces in a 1:3 weight ratio of fillers to nanogels. Filler surface treatments were assessed by thermogravimetric analysis (TGA) and diffuse reflectance spectroscopy (DR-IR). Composites were formulated with a BisGMA/TEGDMA resin blend with 60 wt% loading of silanated or nanogel-functionalized fillers. Materials were evaluated for polymerization kinetics, polymerization stress (PS), volumetric shrinkage, mechanical properties, and photorheology. The statistical analyses were performed using ANOVA and Tukey's test at 5% significance. Filler surface treatments were confirmed by TGA and DR-IR. Nanogel-functionalized fillers were able to significantly reduce the PS for both interfaces' strategies, without compromising the degree of conversion and elastic modulus. Similar storage modulus development during polymerization was observed among materials in photorheology evaluation. The same effect was not observed when similar amounts of free nanogels were added to the resin, in which 15 wt% was required to generate the same magnitude of PS reduction. Moreover, the effects of free nanogel addition to the resin matrix, combined or not with nanogel-modified fillers were evaluated. When both strategies were associated, the PS was reduced in 50% magnitude. Polymerization rate and volumetric shrinkage were

significantly reduced for systems with free nanogel additives into the resin. Notably, the elastic modulus of the materials was not compromised. However, for flexural strength a significant reduction was observed for amino functional silane groups, yet it did not differ statistically from control group when combined with isocyanate-methacrylate nanogels. In contrast, a significant reduction in flexural strength for the thiol nanogel-modified interface was observed. In this way, it is concluded that filler surface treatment modified with a reactive nanogels enables the potential for reduction of polymerization stress, without compromising the elastic modulus. This strategy can be combined with modest amounts of free nanogel additives in the resin phase dramatically reduce overall PS of composites.

Key words: Composite resins. Methacrylates. Silanes. Polymerization. Mechanical stress.

SUMÁRIO

1 INTRODUÇÃO

Os compósitos resinosos são os materiais restauradores mais utilizados na Odontologia devido à sua capacidade de adesão às estruturas dentais quando associados aos sistemas adesivos, propriedades mecânicas suficientes para suportar as cargas oclusais, características estéticas satisfatórias e baixa toxicidade em meio oral. Além disso, podem ser aplicados através de técnicas diretas à estrutura dental com preparos minimamente invasivos (Anusavice et al. 2013; Opdam et al. 2014). Apesar destas inúmeras vantagens, a longevidade dessas restaurações é em média 10 anos, sendo que estudos clínicos apontam que as restaurações adesivas em dentes posteriores ainda apresentam longevidade significativamente menor em comparação às restaurações de amálgama (Moraschini et al. 2015; Rho et al. 2013). As principais causas de falhas das restaurações de resina composta são a formação de novas lesões de cárie nas margens da restauração e a fratura do material restaurador ou estrutura dental. O desenvolvimento de lesões de cárie nas margens de uma restauração tem influência primária do risco de cárie do indivíduo (Opdam et al. 2014), porém fatores intrínsecos ao material podem ter efeitos deletérios que contribuem para essas falhas (Demarco et al. 2012).

A composição básica das resinas compostas é uma matriz orgânica com diferentes combinações de monômeros, reforçada pela dispersão de partículas de carga inorgânicas ligadas à matriz através de agentes de união à base de silano, além de iniciadores responsáveis por desencadear a reação de polimerização (Anusavice et al. 2013). Quando ativados por uma fonte de luz com comprimento de onda específico, o sistema de iniciadores gera radicais livres capazes de quebrar as ligações duplas de carbono dos monômeros metacrilatos, que por sua vez reagem entre si (Rueggeberg 2011). Durante esse processo, os monômeros se aproximam para estabelecer ligações covalentes e formar uma rede polimérica de ligações cruzadas. A distância entre as duas moléculas é reduzida levando à diminuição no volume livre, o que resulta na contração volumétrica do material (Carvalho et al. 1996). Nessa transição da fase de monômeros livres para uma rede polimérica de mobilidade altamente restrita, concomitante à contração volumétrica e ao confinamento devido à

adesão do material aos substratos dentais, tensões são geradas e transferidas para a interface do material (Braga et al., 2005). Além disso, o comportamento viscoelástico do material, caracterizado por sua capacidade de escoamento nos estágios iniciais da reação de polimerização, também é um fator importante no desenvolvimento dessa tensão (Stansbury 2012). Dessa forma, a magnitude da tensão de polimerização vai depender do grau de contração volumétrica juntamente com a evolução do módulo de elasticidade do polímero em formação, nos quais a contração é determinada pela concentração inicial de grupamentos reativos e grau de conversão dos monômeros, enquanto o módulo é uma função da densidade da rede polimérica e o aumento da temperatura de transição vítrea durante a reação (Braga et al. 2005; Calheiros et al. 2004; Stansbury 2012)

A tensão de polimerização pode causar danos na interface entre a restauração e o substrato dental, levando ao desenvolvimento de defeitos e fendas marginais. Clinicamente, isso pode gerar sensibilidade pós-operatória, pigmentação e infiltração bacteriana nas margens da restauração (Ferracane and Hilton 2016; Ferracane and Mitchem 2003). Estudos prévios demonstraram que há uma correlação positiva entre a magnitude da tensão e a extensão da fenda formada, assim como para infiltração marginal e redução da resistência de união (Boaro et al. 2014; Fronza et al. 2015). Além disso, a tensão pode induzir deflexão de cúspides e provocar trincas na estrutura dental (Braga et al. 2012; Rosatto et al. 2015). Esses efeitos deletérios favorecem tanto o desenvolvimento de lesões de cárie nas margens da restauração, bem como a redução das propriedades mecânicas do conjunto dente-restauração (Ferracane 2013; Ferracane and Hilton 2016).

Muitas pesquisas têm focado em desenvolvimento de materiais e estratégias clínicas para minimizar os efeitos negativos associados à tensão de polimerização. Inicialmente, os avanços se concentraram na modificação do sistema de partículas de carga (Chen 2010; Ferracane 2011). A carga inorgânica é adicionada com o propósito principal de aumentar a resistência mecânica e ao desgaste do material (Lawson and Burgess 2015; Manhart et al. 2000). Além disso, com o aumento do conteúdo de carga é possível reduzir a quantidade de matriz resinosa e a concentração de grupamentos reativos,

diminuindo assim o potencial de contração volumétrica. Por outro lado, isso leva a um aumento do módulo de elasticidade do material como um todo, o que diminui sua capacidade de deformação e alivio de tensões (Shah and Stansbury 2014).

Recentemente, a maioria dos estudos têm proposto modificações na matriz orgânica. Estratégias foram desenvolvidas para reduzir o potencial de contração, seja através de monômeros com maior peso molecular, coeficientes de contração molar inferior, ou adição de aditivos pré-polimerizados (i.e., oligômeros, nanogéis) (Bacchi et al. 2016; Fugolin and Pfeifer 2017). Outras pesquisas focam na alteração da cinética da reação, em que taxas de polimerização mais lentas podem fornecer períodos prolongados no estágio em que o material ainda é capaz de se deformar e ceder às forças de contração antes de atingir um alto módulo de elasticidade, ou seja, retardar o ponto de geleificação e vitrificação do polímero. Alterações da taxa de reação foram propostas utilizando agentes de transferência de cadeias, ou através de ligações com capacidade de fragmentação e adição incorporada na cadeia de monômeros dimetacrilatos (Bacchi et al. 2016; Pfeifer et al. 2011; Shah et al. 2017). Esses métodos têm o potencial de diminuir significativamente a tensão de polimerização. Entretanto, há uma complexidade em reduzir a tensão sem comprometer as propriedades viscoelásticas e mecânicas do material, visto que um alto grau de conversão da matriz por consequência aumenta a contração volumétrica e o módulo elástico simultaneamente. Dessa forma, muitos materiais disponíveis comercialmente que possuem uma menor tensão de polimerização, apresentam propriedades mecânicas inferiores (Leprince et al. 2014)

Considerando a composição das resinas compostas, o agente de união é o componente menos explorado quando novas formulações são propostas. Embora essa interface seja a menos abundante do material, ela pode ter efeitos significativos sobre as suas propriedades (Sideridou and Karabela 2009). A superfície das partículas de carga é tratada com um agente bifuncional, usualmente o γ-metacrilioxipropiltrimetoxi (MPS) silano. Essa molécula reage com os grupos silanol presentes nas partículas de carga por meio dos seus próprios grupos silanol, formados a partir da hidrolização dos grupamentos

metóxi presentes em sua estrutura, formando assim ligações siloxano. Em sua outra extremidade, essa molécula apresenta um grupamento metacrilato que se une à matriz resinosa através da copolimerização das duplas ligações carbônicas. Dessa forma são estabelecidas ligações covalentes entre as duas fases do material: orgânica e inorgânica (Anusavice et al. 2013). Essa união é fundamental para a resistência mecânica e ao desgaste do material, para proteger as partículas de carga de deslocamento, diminuir o processo de degradação hidrolítica, além de melhorar a distribuição de tensões da fase menos rígida de matriz orgânica para as partículas de carga inorgânica mais rígidas (Chen 2010; Karabela and Sideridou 2008; Lim et al. 2002; Yoshida et al. 2002).

Entretanto, o MPS pode formar uma interface com múltiplas camadas, através da formação de pontes de hidrogênio entre os grupos silanol ou entre os grupos silanol e a carbonila presente no silano, dependendo da orientação dessas moléculas na superfície da partícula. Desse modo, os grupamentos metacrilatos podem ficar inacessíveis e relativamente imobilizados, sendo incapazes de promover uma união eficiente (Soderholm and Shang 1993). Além disso, a polimerização próxima à superfície das partículas impõe restrições de conformação nas cadeias poliméricas durante a reação, o que resulta em acúmulo de tensões internas no compósito. Quando altas porcentagens de carga são utilizadas, a maior área de superfície das partículas disponível restringe ainda mais o movimento dos monômeros nessas áreas (Halvorson et al. 2003).

Dessa forma, além da utilização de agentes silanos alternativos para melhorar a estabilidade de ligações nessa superfície (Yoshida et al. 2002), alguns estudos propuseram a adição de pré-polímeros nessa região de interface, com o intuito de estender a reação para mais distante da superfície das partículas. Um estudo demonstrou, por meio da funcionalização das partículas de carga com oligômeros, que essa camada interfacial de pré-polímeros é capaz de minimizar o desenvolvimento de tensões em compósitos restauradores (Shah 2012). Em outra estratégia, dendrímeros flexíveis ramificados foram utilizados como agentes de união alternativos de partículas de carga que, incorporadas à uma matriz resinosa modificada de tiol-γ-

metacrilato, reduziram a tensão de polimerização desse material (Ye et al. 2012). Da mesma forma, o uso de um silano modificado com tiouretanos também foi efetivo para diminuir significativamente a tensão de polimerização via mecanismo de transferência de cadeia disponível nessa interface (Faria et al. 2018).

Baseando-se nesse conceito, o uso da interface entre a partícula de carga e a matriz pode ser utilizado não apenas como sítio de ligação entre as duas fases, mas também como área de complacência para aliviar as tensões desenvolvidas durante a reação. Assim, um potencial de relaxamento pode ser projetado na região de interface que, cumulativamente, com base na grande quantidade de área superficial disponível em materiais com alto conteúdo de carga, oferece uma perspectiva para redução significativa da tensão de polimerização. Dessa forma, é possível conseguir uma acomodação da resina e das partículas simultaneamente à polimerização, fornecendo uma união mais estável entre as duas fases, sem comprometer as propriedades mecânicas do material.

No presente estudo, é proposta a modificação da interface de união entre partículas de carga e matriz resinosa de compósitos restauradores utilizando nanogéis associados à agentes silanos alternativos. Nanogéis são partículas poliméricas única ou multi-cadeias, ciclizados e ramificados internamente, tipicamente com tamanho na escala nanométrica. De acordo com sua formulação e processo de síntese, eles podem variar em termos de tamanho, características físicas (i.e., temperatura de transição vítrea, índice de refração, contribuição do módulo híbrido do nanogel para absorção de monômero) e funcionalização (Dailing et al. 2013). O design do nanogel influencia sua área superficial e a taxa de polimerização entre as fases de monômero da matriz e do nanogel, uma vez que eles podem ter sítios reativos para se ligar à matriz resinosa dos compósitos. Alguns estudos demonstraram que a adição de nanogéis reativos dispersos livremente na matriz de compósitos é capaz de reduzir a contração e a tensão de polimerização, sem comprometer as propriedades mecânicas do material (Liu et al. 2012; Moraes et al. 2011). No entanto, esse efeito é limitado uma vez que, em maiores volumes, a dispersão de nanogéis na resina pode aumentar a viscosidade significativamente e

comprometer a consistência do material (Moraes et al. 2011). Com isso, a utilização de nanogéis em quantidades mínimas para funcionalizar as partículas de carga pode ser uma alternativa viável. Além disso, a variação nas propriedades dos nanogéis pode ser utilizada para controlar a interação entre a carga e a matriz, bem como as propriedades dessa interface de maneira geral. O maior controle dessas variáveis, também torna mais fácil determinar o comportamento de transferências e alívio de tensão no material.

Portanto, o objetivo do presente estudo foi desenvolver alternativas para o tratamento de superfície de partículas de carga, e criar uma nova interface de união entre partículas de carga e matriz resinosa, com a finalidade principal de reduzir o desenvolvimento de tensões durante o processo de polimerização de compósitos restauradores utilizados na Odontologia. As partículas modificadas foram aplicadas também em associação à adição de nanogéis dispersos livremente na matriz resinosa, e as propriedades físico-químicas dos compósitos experimentais foram avaliadas.

2 ARTIGOS

2.1 Artigo: Modification of filler surface treatment of composite resins using alternative silanes and reactive nanogels

Artigo submetido ao periódico Dental Materials
*Material suplementar na seção Apêndices

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Abstract

This study probes how modified approaches for filler surface treatment in dental composites based on alternative silanes and functional nanogel additives affects physicochemical properties of these materials with a focus on polymerization stress development. Methods: Nanogels were synthesized from isobornyl methacrylate, ethoxylated bisphenol-A dimethacrylate and isocyanatoethyl methacrylate followed by partial further reaction with 2-hydroxyethyl methacrylate to provide both isocyanate and methacrylate functionalization. A barium glass filler (~1 μm particle size) was treated with either γ-methacryloxypropyltrimethoxysilane (MPS), N-methylaminopropyltrimethoxy (MAP) or N-allylaminopropyltrimethoxy (AAP) silanes. The reactive nanogels were then covalently attached to the aminosilane treated fillers via urea linkages. Surface treatment was characterized by thermogravimetric analysis (TGA) and diffuse reflectance infrared spectroscopy (DR-IR). Composites were formulated with 60wt% of the various functionalized fillers and the materials were evaluated for polymerization kinetics, polymerization stress (PS), volumetric shrinkage, mechanical properties and photorheology. Data were evaluated by one-way ANOVA and Tukey's test at 5% significance level. Results: Filler surface treatments were confirmed by TGA and DR-IR analyses. Nanogel-functionalized fillers significantly reduced PS up to 20%, while the degree of conversion and elastic modulus were not compromised. Similar storage modulus development during polymerization was observed among materials by photorheology although the rate of polymerization was significantly increased for nanogel-based treatments. A significant decrease in flexural strength was observed for amino functional silane groups; however, there was no statistical difference in strength for the MPS control group compared with the nanogel-modified composites. Significance: Filler surface treatment modified with a reactive nanogel enables significant PS reduction, without compromise to degree of conversion or mechanical properties of dental composites.

Keywords: Composite resin, fillers, methacrylates, isocyanates, nanogels, surface treatment, silanization, polymerization, stress, mechanical properties.

Introduction

Composite resins have been used in dentistry as restorative materials for 50 years, with significant improvements over time. At the beginning, advances have focused on the filler systems to improve mechanical properties (Chen 2010; Ferracane 2011). More recently, the focus has turned to the resin matrix with particular attention to reduce polymerization shrinkage and stress, and to improve materials' resistance to degradation in the oral environment (Fugolin and Pfeifer 2017). The polymerization stress (PS) induces early gap formation at the resin-tooth bonded interface, which can cause post-operative sensitivity, facilitate staining and bacterial infiltration with the potential consequence of reduced clinical longevity (Ferracane and Hilton 2016; Fronza et al. 2015; Goncalves et al. 2012; Opdam et al. 2014). Furthermore, PS can cause cusp deflection and cracks on the tooth structure and the material, which along with degradation may lead to fracture of the restoration or tooth (Oliveira et al. 2018; Rosatto et al. 2015).

Among the research strategies devoted to overcome these issues and improve resin composites performance, very few studies have focused on the coupling between the organic resin and inorganic fillers. Fillers surface are commonly treated with γ-methacryloxypropyltrimethoxy silane (MPS) to provide a covalent linkage between both distinct phases. This link is fundamental to mechanical reinforcement and wear resistance, to slow the degradation process, and to promote stress transition from the flexible organic matrix to the stiffer inorganic fillers (Antonucci et al. 2005; Condon and Ferracane 1997; Sideridou and Karabela 2009). However, the MPS's methacrylate functional groups are relatively immobile at the filler surface, which places conformational restrictions to the resin matrix during polymerization resulting in a build-up of internal stresses. Likewise, this interface accumulates stress by itself as the fillers present the lowest compliance in a composite system (Condon and Ferracane 2002).

A previous study demonstrated the application of flexible hyperbranched oligomers to the fillers surface as an alternative coupling agent to lower PS of composites when incorporated to modified a thiol–yne–

methacrylate resin matrix (Ye et al. 2012). Likewise, the use of a thiourethane-modified silane was also beneficial to reduce the PS of composites via chain transfer mechanism (Faria et al. 2018). Based on this concept of using the resin-filler interface not only as a linkage, but also as a source of compliance to minimize stress development during polymerization, herein we contemplate the use of amine functional silanes associated with isocyanate-methacrylate nanogels as fillers surface treatment. The use of nanogels end-tethered to the silane provide an extension of the reactive methacrylate groups away from the surface to interact with the resin matrix. Moreover, nanogels features potential for PS reduction when used as additives in the resin (Liu et al. 2012; Moraes et al. 2011).

Therefore, the objectives of this study were to modify the filler surface treatment using alternative silanes and reactive nanogel additives as a means to alter the physicochemical properties of composites loaded with the experimentally treated fillers. The hypotheses tested were as follows: (1) nanogel-functionalized fillers will reduce the PS of composites and (2) there will be no adverse effect on mechanical properties of composites with nanogel-functionalized fillers in comparison to analog composites with conventional methacrylate silane filler treatment.

Materials and Methods

Nanogel syntheses

Nanogels were synthesized by a batch process from isobornyl methacrylate (IBMA; TCI America, Portland, OR, USA), ethoxylated bisphenol-A dimethacrylate (BisEMA; Esstech, Essington, PA, USA), and isocyanatoethyl methacrylate (IEM; TCI America) at 50:30:20 molar ratio. Azobisisobutyronitrile (AIBN; Sigma-Aldrich, St. Louis, MO, USA) at 1 mol% was used as thermal initiator. Free-radical polymerization was carried out in solution using 15-fold excess of methyl ethyl ketone solvent (MEK; Fisher Scientific, Waltham, MA, USA) at 80°C and a stirring rate of 200 rpm. Methacrylate conversion during synthesis was followed (based on C=C peak area at 1637 cm^{-1}) in mid-IR spectra (Nicolet 6700, Thermo Scientific, Waltham, MA, USA) until 60% conversion was

achieved. Nanogels were precipitated from the clear reaction mixture by dropwise addition into hexanes (15-fold excess; Fisher Scientific). Resulting precipitates were re-suspended in dichloromethane (BDH Chemicals, VWR Analytical, Radnor, PA, USA). In order to obtain reactive polymerizable nanogels, 2-hydroxyethylmethacrylate (HEMA; TCI America) was added to the solution to partially convert isocyanate groups to methacrylate, and reacted at room temperature for 12 hours with a trace amount of dibutyltin dilaurate (Sigma-Aldrich) as catalyst. The polymer precipitation method was repeated, and residual solvent was removed completely under vacuum until the nanogels were obtained as dry powders. At the end nanogels had both isocyanate and methacrylate functionalities (Figure 1).

Nanogels were characterized by triple detector (refractive index, viscosity, light scattering) gel permeation chromatography (GPC; Viscotek, Malvern Instruments, Malvern, UK) in tetrahydrofuran (MilliporeSigma, Burlington, MA, USA) using a series of four columns spanning molecular weights of $10^4 – 10^7$ with absolute Mw based on right/low angle light scattering detection calibrated with a 65 kDa poly(methyl methacrylate) standard.

Tg of nanogel (n = 2) was determined by dynamic mechanical analyzer (DMA; Perkin Elmer 8000, Perkin Elmer, Waltham, MA, USA) by sandwiching 10 mg of nanogel powders in a thin metallic pocket that was then subjected to single cantilever cyclic displacement of 50 m at 1 Hz. The nanogel was heated from 0 to 150 $^{\circ}$C with tan δ data collected in the second cycle of heating at 2°C/min in air.

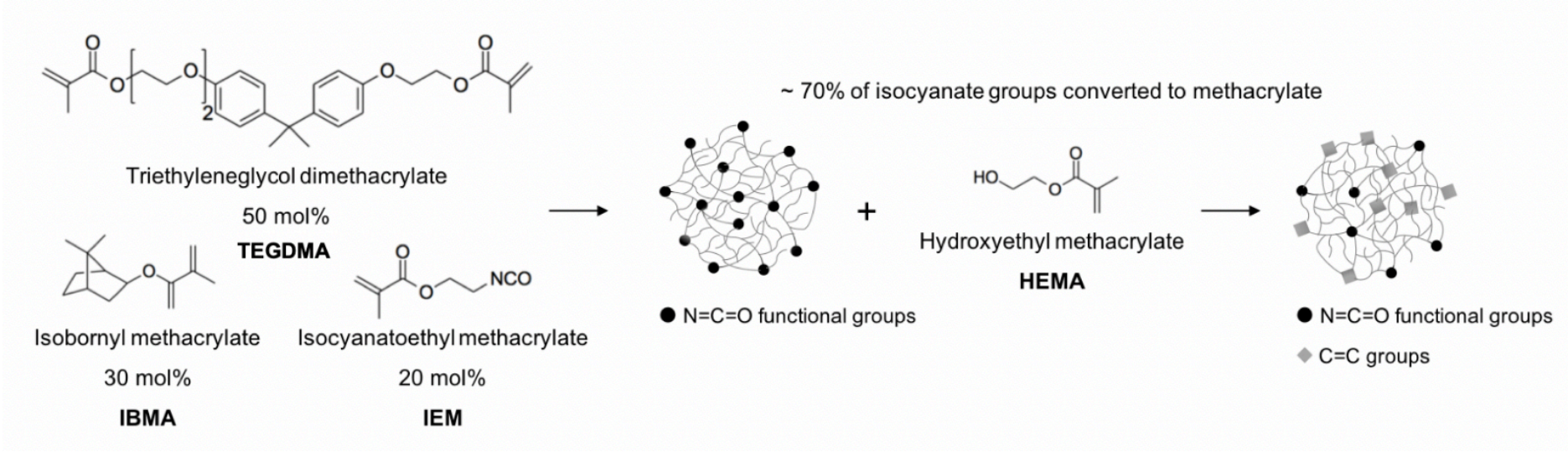

Figure 1. Structures of monomers used in the nanogel synthesis. At the first step internally crosslinked nanogels with chain-end isocyanate functionality is formed. This allows a route for reintroduction of functional methacrylate groups via the hydroxyl group from HEMA. The final nanogels obtained contain both isocyanate and methacrylate functionalities.

Fillers surface treatment

Barium glass filler (1 micrometer, Lot. 161130, Dentsply, York, PA, USA) were treated with three different silanes (Figure 2): the conventional methacrylate γ-methacryloxypropyltrimethoxy (MPS; Sigma-Aldrich), one amine η-methylaminopropyltrimethoxy (MAP; Gelest, Morrisville, PA, USA) and one amine silane containing also a pendant vinyl group η-allylaminopropyltrimethoxy (AAP; Gelest). Fillers were silanated with 5 wt% silane (relative to fillers) in cyclohexane (Sigma-Aldrich) using η-propylamine (Sigma-Aldrich) at 2% as catalyst. The mixture was stirred at room temperature for 30 minutes and then at 60±5°C for additional 30 minutes at atmospheric pressure and then placed in a rotary evaporator at 60°C for the removing of the solvent and the volatile by-products. The powder was then heated at 95±5°C for 1 hour on the rotary evaporator, and finally dried at 80°C in a vacuum oven for 23 hours. Solvent washing with acetone (Sigma-Aldrich) was performed to remove physically adsorbed silane.

Pendant methacrylate (MPS) or amine (MAP and AAP) groups at filler surface were reacted with nanogels. The secondary amino functional silanes (MAP and AAP) covalently connect with the isocyanate-functionalized nanogels forming substituted urea linkages. The reaction was confirmed by proton nuclear magnetic resonance spectroscopy (^{1}H NMR; detailed methodology described in the Appendix). Else, for the MPS control silane nanogels were added to the surface via methacrylate functional groups. The reactions were carried out using a filler to nanogel weight ratio of 1:3 in toluene at room temperature for 4 hours with a trace amount of dibutyltin dilaurate. Multi-step solvent washing of the treated fillers with acetone was performed to remove any unbound nanogel, and then followed by solvent removal during 24 h vacuum storage.

Filler surface treatments were identified by diffuse reflectance Fourier transform infrared spectroscopy (DR-IR; Nicolet 6700) spectroscopy. Spectroscopic grade KBr (Sigma-Aldrich) and fillers were grinded together and placed in the DR-IR accessory. Spectra were taken at 8 cm^{-1} resolution, 64 scans, from 4000 to 1350 cm^{-1} range, using KBr as background.

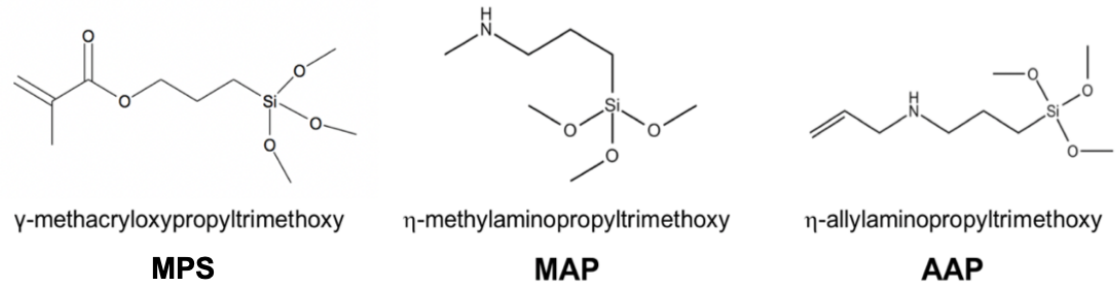

Figure 2. Chemical structures of the silane agents.

Thermogravimetric analysis (TGA; Pyris 7 TGA, Perkin Elmer) was used to determine the amount of silane and/or nanogel on surface of treated fillers. Samples (5±1 mg) were placed in platinum pans in nitrogen atmosphere flow of 20 ml/min and heated from 50 °C to 850 °C with a heating rate of 10 °C min^{-1}. The mass loss, which corresponds to the organic phase lost, as a function of temperature was recorded.

Resin and composites formulation

A resin blend with bisphenylglycidyl dimethacrylate (BisGMA; Sigma-Aldrich) and triethylene glycol dimethacrylate (TEGDMA; Sigma-Aldrich) at 70:30 molar ratio was formulated. The photoinitiator system consisted of camphorquinone (0.3 wt%; Sigma-Aldrich) associated with a tertiary amine ethyl-4-dimethylaminobenzoate (0.8 wt%; Sigma-Aldrich). Composites were formulated at 60 wt% loading of silanated or nanogel-functionalized fillers, which were incorporated to the resins with the aid of a mechanical mixer (DAC 150 Speed Mixer, Flacktek, Landrum, SC, USA) for 5 minutes at 2000 rpm.

Resin and composites testing

Polymerization kinetics was monitored in by Fourier transform near-infrared spectroscopy (FT-NIR, Nicolet 6700) in specimens (n = 3) of 6 mm in diameter and 0.8 mm thick laminated between two glass slides. The area of the methacrylate vinyl absorbance peak centered at 6165 cm^{-1} (Stansbury and Dickens 2001) was used to follow the real-time polymerization reaction continuously for 10 minutes. Specimens were photoactivated for 20 s at an

incident irradiance of 1470 mW/cm^2 at 430-480 nm wavelength (Elipar DeepCure-S LED, 3M ESPE, St. Paul, MN, USA). Measurements were taken at a wavenumber resolution of 4 cm^{-1} with 32 scans per spectrum acquired for static scans before and after polymerization to measure degree of conversion (DC) and 2 scans per spectrum for polymerization kinetics, which provides 2 Hz acquisition rate. Polymerization rate (PR_{max}) was calculated as the first derivate of the conversion vs. time curve.

PS (n = 5) was evaluated with a tensometer (Paffenbarger Research Center, American Dental Association, Chicago, IL, USA) using 6 mm diameter glass rods. Rods were sectioned into lengths of 28 and 5 mm, in which one surface of the 28-mm long rods was polished with a sequence of silicon carbide abrasive papers and felt disks in order to optimize the transmission through the rod end into the specimen during light-activation. The opposite surfaces of the 28- and 5-mm rods were polished with abrasive papers to create a rough surface, followed by silane application. The 28 mm rod were attached to the lower clamp of the tensometer and the 5 mm rods to the upper clamp. Each material was placed between the rods with a Centrix syringe at 1 mm thickness. The tip of the light-curing unit was positioned in contact with the polished lower rod. Force development was monitored for 10 minutes from the beginning of photoactivation (20 s), and the maximum nominal stress (MPa) was calculated by dividing the maximum force value recorded by the cross-sectional area of the rods.

Volumetric shrinkage (n = 5) was evaluated with a non-contact linear variable differential transducer-based linometer (Academic Center for Dentistry, Amsterdam, ND). Composites were placed onto an aluminum disc in linometer and covered with a glass slide, which was adjusted to produce a specimen disc of approximately 1 mm thickness × 6 mm diameter. All specimens were light-activated for 20 s. The displacement caused by linear shrinkage during polymerization was measured and converted to the corresponding volumetric shrinkage. The dynamic shrinkage data was recorded during and extending beyond the irradiation interval for a total period of 10 minutes.

A rheometer (ARES, TA Instruments, New Castle, DE, USA) was used to assess the photorheology of the composites (n = 2). Materials were

placed between two 20 mm parallel quartz disc plates and tested in shear at a frequency of 100 rad/s with 10% strain (ensuring linear viscoelastic regime), while being photopolymerized at 50 mW/cm^2. An optical apparatus (Pfeifer et al. 2011) allowed both curing light and FT-NIR direct transmission access to the specimen within the photorheometer, in this way degree of conversion was followed concomitantly with storage modulus development.

Flexural strength and elastic modulus (n = 5) were determined by the three-point bending test. Bar specimens (n = 5) were fabricated (2 mm x 2 mm x 25 mm) between glass slides and polymerized with three overlapping 20 s light exposures each sides glass side, according to ISO 4049 (Iso 4049. Dentistry - polymer-based restorative materials 2009). Specimens were stored dry for 24 hours in dark containers at room temperature. The three-point bending test was performed on the MTS testing machine using a span of 20 mm and a cross-head speed of 1 mm/min (MTS Mini Bionix II, MTS, Eden Prairie, MN, USA). The flexural strength (FS) in MPa was then calculated as:

$$FS(\sigma) = \frac{3F\iota}{2bh^2}$$

where F stands for load at fracture (N), ι is the span length (20 mm), and b and h are the width and thickness of the specimens in mm, respectively.

The elastic modulus (E) was determined from the slope of the initial linear part of stress–strain curve.

$$E = \frac{F\iota^3}{4bh^3d}$$

where F is the load at some point on the linear region of the stress–strain curve, d the slack compensated deflection at load F, and ι, b, and h are as defined above.

Statistical analysis

Normal distribution was assessed by Shapiro-Wilk test and Brown-Forsythe's method was used to analyze the presence of equal variance. Data from degree of conversion, $PR_{max,}$ PS, volumetric shrinkage, elastic modulus, and flexural strength were evaluated using One-way ANOVA tests (factor: composite, 6 levels). Where appropriate, Tukey post-hoc tests were applied in order to detect pair-wise mean differences among the groups. For all statistical testing, a pre-set, global significance level of 5% was used.

Results

GPC analysis (Table 1) demonstrates that nanogels presented moderate distributions of high-molecular-weight polymer with size of approximately 17±1 nm. The low Mark-Houwink exponent values indicated branched globular structures. DMA (Table 1) of nanogel powders revealed Tg values from 57 to 63 °C.

Table 1. Gel permeation chromatography parameters and glass transition temperature of nanogels.

	M_w (Kg/mol)	**PDI**	**Rh (nm)**	**MH-α**	**Tg (°C)**
Batch 1	484.51	1.48	9.08	0.49	57.3
Batch 2	428.81	2.01	8.24	0.23	63.3
Batch 3	400.83	1.99	8.18	0.40	57.9
Batch 4	426.92	1.76	8.45	0.46	57.1

Molecular weight (M_w), polydispersity index (PDI), hydrodynamic radius (Rh), Mark-Houwink exponent (MH-α), and glass transition temperature (Tg). Data represent single analyses.

Filler surface treatment was estimated by TGA as 0.8 to 1.3 wt% for silanes, and 2.8 to 4.7 wt% for nanogel-functionalized fillers (Figure 3A). The major weight loss associated with nanogel treatment starts around 250 °C, which confirms that nanogels are reacted to the surface. DR-IR (Figure 3B) shows free silanol groups (3742 cm^{-1}) for untreated fillers, which were consumed after

silanization. Methacrylate carbonyl peak at 1706 cm^{-1} (indicated by *) is present for MPS and all nanogel-functionalized fillers. Multiple aliphatic peaks (2856-2962 cm^{-1}) can also be observed for MPS and in a higher intensity for nanogel treatment.

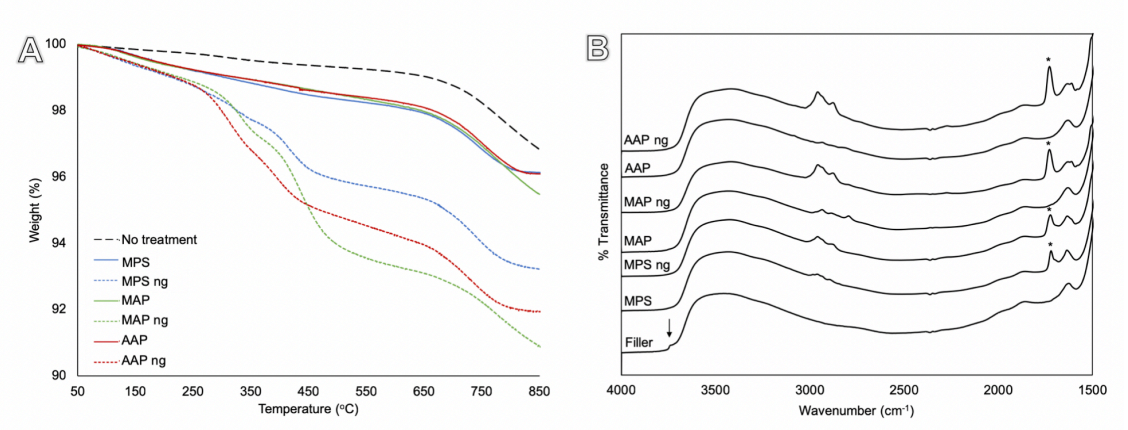

Figure 3. Thermogravimetric analysis displays weight loss of fillers as function of temperature increase. Ffiller surface treatment is estimated as 0.8 to 1.3 wt% for silanes and 2.8 to 4.7 wt% for nanogel additives (A). Diffuse reflectance spectroscopy spectra filler surface treatments. The non-treated fillers show the free silanol groups (3742 cm^{-1} peak indicated by arrow). The methacrylate carbonyl peak at 1706 cm^{-1} (indicated by *) is identified for MPS, MPS ng, MAP ng, and AAP ng. Multiple aliphatic peaks (2856-2962 cm^{-1}) can also be observed in higher intensity for nanogel treatments.

Properties results of composites are presented in Table 2. After 10 minutes polymerization kinetics evaluation (Figure 4A), there was no statistically significant differences among groups for degree of conversion. Although, the rate of polymerization (Figure 4B) was significantly higher for nanogel-functionalized fillers in comparison with its respective control silanes. Nanogel-functionalized fillers were able to significantly reduce the PS, with the lowest values found for MPS and MAP associated with nanogels (Figure 3C). However, the filler surface treatment did not affect the volumetric shrinkage (Table 2, Figure 3D).

Table 2. Mean (standard deviation) for degree of conversion (DC), maximum polymerization rate (PR_{max}), volumetric shrinkage (VS), polymerization stress (PS), elastic modulus (EM) and flexural strength (FS) of composites.

	DC (%)	PR_{max} (%/s)	VS (%)	PS (MPa)	FS (MPa)	EM (GPa)
One-way ANOVA	p = 0.226	p < 0.001	p = 0.829	p < 0.001	p < 0.001	p = 0.430
MPS	65.5 (1.1)	11.0 (0.4) bc	4.1 (0.1)	2.3 (0.1) b	140.3 (18.3) a	6.0 (0.5)
MPS ng	64.1 (0.6)	13.1 (0.3) a	4.1 (0.1)	1.7 (0.1) d	132.5 (14.2) a	6.0 (0.8)
MAP	65.1 (0.5)	9.5 (0.3) d	4.1 (0.1)	2.6 (0.07) a	82.8 (6.9) c	5.8 (0.8)
MAP ng	65.3 (0.3)	11.6 (0.5) bc	4.1 (0.2)	1.7 (0.1) d	127.2 (13.2) ab	6.2 (0.2)
AAP	65.2 (0.2)	10.7 (0.2) cd	4.0 (0.3)	2.5 (0.1) ab	107.9 (2.4) b	6.7 (0.7)
AAP ng	64.0 (1.6)	12.4 (1.0) ab	4.1 (0.1)	2.0 (0.1) c	122.1 (10.6) ab	6.0 (0.8)

Within a column, means followed by the same letter are not statistically different (p > 0.05).

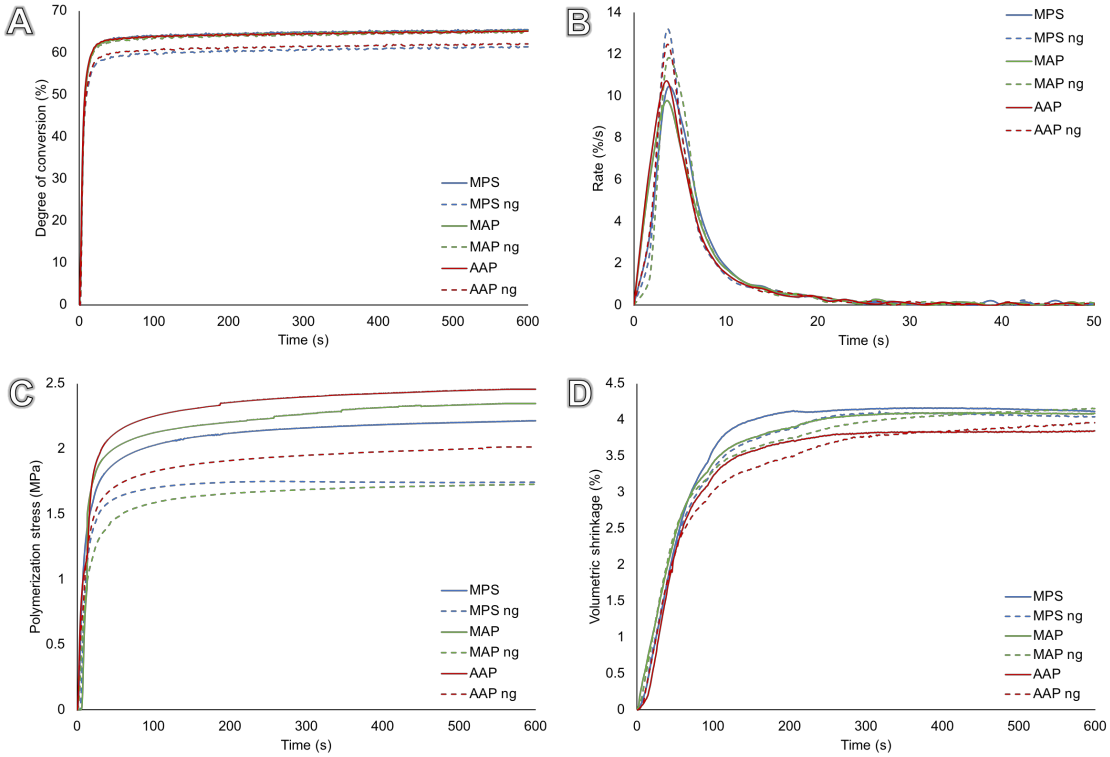

Figure 4. Degree of conversion (A) and rate of polymerization (B), polymerization stress development (C), and volumetric shrinkage (D) as function of reaction time for composites with different surface filler treatments. Notably, there is a reduction in polymerization stress for groups with nanogel-functionalized fillers.

Regarding the mechanical properties, flexural strength of MPS silane and all treatments with nanogel additives provided significantly higher values, while the amino functional silane MAP presented the lowest. Nonetheless, the filler surface treatment did not affect the elastic modulus of the materials. Herewith, real-time photorheology demonstrates similar modulus evolution along with degree of conversion and polymerization reaction progression to all experimental composites (Figures 5A and B).

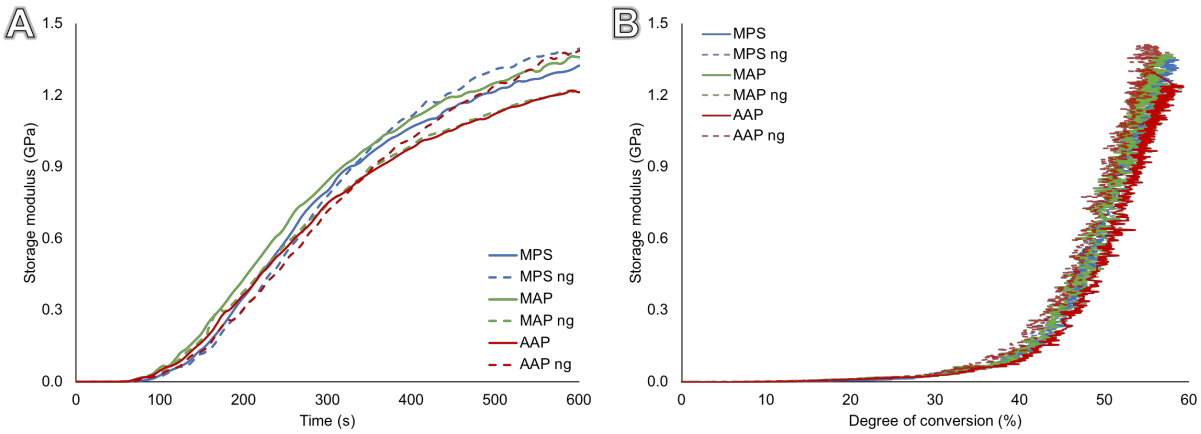

Figure 5. Photorheomether analysis demonstrates the storage modulus development as the reaction progresses (A), as well as storage modulus along with conversion acquirement (B). Note that the elastic modulus development and final values are similar to all materials, independent of filler surface treat

Discussion

The coupling agent between resin matrix and fillers represents the minor portion of the overall composite formulation; however, it serves an essential role in achieving the robust mechanical performance that is demanded of dental composite restoratives. Here, the modification of the resin-filler interface with amino-functional silanes allowed the controlled introduction of a single layer interphase since the nanogels offer no interparticle interactions. This nanogel-derived surface layer contributes negligible dimension to the overall filler particle size yet, this approach significantly reduced PS, without compromise to the mechanical properties of the composites. Therefore, the hypotheses of the study were accepted.

Nanogel functionalized fillers were able to significantly reduce the PS compared to the controls with silane treatment only (Table 2; Figure 4C). The PS development and its magnitude are dependent on volumetric shrinkage along with evolution of elastic modulus, with both properties reliant on the degree of conversion (Braga et al. 2005; Stansbury 2012). Notably, there was no significant decrease in volumetric shrinkage or elastic modulus for the experimental materials (Figure 4D; Table 2). Volumetric shrinkage is determined

by the initial concentration of reactive groups in the composite overall as well as the degree of conversion reached during polymerization. Since the ratio of resin to the inorganic component of the filler do not differ substantially among the groups here, the starting reactive group density is comparable. This along with the similar levels of limiting conversion achieved across the series of composites studied here, means a reduction in shrinkage is not expected. Also related to this, the equivalence of the elastic modulus results for all the materials indicates that the polymer network density and quality is not affected by the presence of the nanogel-modified filler surfaces (Table 2; Figure 5). It is worth noting that the Tg of the bulk nanogels offers a reasonably good match to the Tg obtained when the BisGMA/TEGDMA resin is photocured to its vitrification limiting conversion.

Because neither shrinkage nor modulus are altered for composites with the nanogelmodified filler, we consider that the introduction of a nanogel interphase provides a stress relaxation mechanism that operates during the course of photopolymerization (Figure 4C). Nanogels are synthesized in a solution polymerization process, which results in a swellable structure. Once dispersed in resin, the nanogel polymeric particles, are swollen by monomer (Liu et al. 2014), which presumably occurs whether the nanogels are freely dispersed in the resin phase or tethered to the filler surface. This means an effective volume fraction of the monomer-swollen nanogel rather than a simple calculated volume fraction should be considered, which may have contributed to the reduction in

stress. Additionally, the monomer swollen nanogels function as a transition phase between the resin and filler in terms of the local reaction rate as well as the evolving Tg and mechanical properties. These features along with the highly branched structure of the nanogels may allow compliant interfacial zone during polymerization that can internally absorb some of the developing stress. An important component of this is likely the physical displacement of the copolymerizable methacrylate groups in the nanogels away from the filler surface, which would enable a degree of compliant behavior.

Nanogels were synthesized from a mono-functional monomer (IBMA) and a di-functional crosslinker (BisEMA), with addition of IEM to introduce isocyanate functional groups (Figure 1). In order to avoid macrogelation and control nanogels size, a 15-fold excess of MEK solvent was used along with a

restriction of the reaction to 60 % conversion. Chain transfer agents, such as alkyl thiols, are commonly used to help control nanogel molecular weight and size (Moraes et al. 2011) however, thiols would be consumed by the isocyanate groups from IEM and thus, the chain transfer agent was avoided here. Despite of use of the higher dilution in the nanogel synthesis as compared with previous nanogel synthetic procedures, the molecular weights of the functional nanogels are approximately an order of magnitude greater than those that can be produced with a chain transfer agent under much more concentrated reaction conditions. The use of isocyanate nanogel functionality here was to produce substituted urea linkages through reaction with the secondary amine functional silanes on the filler surface, ultimately forming a polyurea-based interphase. Polyureas are widely used in materials science to produce soft elastomers, rigid thermosets, and foams (Chattopadhyay and Raju 2007). Urea linkages have been found to be more hydrolytically stable than the ester bonds found in methacrylate structures, which are readily hydrolyzed in either basic or acidic solutions. The hydrolysis process diminishes material properties over time and ultimately leads to mechanical failure (Ferracane 2006; Pegoretti et al. 1998; Podgorski et al. 2015). In this way, this alternative linkage has potential advantages for application at the critical filler-resin interface.

Notwithstanding, it is acknowledged that the pervasive use of methacrylate resins as the resin phase component of dental composites requires accommodation by coupling agent. Therefore, methacrylate groups were introduced into the nanogel structures via partial conversion of the pendant isocyanates through reaction with hydroxyl groups of HEMA. This provides the nanogels appropriate orthogonal functionality to covalently attach to the filler while presenting direct copolymerizabilty with the resin matrix to promote proper mechanical properties. However, even when these isocyanate/methacrylate functional nanogels were added to MPS silanated fillers, the mechanical properties obtained for the photocured composites indicate that suitable coupling was achieved between the filler and matrix phases (Table 2). For the filler surfaces treated with MPS or AAP that likely provide residual silane-based vinyl groups as well as to the methacrylate groups within the tethered nanogel layer, this offers an additional point of connection with the resin matrix to insure a

strong connection between the composite phases. This is highlighted by the good mechanical properties observed with the MPS and AAP silane-only surface treatments (Table 2), albeit without the benefit of reduced PS that is attributed to the tethered nanogels. The restoration of mechanical properties when the non-copolymerizable MAP surface treatment is modified by appending the reactive nanogel layer provides a good demonstration of the filler-bound nanogel interaction with resin while the good mechanical strength of the AAP-only filler surface treatment indicates effective copolymerization between the silane-based allyl groups and the methacrylate resin.

Furthermore, the final degree of conversion attained was also unaffected by silane type or nanogel-functionalized fillers (Table 2; Figure 4A). However, the presence of nanogels does provide a significant increase in the photopolymerization rate (Table 2; Figure 4B). Previous studies have demonstrated that the use of nanogel additives dispersed in a monomer matrix can enhance, reduce or leave polymerization rates unaltered (Liu et al. 2012; Moraes et al. 2011). As compared with neat monomer, the internal monomer-swollen nanogel domain presents a localized higher viscosity environment, particularly with the highly branched nanogels used here. Therefore, when polymerization is initiated, depending on the amount of nanogel added, varying proportions of monomer will be in this more mobility-restricted state and the overall auto-acceleration behavior would also vary accordingly (Liu et al. 2012; Moraes et al. 2012).

The viscoelastic behavior of the material characterized by its resistance to flow in the initial stages of the reaction, is also an important factor for stress development (Braga et al. 2005; Stansbury 2012). Despite the differences in polymerization rate, the rheology during polymerization was not affected, as demonstrated by storage modulus acquirement over time as well as in terms of degree of conversion (Figure 5). The effect of low amounts of nanogels in resin viscosity is minimal as is typically observed for globular hyperbranched or dendritic polymeric additives (Moraes et al. 2011). Likewise, no obvious differences in handling characteristics were noticed here for the experimental and control composites. Moreover, the final storage modulus

acquired corroborates with results from the three-point-bending test, in which no differences in final modulus were observed between groups (Table 2).

Herein we evaluated filler surface modification with 1 μm glass fillers only, while modern dental composites are multicomponent mixtures of fillers with a distributed range of sizes. Further studies should check the proposed surface treatment that include fumed silica or other nanoscale particles, which feature a greater surface area and offer features such as enhanced filler packing and wear resistance. As mentioned, approaches that provide surface-active nanogels of even smaller dimension (<10 nm) would also be of interest. The current combination of amino silanes with isocyanate nanogels may provide a more reliable stable interface between filler and resin matrix; however, longer-term studies regarding hydrolytic and mechanical stability of both the modified silane-based interfaces and the nanogel-based interphases need to be carried out.

Conclusion

Filler surface treatment modified with reactive nanogels enables the potential for a significant reduction in PS, without compromise to degree of conversion or physical/mechanical properties of photocurable dental composites. The production of this substantial stress reduction based on a relatively small nanogel content located exclusively at the filler surface, highlights the potential of this intentionally engineered resin-filler interphase region in heterogeneous composite materials.

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2.2 Artigo: Nanogel based filler-matrix interphase reduces polymerization stress of composites

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*Material suplementar na seção Apêndices

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Abstract

A novel filler-resin matrix interphase structure was developed and evaluated for dental composite restoratives. Nanogel additives were chemically attached to the filler surface in order to use this created interphase as a potential source of compliance to minimize stress development during polymerization. In addition, we evaluated the effects of free nanogel dispersion into the resin matrix, combined or not with nanogel-modified fillers. Nanogels with varied characteristics (i.e. size of 5 and 11 nm; glass transition temperature (Tg) from 28 to 65 ^{o}C) were synthesized. Glass fillers were treated with trimethoxyvinylsilane and further reacted with thiol-functionalized nanogels via a free-radical thiol-ene reaction. γ-Methacryloxypropyltrimethoxysilane-surface treated fillers were used as a control. Composites were formulated with BisGMA/TEGDMA resin blend with 60 wt% fillers using nanogel-modified fillers and/or free nanogel additives at 15 wt% in the resin phase. Polymerization kinetics, polymerization stress, volumetric shrinkage, rheological, and mechanical properties were evaluated to provide comprehensive characterization. Nanogel-modified fillers significantly reduced the polymerization stress from 2.2 MPa to 1.7 - 1.4 MPa, resulting in 20% stress reduction. A significantly greater nanogel content was required to generate the same magnitude stress reduction when the nanogels were only dispersed in the resin phase. When the nanogel-modified filler surface treatment and resin-dispersed nanogel strategies were combined, there was a stress reduction of 50% (values of 1.2 - 1.1 MPa). Polymerization rate and volumetric shrinkage were significantly reduced for systems with nanogel additives into the resin. Notably, the flexural modulus of the materials was not compromised although, a slight reduction in flexural strength associated with the nanogel-modified interphase was observed. Overall, modest amounts of free nanogel additives in the resin phase can be effectively combined with very limited nanogel content filler-resin interphase to lower volumetric shrinkage and dramatically reduce overall polymerization stress of composites.

Keywords: Polymers, methacrylates, silanes, light-curing of dental resins, polymerization, stress

Introduction

Polymerization stress (PS) in dental composites can damage the resin-tooth bonded interface, exhibiting a positive correlation with gap formation and leakage of restorations (Boaro et al. 2014; Fronza et al. 2015). It can also lead to cuspal deflection, tooth cracking, reduced bond strength, and lowered mechanical properties of the restorative (Braga et al. 2013; Nayif et al. 2008). During polymerization, the build-up of post-gel stress begins with the evolution of elastic modulus (EM) along with the degree to which the free shrinkage associated with polymerization is constrained by bonding to substrates (Braga et al. 2005). Free shrinkage is determined by initial reactive group density within the resin and the degree of conversion (DC) attained, while EM is a function of polymer network density and increasing glass transition temperature (Tg) as polymerization occurs (Stansbury 2012). Addition of fillers to the resin affects both parameters. Increased filler volume fraction accounts for a reduction in the overall resin reactive group concentration, which reduces bulk shrinkage; however, increased filler loading also produces a significant increase in EM that can counter the stress reduction of lower shrinkage (Shah and Stansbury 2014).

γ-methacryloxypropyltrimethoxysilane is commonly used to provide a covalent linkage between fillers and resin matrix, which increases bulk mechanical properties through transfer of stresses between the inorganic and organic phases (Wilson et al. 2007). This coupling at the filler surface places local conformational restrictions on the resin network during polymerization. Despite the reactive methacrylate functional groups from the silane being relatively immobile and buried, which leads to relatively inefficient coupling between two phases, the resin-filler interface contributes to the build-up of significant internal stresses in the composite during polymerization (Sideridou and Karabela 2009; Soderholm 1984).

Most advances to reduce PS focus on modification of the polymeric network. Step-growth thiol-Michael resins have demonstrated reduced PS compared to conventional methacrylates. Nevertheless, further investigations are needed to achieve optimal proportions of resin, fillers, and photobase initiators to suit clinical use (Huang et al. 2018). Addition–fragmentation chain

transfer capable linkages incorporated into dimethacrylate monomers also reduce stress. However, concentrations higher than 5 wt% of this compound lower significantly both polymerization kinetics and final conversion (Shah et al. 2017). Although advantages of chain-transfer reactions by use of thiols (Pfeifer et al. 2011) or methacrylate-thiol-ene systems (Boulden et al. 2011) are promising to lower PS, the use of small molecule thiols is usually related to reduced shelf life and unpleasant odor prior to polymerization. These drawbacks can be overcome by the use of thiols as oligomers, such as off-stoichiometric thiourethanes (Bacchi et al. 2016; Bacchi et al. 2018), nonetheless its effect to lower PS is concentration dependent, in which higher amounts increase resin viscosity, impairing addition of fillers and compromising handling characteristics. Recently, the use of a thiourethane modified silane was demonstrated to reduce PS of composites as well (Faria et al. 2018).

Another potential alternative to reduce shrinkage and PS is the use of reactive nanogels (Liu et al. 2012; Moraes et al. 2011). Nanogels are highly tailorable polymeric particles are very attractive for biomedical applications, such as drug delivery systems and tissue engineering (Jiang et al. 2014; Zhang et al. 2016). Nanogels are internally cyclized and branched polymers which can be varied in terms of size, physical characteristics (i.e. Tg, refractive index, and hybrid modulus contribution of a monomer-swollen nanogel), and chemical functionalities. The nanogel design as well as the variation in loading levels results in control over the interfacial surface area and polymerization rate between the matrix monomer and nanogel phases. Nanogel addition potentially provides enhanced polymerization rates with increased limiting conversion while significantly reducing both the rate and extent of PS (Dailing et al. 2013). Reactive nanogel addition to resin and composites has been demonstrated to reduce stress without compromise to mechanical properties. However, nanogel dispersion into resin can increase resin viscosity and composite paste consistency dramatically (Moraes et al. 2011).

To overcome these issues, herein we developed and propose a novel interphase structure between fillers and resin matrix based on minimal amounts of nanogel additives intentionally positioned at the filler surface, in order to use this interphase as a source of compliance to minimize stress development during

polymerization. This concept relies on small relaxation potential designed into the interphase region that offers the prospect for substantial bulk stress reduction based on the high overall interfacial surface area available in highly filled composite materials. In this way, the utility of the interface extends beyond just a connection between the phases.

Therefore, the objective of this study was to treat filler surfaces with systematically varied nanogels in order to reduce PS of restorative composites. In addition, we evaluated the effects of a modest content of free nanogel addition to the resin matrix, which can be combined with nanogel-modified fillers, in terms of material physical-chemical properties. The hypotheses tested were as follows: (1) nanogel-modified fillers will reduce PS of composites and (2) there will be no compromise to EM of composites relative to control materials.

Materials and Methods

Nanogel syntheses

Three nanogels with different sizes and Tg's were prepared (Table 1). Ng 1 and 2 were synthesized from isobornyl methacrylate (IBMA) and urethane dimethacrylate (UDMA) at 70:30 molar ratio. To avoid macrogelation and control nanogel molecular weight/particle size, Ng 1 used 15 mol% of a chain-transfer agent (2-mercaptoethanol; ME) and six-fold excess of solvent (methyl ethyl ketone; MEK), while Ng 2 used 5 mol% ME and four-fold excess of MEK. In order to provide a lower Tg, Ng 3 was synthesized with butyl methacrylate (BMA) replacing IBMA and using 15 mol% ME with a six-fold excess of MEK. Azobisisobutyronitrile (AIBN) at 1 mol% was used as thermal initiator. Free-radical polymerization was carried out in solution using a four or six-fold excess of methyl ethyl ketone solvent at 80 °C and a stirring rate of 200 rpm. Methacrylate conversion during nanogel synthesis was followed (based on C=C peak area at 1637 cm^{-1} relative to the C=O absorbance at 1720 cm^{-1}) in mid-IR spectra (Nicolet 6700, Thermo Scientific, USA). When the reaction reached 60% conversion, pentaerythritol tetra(3-mercaptopropionate) (PETMP; 10 mol%) was added to introduce pendant thiol functionalities in the nanogels as the reaction progressed until 85% conversion. Nanogels were precipitated from the clear

reaction mixture by dropwise addition into hexanes (10-fold excess). The residual solvent was removed and nanogels were obtained as powders.

Polymeric nanogels were characterized by triple-detector gel permeation chromatography (GPC), the Tg of nanogels was determined by dynamic mechanical analysis (DMA), and Ellman's reagent test was used for quantitating free sulfhydryl groups of nanogels. Detailed characterization methodologies are described in the Appendix.

Filler surface treatment

To introduce the thiol-functionalized nanogel to the surface of a bare barium glass filler (average diameter 1 μm (Dentsply Sirona), the filler was initially treated with trimethoxyvinylsilane (VIN). Separately, the control filler was prepared by analogous treatment with γ-methacryloxypropyltrimethoxysilane (MET). Silanization methods are described in the Appendix.

Pendant vinyl groups from VIN on the filler surface were reacted with nanogels via a free-radical thiol-ene 'click' reaction (Lowe 2010). The reaction was carried out using a filler to nanogel weight ratio of 1:3 in toluene at 70 °C and a stirring rate of 200 rpm with 1% AIBN as initiator. In a pilot study, reaction times of 24, 48 and 72 h were tested regarding the extent of nanogel attachment in coordination with composite property testing. Multi-step solvent washing of the treated fillers with acetone was performed to remove any unbound nanogel, which was then followed by solvent removal during 24 h vacuum storage.

Filler treatments were analyzed by diffuse reflectance Fourier transform infrared spectroscopy (DR-IR) spectroscopy, thermogravimetric analysis (TGA) and energy dispersive X-ray (EDX) spectrometry analysis, as described in the Appendix. Filler surface images were obtained by transmission electron microscopy (TEM; JEM 2100, JEOL, Japan).

Resin and composite formulation

A resin blend was formulated with bisphenol A glycidyl dimethacrylate (BisGMA; Esstech, USA) and triethylene glycol dimethacrylate (TEGDMA; Esstech) in 70:30 molar ratio. The visible light photoinitiator system consisted of camphorquinone (0.3 wt%; Sigma Aldrich) and ethyl 4-dimethylaminobenzoate

(0.8 wt%; Sigma Aldrich). Fillers were mechanically mixed into the resins (DAC 150 Speed Mixer, Flacktek, USA; 5 min at 2000 rpm). Besides the nanogelfunctionalized fillers, the different nanogels were also tested as free additives in the resin. In this way, four sets of materials were formulated and tested: resin systems containing 15 wt% of free nanogel additives; composites with 60 wt% MPS fillers and 15 wt% of nanogel additives; composites with 60 wt% VIN nanogel-functionalized fillers; and composites with 60 wt% VIN nanogel-functionalized fillers combined with 15 wt% of nanogel additives.

Resin and composites testing

Real-time polymerization kinetics was monitored by Fourier transform near-infrared spectroscopy (FT-NIR, Nicolet 6700). Specimens (n=3) were light-activated for 20 s at an incident irradiance of 1470 mW/cm^2 at 430-480 nm wavelength (Elipar DeepCure-S LED, 3M ESPE, USA). The area of the methacrylate vinyl absorbance band centered at 6165 cm^{-1} (Stansbury and Dickens 2001) was used to follow the polymerization reaction (FT-IR settings are presented in the Appendix). Measurements were taken before and after polymerization to assess DC and provide the dynamic polymerization kinetic data, which was collected for 10 minutes during and continuing after curing light exposure. Polymerization rate (R_{Pmax}) was calculated as the maximum in the first derivative of the conversion vs. time curve.

PS (n=5) was evaluated with a tensometer (Volpe Research Center, American Dental Association), as described in the Appendix. FT-NIR spectroscopy was simultaneously incorporated in direct transmission mode via fiber optic cables (1 mm diameter single fiber) to obtain the concomitant reaction kinetics profile correlated with stress evolution.

Volumetric shrinkage (VS; n=5) was evaluated with a non-contact linear variable differential transducer-based linometer (Academic Center for Dentistry Amsterdam, ND), as described in the Appendix.

Viscosity measurements of the nanogel resins blends (n=5) were performed using a cone-plate digital viscometer (CAP 2000, Brookfield, USA). Rheology of the composites (n=2) was assessed by photorheometry (ARES, TA Instruments, USA), while being photopolymerized at 50 mW/cm^2 (Mercury arc

lamp 460 nm, Acticure 4000, EXFO, USA) for 10 minutes. Detailed rheology testing is described in the Appendix.

The three-point bending test (Iso 4049. Dentistry - polymer-based restorative materials 2009) was used to determine the EM and flexural strength (FS) of the materials (n=5), as described in the Appendix.

Statistical analysis

Normal distribution and equal variance were assessed by Shapiro-Wilk and Brown-Forsythe's tests. Data from DC, $R_{Pmax,}$ PS, VS, EM, and FS were evaluated using One-way ANOVA for resin formulations (factor: material, 4 levels) and composites (factor: material, 10 levels). Tukey post-hoc tests were applied to detect pair-wise mean differences among groups. For all statistical testing, a pre-set global significance level of 5% was used.

Results

GPC analysis demonstrated similar molecular weight for Ng1 and Ng3, and a higher molecular weight for Ng2 with a consequently larger hydrodynamic radius as intended by the use of a reduced chain transfer agent concentration. According to DMA analysis, the nanogels presented different Tg's as expected based on the different monomers and reactant ratios selected. Elman's reagent test assessed slightly higher thiol content for Ng3 (Table 1) compared with the other nanogels.

Table 1. Gel permeation chromatography parameters, glass transition temperature and SH content from Elman's reagent test.

	Composition	M_n (Kg/mol)	PDI	Rh (nm)	Tg (°C)	SH (mMol/g)
Ng 1	IBMA/UDMA 70:30 15 mol% ME + 10 mol% PETMP	17.8	1.1	2.5	49	0.09
Ng 2	IBMA/UDMA 70:30 5 mol% ME + 10 mol% PETMP	182.3	5.4	5.8	65	0.08
Ng 3	BMA/UDMA 70:30 15 mol% ME + 10 mol% PETMP	19.3	1.4	2.6	28	0.13

Number average molecular weight (M_n), polydispersity index (PDI), hydrodynamic radius (Rh), glass transition temperature (Tg), and thiol content (SH) per gram of nanogel. Data represent single analyses.

Filler surface treatment was estimated by TGA as 1 wt% for silane, and an additional 3±1 wt% for nanogels (Figure 1A). The amount of nanogel covalently added to the filler surface was optimized by varying the reaction time in order to provide an appropriate nanogel content to modulate stress development with no decrease in EM (Appendix Figure 3). DR-IR (Figure 1B) showed he presence of methacrylate carbonyl peak (1706 cm^{-1}) and multiple aliphatic peaks (2856-2962 cm^{-1}) for nanogel surface treatments. EDX analysis identified C, O, Al, Si, and Ba in the composition of the silanated fillers. S correspondent to thiol functional groups was identified in the nanogel-modified fillers (Figure 2C, D; Appendix Table 1). Elemental mapping demonstrated a uniform surface distribution of S on the fillers (Figure 2E; Appendix Table 2 and Figure 4). Nanogel attachment to the filler surface was further confirmed with TEM images (Figure 2F), which indicates nanogels both isolated and in agglomerates on the filler surface (Figure 2G, H).

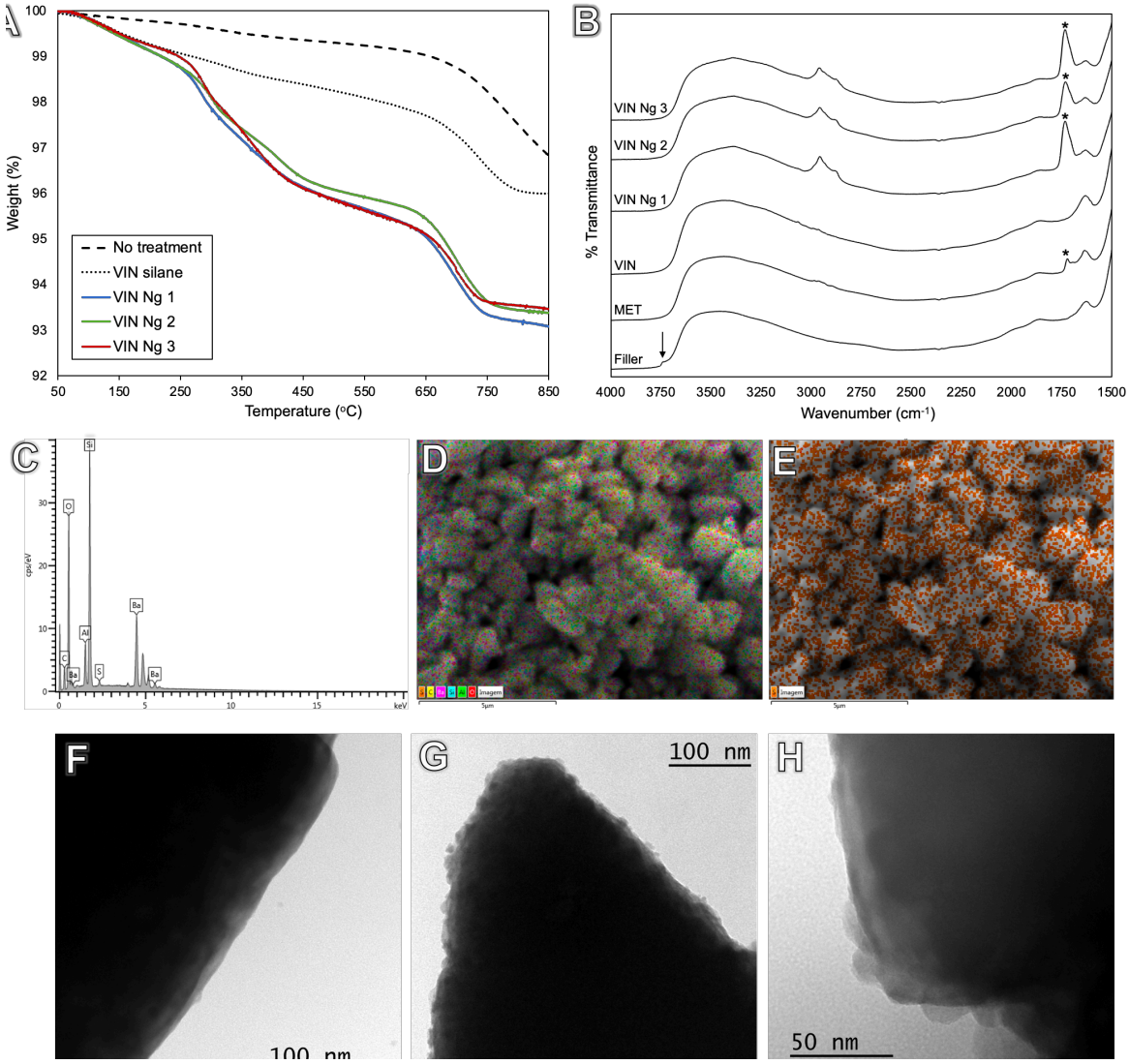

Figure 1. Thermogravimetric analysis displays filler surface coverage with silane (1 wt%) in relation to the non-treated filler, and nanogels added (3±1 wt%). The major weight loss associated with nanogel treatment starts around 250 °C, which along with the mass loss confirm that nanogels are reacted to the surface (A). Diffuse reflectance spectroscopy shows free silanol groups (3742 cm^{-1} indicated by arrow) for untreated glass fillers, which were consumed after silanization. Methacrylate carbonyl peak at 1706 cm^{-1} (indicated by *) is present for MPS silane and in a higher intensity for nanogel treatments. Multiple aliphatic peaks (2856-2962 cm^{-1}) can also be observed for nanogel treatments (B). Energy dispersive X-ray spectrometry analysis identified C, O, Al, Si, and Ba in silanated fillers composition (C,D). Elemental mapping demonstrates uniform distribution of S on the fillers surface, correspondent to thiol-functional groups on the

surface-bound nanogels (E). The filler surface can be observed in transmission electron microscopy image with no treatment (300K×, F) and with nanogel attachment found both isolated and in agglomerates (300K×, G), with size compatible to GPC characterization (VIN Ng 2 at 500K×, H).

Properties of the resin systems and composites are presented in Table 2. Resins without any glass filler but with 15 wt% free nanogel loading demonstrated significantly lower PS and VS, in which the smaller and lower Tg nanogels generated the greater PS reduction (Figure 2C,D). R_{Pmax} and DC were also significantly decreased for these systems (Figure 2A,B). Nonetheless, the slightly lower DC did not affect the mechanical properties as both EM (Figure 2E) but FS was found to be significantly higher for Ng 1 in comparison to the others. A significant increase in resin viscosity ($p < 0.001$) was found with nanogel addition, in which the nanogels of larger size and higher Tg had the more pronounced effect (Figure 2F).

When MPS-silanated fillers were associated with free nanogel loaded into the resin phase, the composites demonstrated a compressed range of PS reduction with all nanogels yielding significant lower PS and VS compared to the MPS control (Table 2). A control composite with filler treated with the VIN silane produced a PS value of 2.3±0.1 MPa, similar to the MPS control. As found in the resin systems, here the DC and R_{Pmax} were also significantly reduced, but with no consequences in mechanical properties. Afterward, VIN nanogel-based were able to significantly reduce PS in a magnitude similar to the free nanogel addition in composites (reduction of ~ 20 %), unlike the lack of significant decrease in VS. Furthermore, there was a significant reduction in DC but not for the R_{Pmax} compared to the control, with exception of VIN Ng3. The EM of nanogel-based filler composites was similar to control; however, the FS was significantly lower.

Table 2. Degree of conversion (DC), maximum polymerization rate (R_{Pmax}), polymerization stress (PS), volumetric shrinkage (VS), elastic modulus (EM) and flexural strength (FS) of resins* and composites using different nanogels.

	DC (%)	**R_{Pmax}(%/s)**	**PS (MPa)**	**VS (%)**	**EM (GPa)**	**FS (MPa)**
Resin						
One-way ANOVA	*p < 0.001*	*p < 0.001*	*p < 0.001*	*p < 0.001*	*p = 0.056*	*p = 0.010*
Control resin*	63.9 (0.4) a	9.4 (0.2) a	2.8 (0.1) a	6.4 (0.5) a	2.7 (0.2)	121.7 (3.6) ab
Ng 1*	59.8 (0.2) c	5.1 (0.1) b	1.5 (0.2) bc	5.3 (0.2) b	3.0 (0.1)	129.4 (1.0) a
Ng 2*	60.3 (0.3) bc	5.5 (0.1) b	1.7 (0.1) b	5.2 (0.3) b	2.8 (0.1)	118.1 (4.7) b
Ng 3*	60.7 (0.1) b	5.4 (0.3) b	1.2 (0.3) c	5.0 (0.2) b	2.7 (0.2)	118.7 (6.0) b
Composite						
One-way ANOVA	*p < 0.001*	*p < 0.001*	*p < 0.001*	*p < 0.001*	*p = 0.447*	*p < 0.001*
Control MPS	64.6 (0.4) a	10.9 (0.4) a	2.2 (0.1) a	4.3 (0.2) a	6.3 (0.3)	145.7 (8.7) a
MPS + Ng 1	60.4 (0.4) bc	8.7 (0.2) bc	1.7 (0.1) b	3.4 (0.1) b	6.2 (0.2)	141.5 (10.6) a
MPS + Ng 2	60.2 (0.8) c	8.2 (0.3) c	1.7 (0.1) b	3.3 (0.1) b	6.2 (0.1)	132.2 (3.9) ab
MPS + Ng 3	60.3 (1.5) c	7.8 (0.1) c	1.8 (0.1) b	3.1 (0.1) b	6.0 (0.1)	126.2 (6.2) abc
VIN Ng 1	62.6 (1.1) ab	9.9 (0.6) ab	1.7 (0.1) b	4.1 (0.2) a	6.0 (0.1)	107.6 (14.2) bc
VIN Ng 2	60.9 (0.3) bc	9.7 (0.2) ab	1.7 (0.1) b	4.2 (0.3) a	6.4 (0.4)	108.4 (15.2) bc
VIN Ng 3	60.3 (0.9) c	9.2 (0.4) bc	1.4 (0.1) c	4.0 (0.1) a	6.3 (0.3)	112.0 (9.1) bc
VIN Ng 1 + Ng 1	57.3 (0.5) d	5.4 (0.3) d	1.1 (0.1) d	3.1 (0.1) b	6.1 (0.2)	102.8 (2.2) c
VIN Ng 2 + Ng 2	56.7 (0.3) d	6.7 (1.0) d	1.2 (0.1) d	3.1 (0.2) b	6.2 (0.2)	95.8 (6.5) c
VIN Ng 3 + Ng 3	61.0 (0.1) bc	7.8 (0.5) c	1.2 (0.1) d	3.0 (0.2) b	6.2 (0.2)	94.1 (8.6) c

Within a column, means followed by the same letter are not statistically different (p > 0.05)

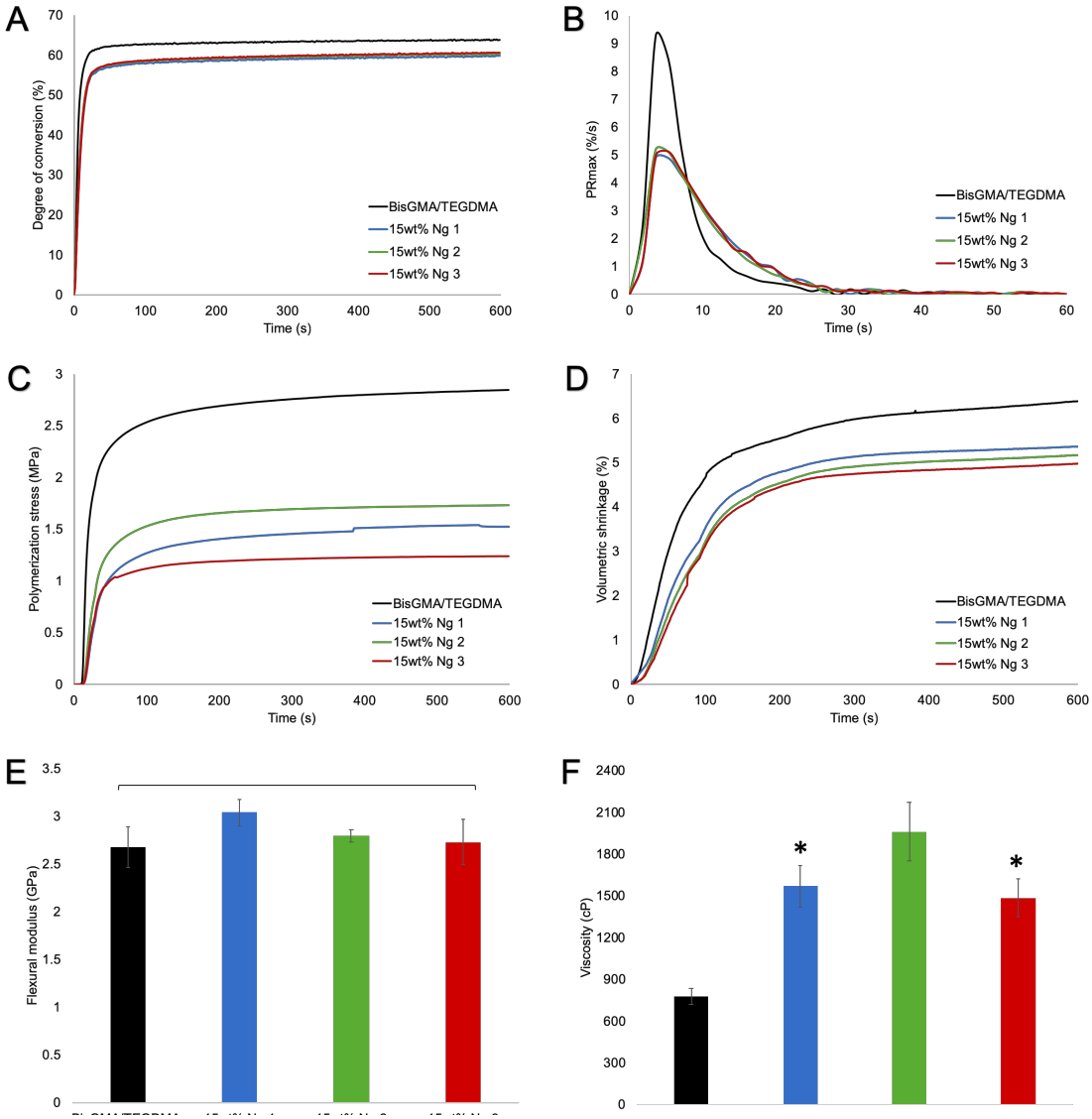

Figure 2. Polymerization kinetics of BisGMA/TEGDMA shows slightly diminished degree of conversion when resin is loaded with 15 wt% of nanogels (A). In contrast, the maximum polymerization rate is noticeably lower for nanogel systems (B). The polymerization stress with nanogel loading is approximately half that of the control resin (C) and it accompanies a decrease in volumetric shrinkage as well (D). The smaller, lower Tg nanogel additive tended to provide a greater degree of stress reduction than the larger, higher Tg nanogel analog (C). Notably, the elastic modulus of nanogel loaded resins is similar to control (E). Incorporation of nanogel increased resin viscosity significantly, especially in the case of the larger size Ng 2 (F).

Finally, the combined nanogel-modified fillers with free nanogel loading in resin produced a significant stress reduction of ~ 50% relative to the control (Table 2 and Figure 3). There was a significant decrease in VS, DC and R_{Pmax} compared to the control composite while notably, the EM was not compromised. Only the FS was significantly diminished as was also the case with the VIN Ng composites. When an equivalent portion of filler is replaced by free nanogel at 5 wt%, it still presents similar PS and FM as the MPS control (Appendix Figure 5). Photorheology (Figure 3F) shows the real-time modulus evolution during polymerization. The control demonstrated an early-stage increase in modulus compared to free nanogel addition or nanogel-modified fillers, with later modulus acquirement when both are combined, yet with similar final storage modulus.

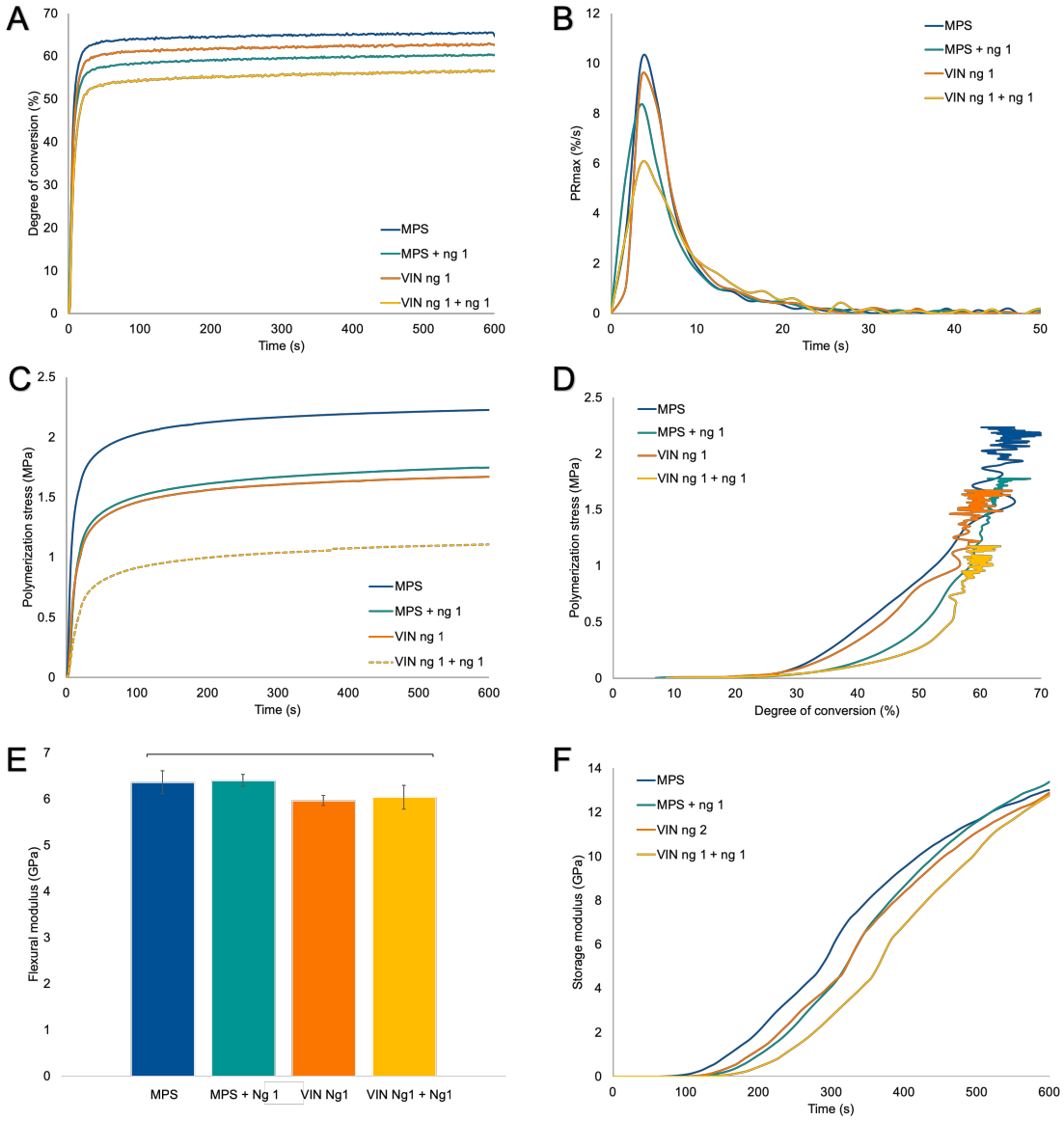

Figure 3. Real-time polymerization shows a slightly lower degree of conversion for the different composite systems compared to MPS control composite (A), while the polymerization rate is slower in systems with free nanogel addition but similar to control for nanogel-based fillers (B). Composite polymerization stress profiles demonstrate a reduction in polymerization stress by about 20% for free nanogel addition and nanogel-based fillers, but a 50% reduction when both strategies are combined (C). The MPS control composite and nanogel-based fillers present stress development at lower degree of conversion than the systems with free nanogel loading (D). The elastic modulus is similar to control for all experimental materials (E). Real-time modulus development during polymerization shows early increase in modulus for MPS control, followed by

nanogel based-fillers and free nanogel addition with the latest modulus rise observed when both approaches are combined. Notably, the final storage modulus is similar for all groups (F).

Discussion

Nanogels with different sizes and Tg's were synthesized from mono-functional monomers and a di-functional crosslinker, with available thiol functionalities to covalent connect with the vinyl pendant groups from the silane on the filler surface via thiol-ene reaction (Boulden et al. 2011; Hoyle and Bowman 2010). The residual thiol groups can participate in the matrix phase methacrylate network formation via chain transfer reaction to couple the matrix and filler in the final polymerized composite (Pfeifer et al. 2011). Nanogel-modified fillers engender ~20% magnitude reduction of PS, regardless of the nanogel used (Table 2). Therefore, the first hypothesis of the study was accepted.

Chain transfer reactions involve the exchange of an active radical from a propagating polymer chain to create a nanogel-bound thiol radical that then initiates incipient growth of a new polymer chain (Bacchi et al. 2016). This process completes the chemical connection between nanogel and matrix and if the nanogel is pre-attached to a filler particle, then it bonds the filler and matrix via a hybrid monomer/nanogel interphase since nanogels are readily swollen by monomer (Dailing et al. 2013). It should also be noted that chain transfer reactions are chain breaking, which means that the polymerization progresses through a radically assisted step-growth reaction, else than chain growth polymerization of methacrylates (Fairbanks et al. 2009). Within this mechanism, even in dense crosslinking systems, high molecular weight polymers are formed at later DC, reducing the magnitude of the viscoelastic effects on internal and interfacial stress through flow during the delayed gelation and vitrification stages (Bacchi et al. 2018; Pfeifer et al. 2011). Consequently, the PS development is diminished by a greater flowability within the polymer system, as demonstrated here in all nanogel-modified systems (Table 2).

Among nanogels, Ng 3 provided the lowest PS among resin systems and at the interphase (Table 2; Figure 2C) presumably because of its higher thiol bonds concentration (Table 1) and lower Tg as a bulk nanogel that may produce a more compliant domain either within the resin or at the filler interface (Charton et al. 2007). Interestingly, the same magnitude of PS reduction of the nanogel-based interphases is not observed for similar amounts (up to 5 wt%, in comparison with 3±1 wt% nanogel attached to the filler, as showed by TGA in Figure 1A) of nanogel dispersed in the resin. Equivalent stress reduction was only achieved with 15 wt% of free nanogel loaded in the composite (Appendix Figure 5). This likely means that not only did the chain transfer process provide stress relief, but it also arises from the interphase itself (Faria et al. 2018). The filler surface end-tethered with nanogel swelled by monomers from the resin phase feature a relatively flexible interphase with a relaxation potential to relieve stress during polymerization (Table 2). The compliance of the system is probably increased during the polymerization, which assist stress accommodation during the reaction. This is an internalized version of the lower stress that is observed when the external compliance of the measurement device is increased (Meira et al. 2011).

When both strategies of nanogel attached to the filler and dispersed in the resin matrix were combined a synergic effect was observed and there was a stress reduction of ~50% magnitude (Figures 3C). The addition of free nanogel to the resin matrix reduces the overall reactive group concentration of BisGMA/TEGDMA, which decreases VS and consequently PS (Table 2) (Braga et al. 2005; Moraes et al. 2011). Moreover, the simultaneous measurement of both real-time conversion and stress development demonstrated a delay to higher conversion for the onset of vitrification for the nanogel compositions (Figure 3D). The R_{Pmax} was also decreased for these systems (Figure 3B) as might be expected once the presence of nanogel also increased the viscosity of the resin blend (Figure 2F) (Liu et al. 2012; Liu et al. 2014). A statistically significant decrease in DC is observed for the nanogel-modified materials, with the greatest reduction when both strategies of nanogel introduction are combined. Because DC directly influences volumetric shrinkage and EM, which combine to produce stress (Braga et al. 2005), lower DC values could contribute

to diminished PS. However, the marginally lower DC for the experimental materials did not lead to any decrease in EM (Table 2) and as such, small reductions in final conversion of compositionally different materials, absent any modulus reduction, would not be expected to contribute significantly toward lower PS.

There was a substantial reduction of FS for the nanogel-modified filler materials (Table 2). This effect is not evident when the same nanogels are freely dispersed in the resin phase, which suggests that shortened polymer chains in the vicinity of the critical filler interface due to the chain transfer mechanism may be limiting the ultimate strength of the composite. Indeed, when fillers treated with VIN only were tested with no nanogel addition, the FS of the composite was 135.5±6.8 MPa. A potential means to probe this question would involve the use of methacrylate-functionalized nanogels attached to the filler surfaces to allow direct copolymerization between matrix and filler-tethered nanogel interphase.

Besides, the thiol functionality forms a thiol-carbon bond via chain-transfer that is more flexible than carbon–carbon bonds that are formed via copolymerization of the methacrylate on the filler surface (Kloxin et al. 2009). It should be noted that any residual vinyl silane groups on the filler surface can copolymerize with the methacrylate network of the matrix, but access may be limited under the nanogel layer. Even so, the FS values still exceed the requirements for composites FS test (Iso 4049. Dentistry - polymer-based restorative materials 2009).

On the contrary of the FS, the EM was not compromised for all our experimental systems (Table 2). Thereby, the second hypothesis was also accepted. This is important since a PS reduction is usually accompanied by a decrease in EM (Braga et al. 2005; Stansbury 2012). The modulus retention indicates that the hybrid matrix/nanogel interphase has an overall crosslink density similar to the BisGMA/TEGDMA control network. This may be attributed to the fact that thiol-ene step-growth polymerization reaction induces a higher crosslinking density, as well as the later modulus acquirement induced by the chain transfer mechanism (Fairbanks et al. 2009; Pfeifer et al. 2011), as demonstrated in the photorheology outcomes (Figure 3F). In this way, the gelation and vitrification points are not reached until high functional group

conversions, which collaborate for a lower PS without compromising the quality of the polymer network.

Despite the exciting results, this research presents its limitations. A reduction in FS of the composites appear to be reliant on this current nanogel-based interphase. Alternative functional silanes on the filler surface with different complimentary functionality and reactive sites within the nanogels should be explored in future researches. The interface design presented here provides a generic approach with other potential applications that can be explored to improve materials, at the same time that accommodates existing resins and fillers used in dental composites, which facilitates the translation for clinical application.

Conclusion

A nanogel based filler-matrix interphase is able to reduce PS even with minimum amounts of nanogel, which can be combined with free nanogel additives in the resin phase to lower VS and dramatically reduce overall PS of composites. This was accomplished without compromise to modulus and we see excellent potential for implementation of this designed interphase approach.

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3 DISCUSSÃO

O presente estudo demonstrou a influência da estrutura da interface entre partículas de carga e matriz resinosa nas propriedades físico-químicas dos compósitos restauradores. O tratamento de superfície realizado nas partículas tem o objetivo principal de ligar as duas fases de naturezas distintas, orgânica e inorgânica, e assim viabilizar propriedades mecânicas satisfatórias para o material. Mais do que isto, demonstrou-se o potencial de que essa interface pode ser explorada para outras finalidades. Neste ponto, o foco foi utilizar-se da modificação da interface para controlar o desenvolvimento de tensões durante a polimerização dos compósitos, sem que fossem comprometidas as outras propriedades do material de maneira geral.

O tratamento de superfície convencional com o agente silano MPS, utilizado neste estudo como controle, funcionaliza as partículas de carga com grupamentos metacrilato relativamente rígidos. Durante a polimerização, ocorre a ligação dos monômeros da matriz nesses sítios reativos das partículas tratadas, e uma subsequente restrição da mobilidade nessa área. Isso resulta em um aumento no acúmulo de tensões na interface ente carga e matriz que, em função de uma resultante interface rígida, não permite o alívio dessas tensões e, consequentemente, aumenta a tensão interna do material de forma geral. (Soderholm and Shang 1993; Wilson et al. 2007).

Em uma primeira abordagem, uma interface formada por ligações de poli-ureias foi desenvolvida através de agentes silanos alternativos à base de amina associados à nanogéis funcionalizados com grupamentos isocianato, capazes de se ligar aos silanos, e metacrilatos para copolimerizar com a matriz resinosa. Quando essas partículas modificadas foram incorporadas em compósitos, houve uma redução significativa da tensão de polimerização em uma magnitude de 20 a 34%, dependendo do agente silano utilizado.

Em virtude da sintetização dos nanogéis em solvente, estes formam um arcabouço flexível permitindo a penetração de monômeros em seu interior e, dessa forma, expandindo. Supõem-se que essa camada formada por cadeias pré-polimerizadas relativamente móveis e monômeros livres tiveram um comportamento semelhante à molas de um modelo viscoelástico (Anusavice et

al. 2013), capazes de se deformar para aliviar as tensões internas. Por conseguinte, há uma maior complacência que, projetada na superfície das partículas de carga, aumenta a complacência do sistema em geral, diminuindo a magnitude da tensão de polimerização. Além disso, há uma extensão dos grupamentos metacrilatos reativos, ficando mais distantes da superfície da partícula, e assim prontamente disponíveis para copolimerizar com a matriz.

No segundo estudo, foram utilizados nanogéis funcionalizados com grupamentos tiol, que por sua vez foram reagidos na superfície das partículas através de uma reação tiol-ene com grupamentos vinilos de um agente silano. Neste caso, além do efeito da interface formada por nanogéis para aliviar o as tensões, os grupamentos tiol atuam como agentes de transferência de cadeia. Com isso, o radical livre ativo de uma cadeia polimérica em crescimento é transferido para outra molécula, interrompendo seu crescimento, e um novo núcleo de crescimento é formado. Esse mecanismo diminui a taxa da reação e forma, inicialmente, cadeias menores, o que retarda a geleificação do material e permite uma movimentação mais livre das cadeias pela maior fluidez do material nos estágios iniciais da polimerização (Hoyle and Bowman 2010; Pfeifer et al. 2011). Dessa forma, há um menor desenvolvimento de tensões internas. De fato, essa estratégia de interface também foi capaz de reduzir significativamente a tensão final, em aproximadamente 20% comparado ao grupo controle. Entretanto, essa redução tem, provavelmente, uma maior influência da interface de nanogéis em si, do que da ação dos grupamentos tiol, visto que não houve uma diminuição significativa na taxa de reação para esses materiais. Como essa estrutura de interface é formada por quantidades mínimas de nanogéis (determinada por termogravimetria em 3% em peso de nanogéis), e a concentração dos grupamentos tiol também é baixa.

É interessante ressaltar que a redução da tensão de polimerização, para ambas estratégias de interface, não foi acompanhada de uma diminuição na contração volumétrica ou no módulo de elasticidade do material. Visto que o desenvolvimento de tensões está diretamente relacionado com essas duas propriedades, em que a contração é determinada pela concentração inicial de grupamentos reativos e o grau de conversão dos monômeros, enquanto o módulo é uma função da densidade da rede polimérica e o aumento da

temperatura de transição vítrea durante a reação (Boaro et al. 2010; Braga and Ferracane 2002), pode-se concluir que não houve uma alteração na conformação da rede polimérica de maneira geral. Isto é confirmado também nos resultados encontrados na cinética de polimerização e fotoreologia dos materiais avaliados.

As interfaces desenvolvidas com nanogéis podem ainda ser combinadas com outras estratégias para promover uma redução de tensão ainda maior, como apresentado no segundo estudo. Os mesmos nanogéis à base de tiol foram dispersados livremente na matriz resinosa, o que resultou em uma redução de tensão semelhante à interface modificada. Entretanto, vale ressaltar que uma quantidade maior de nanogéis foi necessária (15% em peso). Nessa situação, houve também uma redução da contração volumétrica do material em virtude da menor densidade de grupamentos reativos, além de uma menor da taxa de reação. Este efeito, por sua vez, pode estar associado a um maior efeito dos agentes de transferência de cadeia, além de um moderado aumento da viscosidade ocasionado pela adição dos nanogéis (Moraes et al. 2011). Quando a interface modificada por nanogéis foi associada à adição de nanogéis livres, houve uma redução drástica da tensão de polimerização final de aproximadamente 50%, comparado ao grupo controle. Notavelmente, o módulo de elasticidade do material também não foi comprometido nessa situação.

Em relação à resistência flexural, a utilização dos silanos contendo grupamento funcional amina por si só não foram capazes de manter uma resistência adequada. No entanto, quando associados aos nanogéis funcionalizados com grupos reativos metacrilatos capazes de copolimerizar com a matriz resinosa, uma união eficiente entre as duas fases, com valores de resistência comparáveis ao controle, foi alcançada. Por outro lado, a ligação promovida pelos grupamentos vinil do silano ligados aos nanogéis funcionalizados com tiol resultaram em uma resistência flexural inferior. Esses resultados podem ser explicados pela característica mais flexível da ligação entre carbono e tiol, comparada à uma estrutura mais rígida proveniente da reação de dois carbonos (Kloxin et al. 2009). Contudo, apesar dos valores serem significativamente inferiores ao grupo controle, a resistência à flexão

desses materiais ainda está de acordo com as normas requisitadas pela Organização Internacional de Estandardização (Iso 4049. Dentistry - polymer-based restorative materials 2009).

Os resultados apresentados neste estudo são promissores e instigam possibilidades para novas pesquisas nesse seguimento. Diferentes combinações de funcionalidades e propriedades da interface devem ser estudadas, assim como a estabilidade físico-química dessas novas interfaces e seu comportamento à longo prazo. Ao mesmo tempo, acomoda resinas e partículas de carga já utilizadas em compósitos restauradores, o que facilita a transição da pesquisa para a aplicação clínica.

4 CONCLUSÃO

A modificação da interface de união entre partículas de carga e matriz resinosa utilizando agentes silanos alternativos associados à nanogéis apresenta um potencial para redução significativa da tensão desenvolvida durante a reação de polimerização de compósitos restauradores. Essa diminuição da tensão de polimerização não alterou a contração volumétrica ou comprometeu o módulo de elasticidade do material. Essa estratégia pode ser combinada com a adição de nanogéis livres na matriz, produzindo um efeito sinérgico para uma maior redução da tensão de polimerização e, nesse caso, para redução da contração em si.

Diferentes características projetadas no tratamento de superfície das partículas de carga influenciam as propriedades finais do material restaurador. Essa estratégia trás uma nova abordagem genérica de tratamento de superfície, que pode ser explorada para melhorar os materiais de forma geral.

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APÊNDICES

Apêndice 1: Modification of filler surface treatment of composite resins using alternative silanes and reactive nanogels

Materials and Methods

Proton nuclear magnetic resonance spectroscopy

As a small molecule model, N-allylmethylamine and butyl isocyanate (Sigma-Aldrich, St. Louis, MO, USA) were reacted in dichloromethane at 1:1 molar ratio with a trace amount of dibutyltin dilaurate (Sigma-Aldrich). Each of the reactants as well as the reaction product obtained with no purification other than solvent removal were analyzed by proton nuclear magnetic resonance spectroscopy (1H NMR; Figure 1A). This was done to determine the ease and efficiency of the reaction between a secondary amine and an alkyl isocyanate, which directly corresponds to the silane-nanogel linkages formed here. With the 1H NMR spectra, we demonstrate that the secondary alkyl amine quantitively adds to the alkyl isocyanate providing a N,N-dialkyl-N'-alkyl urea, without any production of residual by-products.

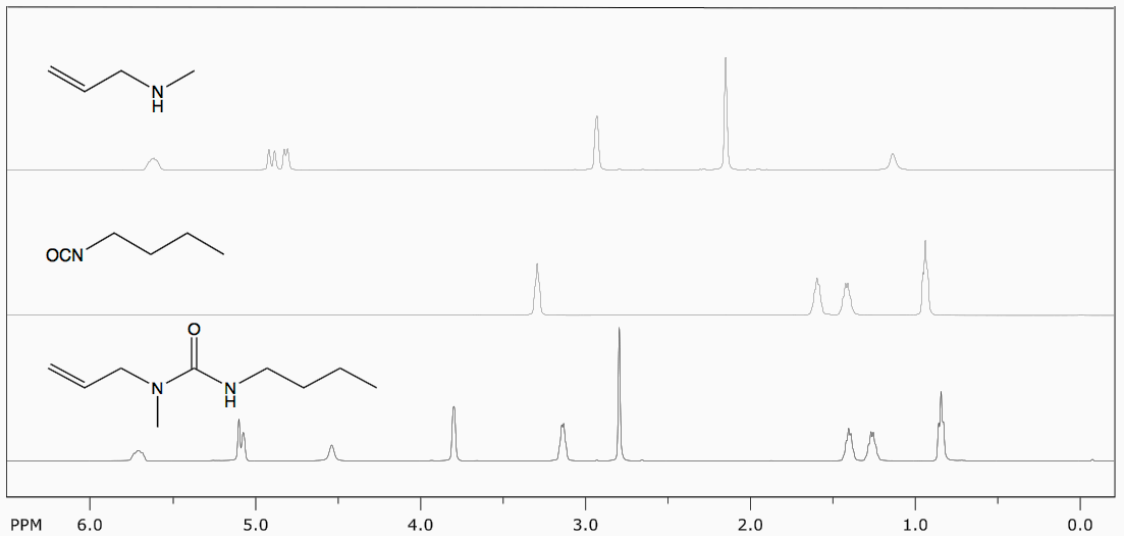


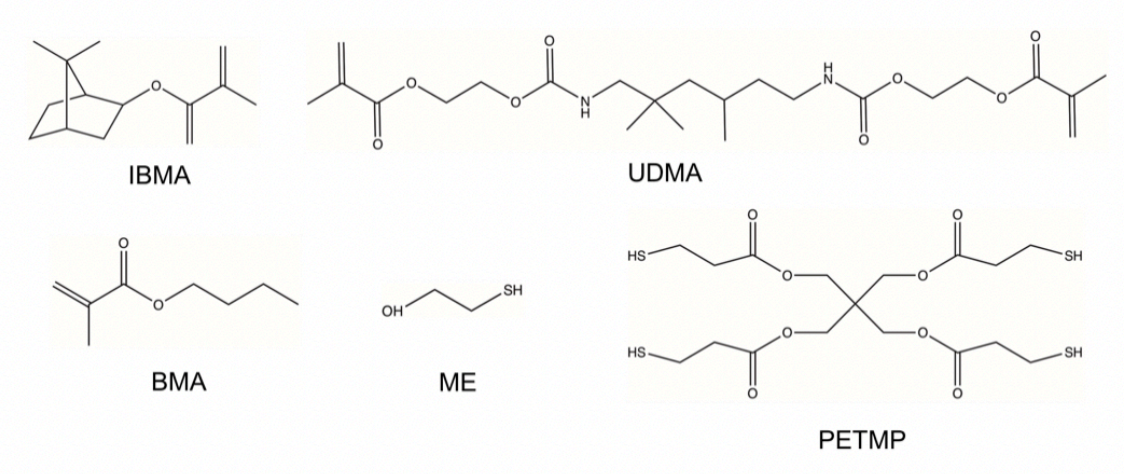
Figure 1A. NMR 1H spectra of allylmethylamine (top), butyl isocyanate (center), and the final Nallyl-N-methyl-N'-butylurea.

Apêndice 2: Nanogel based filler-matrix interphase reduces polymerization stress of composites

Materials and Methods

Nanogel syntheses

Appendix Figure 1 shows the chemical structures of the monomers (all from Esstech, USA) used in the nanogel syntheses.



Appendix Figure 1. Chemical structures of the monomers used in the nanogel syntheses: mono-functional monomers isobornyl methacrylate (IBMA) and butyl methacrylate (BMA); di-functional crosslinker urethane dimethacrylate (UDMA); 2-mercaptoethanol (ME), and pentaerythritol tetra(3-mercaptopropionate) (PETMP).

Polymeric nanogels' number average molecular weight (Mn), polydispersity index (PDI), and hydrodynamic radius (Rh) were characterized using gel permeation chromatography (GPC; Viscotek, Malvern Instruments, UK) with triple detectors detectors (refractive index, right angle light scattering, and differential viscometer) with tetrahydrofuran (EMD Millipore, USA) used as mobile phase. GPC calibration was based on a series of linear polystyrene standards of known molecular weight and dispersity.

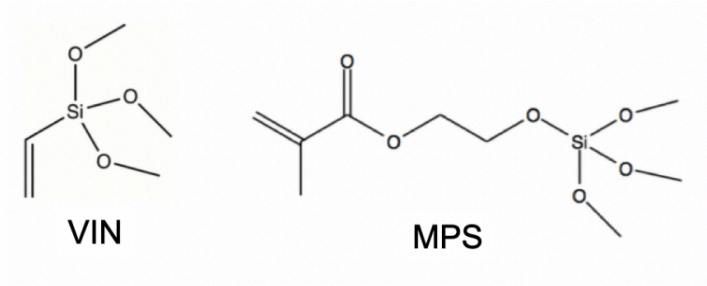
Tg of nanogel powders (n = 2) was determined by dynamic mechanical analyzer (DMA; Perkin Elmer 8000, USA) by sandwiching 10 mg of

nanogel in a thin metallic pocket that was then subjected to single cantilever cyclic displacement of 50 m at 1 Hz. The nanogel was heated from 0 to 150 ˚C with tan δ data collected in the second cycle of heating at 2 ˚C/min in air.

Ellman's reagent test (Thermo Scientific, USA) was used for quantitating free sulfhydryl groups of nanogels in solution.

Fillers surface treatment

For both silanes (Appendix Figure 2), i.e. trimethoxyvinylsilane (VIN; Sigma Aldrich, USA) and methacrylate γ-methacryloxypropyltrimethoxy silane (MPS; Sigma Aldrich), fillers were silanized with 5 wt% silane (relative to fillers) in cyclohexane using η-propylamine at 2 wt% as catalyst. The mixture was stirred at room temperature for 30 minutes and then at 60±5 ˚C for additional 30 minutes at atmospheric pressure and then placed in a rotary evaporator at 60 ˚C for the removing of the solvent and the volatile byproducts. The powder was then heated at 95±5 ˚C for 1 h on the rotary evaporator and finally was dried at 80 ˚C in a vacuum oven for 23 h. Extensive solvent washing with acetone was performed to remove physically adsorbed silane.



Appendix Figure 2. Chemical structures of the silanes: trimethoxyvinylsilane (VIN) and γ-methacryloxypropyltrimethoxysilane (MPS).

Filler treatments were identified by diffuse reflectance Fourier transform infrared spectroscopy (DR-IR; Nicolet 6700, Thermo Scientific, USA) spectroscopy. Spectroscopic grade KBr and filler powders were ground together and placed in the DR-IR accessory sample slide. Spectra were taken at 8 cm^{-1} resolution, 64 scans, from 4000 to 1350 cm^{-1} range, using KBr as background.

Thermogravimetric analysis (TGA; Pyris 7 TGA, Perkin Elmer, USA) was used to determine the amount of nanogel deposited on surface of treated fillers. Samples (5±1 mg) were placed in platinum pans in nitrogen atmosphere flow of 20 ml/min and heated from 50 ^{o}C to 850 ^{o}C with a heating rate of 10 $^{\circ}$C min^{-1}. The mass loss as a function of temperature was recorded.

Energy dispersive X-ray spectrometry (EDX; Oxford Instruments SDD X-MaxN) analysis coupled to a scanning electron microscope (JSM IT 300, JEOL, Japan) was used to identify the elemental composition of filler surface treatment. Fillers were placed on stubs and sputter-coated with carbon. Each spectrum was acquired for 300 s (voltage 15 kV, working distance 10 mm). Images showing the identified chemical elements and their relative concentration were obtained from five different spectra of each material at different locations on the stub.

Filler surface images were obtained by transmission electron microscopy (TEM; JEM 2100, JEOL, Japan). Fillers were dispersed in acetone, then few mL of the solution were dropped in formvar grids and TEM images were then obtained. Images were obtained at magnification of 300K and 500K×.

Polymerization kinetics

Real-time polymerization kinetics was monitored by Fourier transform near-infrared spectroscopy (FT-NIR, Nicolet 6700) in specimens (n=3) of 6 mm in diameter and 0.8 mm thick laminated between two glass slides. Specimens were light-activated for 20 s at an incident irradiance of 1470 mW/cm^2 at 430-480 nm wavelength (Elipar DeepCure-S LED, 3M ESPE, USA). The area of the methacrylate vinyl absorbance band centered at 6165 cm^{-1} (Stansbury and Dickens 2001) was used to follow the polymerization reaction. Measurements were taken at a wavenumber resolution of 4 cm^{-1} with 32 scans per spectrum acquired for static scans before and after polymerization to measure degree of conversion (DC) and 2 scans per spectrum for dynamic measurements of polymerization kinetics, which provides a 2 Hz acquisition rate. Data was collected for 10 minutes during and continuing after curing light exposure. Polymerization rate (R_{Pmax}) was calculated as the first derivate of the conversion vs. time curve.

Polymerization stress

Dynamic polymerization stress was evaluated with a tensometer (Volpe Research Center, American Dental Association). Glass rods (6 mm diameter) were sectioned into lengths of 28 and 5 mm. One surface of the 28-mm long rods was polished with a sequence of silicon carbide abrasive papers felt disks in order to optimize the transmission of light through the rod end into the specimen during photoactivation. The opposite surfaces of the 28- and 5-mm rods were polished with 600 grit using abrasive papers to create a rough surface. Silane was applied to these surfaces. The rods were subsequently attached to the tensometer. The 28 mm rod were attached to the lower clamp and the 5 mm rods to the upper clamp. Composite was placed (6 mm x 1 mm) between the rods with a Centrix syringe. The tip of the light-curing unit was positioned in contact with the polished lower rod. Force development was monitored for 10 minutes from the beginning of light-activation, and the maximum nominal stress (MPa) was calculated by dividing the maximum force value recorded by the cross-sectional area of the rods.

Volumetric shrinkage

A constant volume of each material was placed onto an aluminum disc in a non-contact linear variable differential transducer-based linometer (Academic Center for Dentistry Amsterdam, The Netherlands). The material was covered with a glass slide, which was adjusted to produce a specimen disc (approximately 1 mm × 6 mm). Both resins and composites specimens were irradiated for 20 s through the glass slide. The displacement of the aluminum disk, caused by the lifting action of the material's shrinkage, was registered during and extending beyond the irradiation interval for a total period of 10 minutes. The linear shrinkage during polymerization was measured and converted to the corresponding volumetric shrinkage (de Gee et al. 1993), as follows:

$$lin\% = \frac{\Delta L}{L + \Delta L} \times 100\%$$

where ΔL is the recorded displacement and L the thickness of the sample after polymerization. The volumetric shrinkage derived from the linear shrinkage is given by:

$$vol\% = 3lin\% - 0.03(lin\%)^2 + 0.0001(lin\%)^3$$

Rheology

Viscosity measurements of the nanogel resins blends (n=5) were performed using a cone-plate digital viscometer (CAP 2000, Brookfield, USA). A defined volume of the materials was tested at room temperature (23 °C) using a 14 mm diameter spindle 200 rpm and 1 Hz (hold time: 15 s; run time: 30 s). Rheology of the composites (n=2) was assessed in a photorheometer (ARES, TA Instruments, USA), with materials placed between two 20 mm parallel quartz disc plates and tested in shear at a frequency of 100 rad/s with 10% strain (ensuring that the test was carried out within the linear viscoelastic regime), while being photopolymerized at 50 mW/cm^2 (mercury arc lamp 460 nm, Acticure 4000, EXFO, USA) for 10 minutes. An optical apparatus (Pfeifer et al. 2011) allowed both curing light and FT-NIR direct transmission access to the specimen within the photorheometer, in this way methacrylate conversion was followed concomitantly with modulus development.

Mechanical properties

The three-point bending test was used to assess the flexural strength and elastic modulus. The bar specimens were prepared in dimensions of 2 mm x 2 mm x 25 mm according to ISO 4049 (Iso 4049. Dentistry - polymer-based restorative materials 2009). Specimens (n = 8) were fabricated between glass slides and polymerized with three overlapping 20 s light exposures each sides glass side. Specimens were stored dry for 24 h in dark containers at room temperature. The three-point bending test was performed on the MTS testing machine using a span of 20 mm and a cross-head speed of 1 mm/min (MTS Mini Bionix II, MTS, Eden Prairie, MN, USA). The flexural strength (FS) in MPa was then calculated as:

$$FS\ (\sigma) = \frac{3F\iota}{2bh^2}$$

where F stands for load at fracture (N), ι is the span length (20 mm), and b and h are the width and thickness of the specimens in mm, respectively.

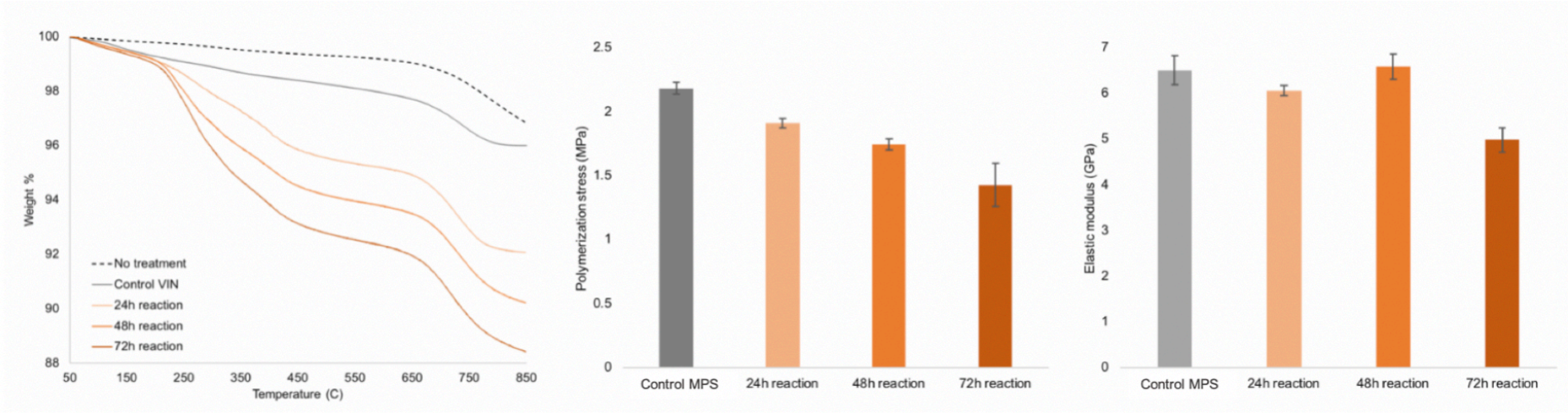
The elastic modulus was determined from the slope of the initial linear part of stress–strain curve.

$$E\ = \frac{F\iota^3}{4bh^3d}$$

where F is the load at some point on the linear region of the stress–strain curve, d the slack compensated deflection at load F, and ι, b, and h are as defined above.

Results

In a pilot study, fillers were reacted with nanogel (Ng 2) at the times of 24, 48 and 72 h in order to create different concentrations of nanogel on the surface (Appendix Figure 3). It is noticeable that polymerization stress progressively decreases with higher amount of nanogel attached to the surface, i.e. longer nanogel addition reaction times, providing a more complete nanogel layer on the surface as well as a higher thiol concentration (Appendix Table 2 and Appendix Figure 4). However, there may be a limit with respect to the final polymeric elastic modulus, as is presented in the plot that indicates at 72 h reaction, the modulus may be decreasing as well. The coverage for 48 h is estimated by TGA to be 3 wt%, which would offer reasonable stress reduction with no compromise in the mechanical properties of the material.



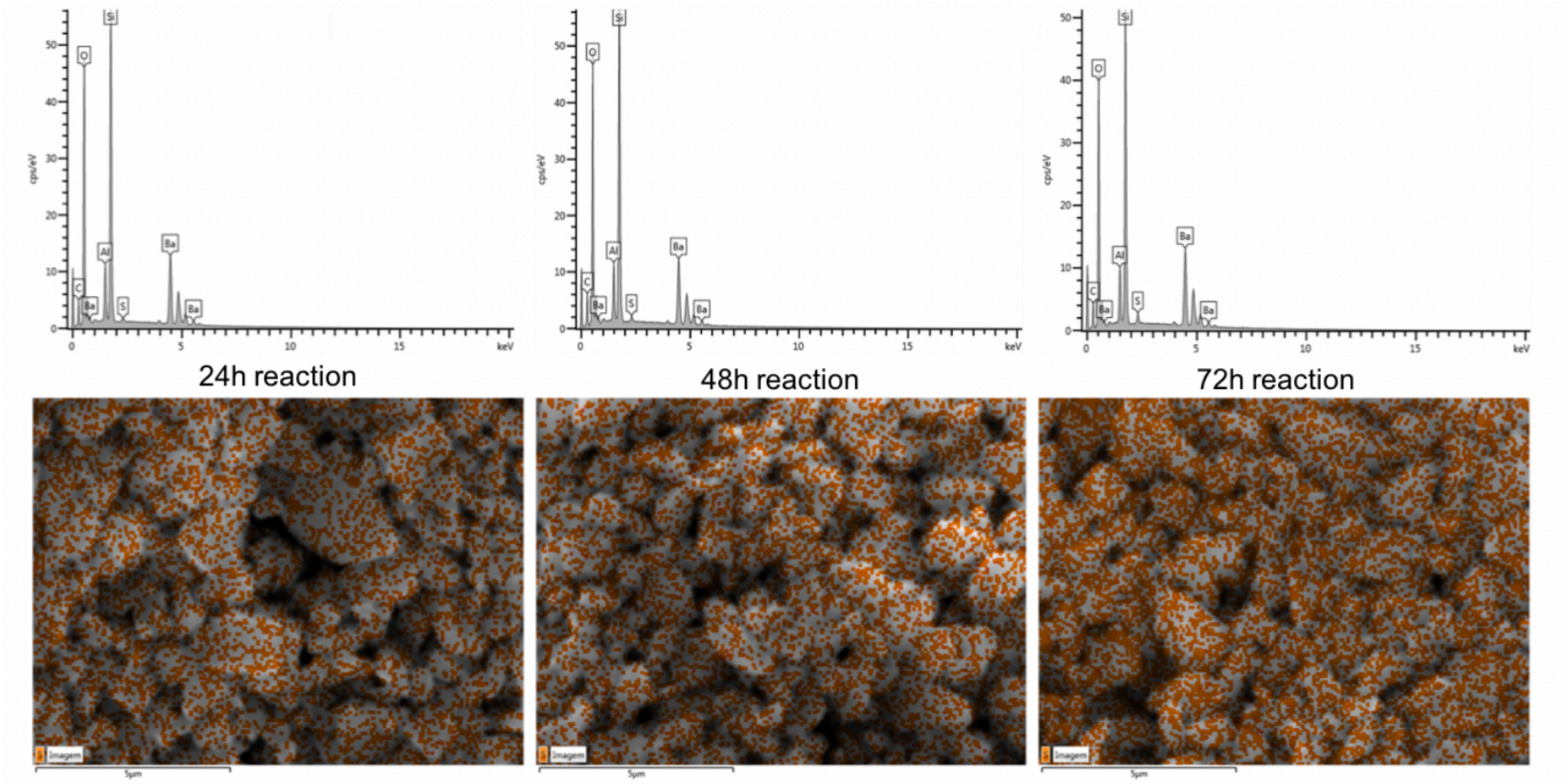
Appendix Figure 3. TGA analysis of fillers reacted with nanogels for 24, 48 and 72 h, and its respectively composites results for polymerization stress and elastic modulus.

Appendix Table 1. Apparent element concentration for fillers with different surface treatments.

	No treatment	VIN silane	VIN Ng 1	VIN Ng 2	VIN Ng 3
C	4.6 (0.5)	6.3 (0.2)	7.0 (1.2)	4.4 (0.2)	7.7 (0.5)
O	96.6 (8.2)	128.8 (11.2)	114.2 (2.3)	64.5 (1.5)	103.0 (5.1)
Al	5.8 (5.8)	7.3 (0.4	6.6 (0.3)	4.3 (0.1)	6.1 (0.2)
Si	33.4 (2.3)	40.8 (1.8)	36.5 (0.3)	25.3 (0.2)	34.0 (1.2)
Ba	56.0 (1.6)	55.8 (0.8)	51.1 (2.0)	47.5 (0.8)	47.7 (0.7)
S	-	-	0.4 (0.0)	0.6 (0.1)	0.7 (0.3)

Appendix Table 2. Apparent element concentration for fillers threated with nanogels for different reaction times.

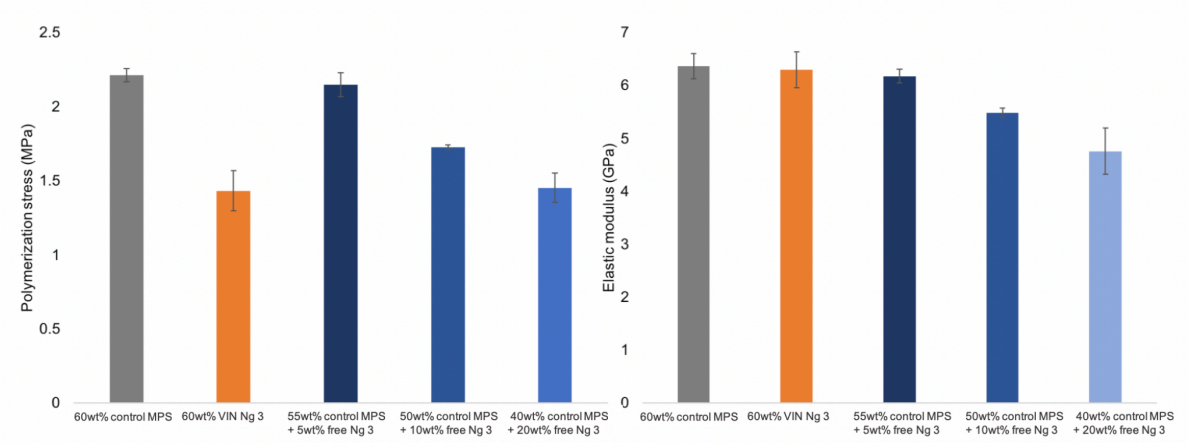
	VIN Ng 2 24 h	VIN Ng 2 48 h	VIN Ng 2 72 h
C	5.4 (0.9)	4.4 (0.2)	5.8 (1.0)
O	93.0 (17.2)	64.5 (1.5)	109.5 (24.1)
Al	5.6 (0.8)	4.3 (0.1)	6.3 (0.9)
Si	32.2 (4.0)	25.3 (0.2)	35.4 (4.5)
Ba	49.3 (1.4)	47.5 (0.8)	50.0 (0.2)
S	0.2 (0.0)	0.6 (0.1)	1.2 (0.3)



Appendix Figure 4. Elemental composition through EDX and S mapping for 24, 48 and 72 h nanogel addition reaction to the fillers.

Discussion

Different loading of fillers and free nanogel (Ng 2) were evaluated, but always keeping the total loading of 60 wt% (Appendix Figure 5). When an equivalent portion (in terms of weight fraction not volume fraction) of the glass filler is replaced by nanogel at 5 wt%, it still presents similar PS and EM as the MPS control. At free nanogel loading levels of 10 and 20 wt%, the PS is decreased while the EM is also reduced as expected with the lower inorganic filler content. This demonstrates that the interphase created at the filler surface with minimum amount of nanogel (3 wt%) has the potential to significantly reduce the PS without compromising the EM, and this effect is not observed when similar amount of free nanogel (5 wt%) is added to the resin.



Appendix Figure 5. Polymerization stress and elastic modulus of composites with different filler and free nanogel loadings.

ANEXOS

Anexo 1. Verificação de originalidade e prevenção de plágio

Modificação da interface de união entre partículas de carga e matriz resinosa de compósitos restauradores

Tese

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Anexo 2. Comprovante de submissão do artigo

Decision Letter - Accept: 18 March 2019

Ref: DEMA_2019_80_R1
Title: Modification of filler surface treatment of composite resins using alternative silanes and functional nanogels
Journal: Dental Materials

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