



Effects of polymerization initiator complexation in methacrylated β -cyclodextrin formulations

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Summary Objectives. Methacrylated β -cyclodextrin (MCD) is a candidate dental monomer that can complex molecules within its hydrophobic cavity. This study determined the effects of complexation of polymerization initiators such as camphorquinone (CQ) and ethyl-4-dimethylaminobenzoate (4E) with MCD on the flexural strength (FS) and degree of conversion (DC) of resulting dental composite formulations.

Methods. Complexation of CQ and 4E with MCD was studied by thin layer chromatography. A mass fraction of 44% 2-hydroxyethylmethacrylate or triethyleneglycoldimethacrylate was mixed separately with a mass fraction of 56% MCD to produce a workable formulation. The mixture was activated with varied amounts of CQ and 4E. One part by mass of the activated resin formulation was mixed with three parts by mass of glass filler. Specimens for FS were prepared by filling molds with composites and curing for 2 min. The cured specimens were immersed in 37 °C water for 24 h and FS was measured with an Instron machine at a crosshead speed of 0.5 mm/min. DC in MCD-based resin formulations was measured with a differential photocalorimeter under nitrogen.

Results. MCD appears to form inclusion complexes with CQ and 4E. As a result, FS and DC of MCD-based composites vary significantly as a function of the concentration of polymerization initiators used in the formulations.

Significance. Complexation of polymerization initiators with MCD can influence the FS and DC in MCD-based dental formulations and should be taken into consideration when evaluating MCD as a dental monomer.

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Introduction

β -Cyclodextrin (BCD) is a cyclic oligosaccharide consisting of seven glucose units linked by α -1,4

bonds. It has a hollow truncated cone shape, and there are no hydroxyl groups inside its cavity. As a result, the hydrophobicity of the cavity gives BCD the ability to include hydrophobic molecules within its cavity. Such inclusion complexes of BCD with low molecular weight compounds, including a number of hydrophobic monomers, are well documented.¹⁻³ Inclusion complexes of

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BCD find wide-ranging applications such as controlled release of water insoluble, highly reactive, or volatile materials, such as fragrances, catalysts, and low molecular weight additives.⁴⁻⁷ Other uses include extraction and recovery of trace organics from effluent streams,⁸⁻¹⁴ solubilization of poorly water soluble materials, and reduction of solvent requirements in chemical processes and products, such as electroplating solutions, paints, and printing inks.¹⁵⁻¹⁷ Chiral resolution via chromatography as a stationary phase modifier, and direction of chiral or site-specific substitution in chemical synthesis have been reported as additional uses.¹⁸⁻²⁴

Methacrylated β -cyclodextrin (MCD) comprises a family of candidate dental comonomers if all or some of the hydroxyl groups of BCD are substituted with methacrylate groups.²⁵ There is evidence that MCD can form inclusion complexes with polymerization initiators such as camphorquinone (CQ), ethyl-4-dimethylaminobenzoate (4E), benzoylperoxide (BP), and other compounds, as indicated by computer modeling and by matrix assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF-MS).^{25,26} Because the molar concentration of polymerization initiators used in conventional dental monomers is relatively small, complexation of some of these initiators within MCD molecules might alter polymerization rates. Such complex formation could affect the properties of MCD-based composites. The purpose of this study was to investigate whether such MCD-polymerization initiator complexation occurs and to test the hypothesis that properties of MCD-based composites are affected by such complex formation. The properties chosen for the study were flexural strength and degree of conversion.

Materials and methods

Synthesis of methacrylated β -cyclodextrin

A mixture of 232 ml of methacrylicanhydride, 212 ml of pyridine, and 0.064 g of butylated hydroxytoluene (BHT; inhibitor) was transferred into a 1000 ml three-necked stoppered flask containing a stir bar. BCD (45.36 g, dried in vacuo at 115 °C for 48 h) was added in small portions to the flask, the mixture was stirred for 48 h at room temperature. The clear solution was decanted into a beaker containing ice-cold distilled water (6 °C); whereupon MCD precipitated as a creamy white solid. The solid was filtered and dissolved in anhydrous methanol and re-precipitated with water. This was done two more times to obtain the product. The yield of MCD was about 64% of the theoretical based on the BCD. A small amount of MCD was sent for elemental analysis to Galbraith Laboratories (Knoxville, TN, USA). The ¹H NMR spectrum of the product was obtained on a JEOL 270-MHz FT-spectrophotometer (Peabody, MA, USA) using deuterated dimethylsulfoxide as solvent and tetramethylsilane (TMS) as internal reference. The spectrum showed that hydroxyl groups had been esterified in the MCD (Table 1).

Estimation of number of methacrylate groups in MCD

The number of double bonds (DBs) per molecule of MCD was determined ($n = 3$) by bromination followed by titration.²⁷ A known quantity of approximately 13 mg of MCD, weighed to 0.01 mg accuracy, was dissolved in 10 ml of glacial acetic acid. An equal volume of distilled water was then added to the mixture followed by the addition of

Table 1 Materials.

Acronym	Chemical	Lot No.	Manufacturer
BCD	β -Cyclodextrin	G6020-42	American Maize-Products Co. (now Cerestar USA, Inc., Hammond, IN, USA)
MA	Methacrylicanhydride	15029ER	Aldrich Chemical Co. Milwaukee, WI, USA
Py	Pyridine	05846BQ	Aldrich Chemical Co.
BHT	Butylated hydroxytoluene	No Lot No.	Aldrich Chemical Co.
HEMA	2-Hydroxyethylmethacrylate	03430LU	Aldrich Chemical Co.
TEGDMA	Triethyleneglycoldimethacrylate	488-16-07	Esschem Inc. (now Esstech), Linwood, PA, USA
Bis-GMA*	Nupol 46-4005	125-101	Freeman Chemical Corp, Port Washington, WI, USA
CQ	Camphorquinone	06724AW	Aldrich Chemical Co.
4E	Ethyl-4-dimethylaminobenzoate	15014PN	Aldrich Chemical Co.

*Bis-GMA is the reaction product(s) of the diglycidylether of bisphenol A and methacrylic acid, primarily {2,2-bis[4-(2-hydroxy-3-methacryloxyprop-1-oxy)phenyl]propane}.

50 ml of a solution having an amount-of-substance concentration of $c(\text{KBrO}_3\text{-KBr}) = 0.001 \text{ mol/l}$ (0.278 g KBrO_3 and 1.750 g KBr in 1 l). The mixture was acidified with 5 ml of concentrated HCl and was stirred overnight in a dark environment. About 1 ml of a mass fraction of 10% KI solution was added to the mixture, and the liberated iodine was titrated with a solution having an amount-of-substance concentration of $c(\text{sodium thiosulfate}) = 0.005 \text{ mol/l}$ with 1 ml of a mass fraction of 1% starch solution as indicator at the end point. The method was tested by the use of acetic acid solutions containing known amounts of methylmethacrylate as control.

Complexation of MCD with polymerization initiators

Thin-layer chromatography (TLC) was used to identify the complexes of MCD with CQ and with 4E. Equimolar amounts of MCD and CQ were dissolved together in methanol and the solution was evaporated to dryness with slow stirring. The dry MCD/CQ complex was then dissolved in ethylacetate to give a solution of a mass fraction of 5%. A similar solution of MCD/4E complex in ethylacetate was prepared separately. With the use of a capillary tube, the solutions were spotted on to a Whatman linear-K silica gel plate. A mixture containing 25 volume fraction methanol and 75 volume fraction toluene was used as the migrating solvent. The spots of the complexes, which showed about the same UV absorption as did the individual components, were visualized by UV fluorescence and then R_f values were determined.

Resin and composite formulations

Formulations with equimolar polymerization initiator concentrations

2-Hydroxyethylmethacrylate (HEMA, mass fraction of 44%) and triethyleneglycoldimethacrylate (TEGDMA, mass fraction of 44%) were each mixed separately with a mass fraction of 56% MCD to produce a formulation of workable viscosity. The MCD/HEMA and MCD/TEGDMA mixtures were activated with equimolar amounts: (0.2, 1.5, 2.7, 4.0, 5.1, 6.28, or 7.4) mol fraction (%) of both CQ and 4E. For comparison a resin mixture containing a mass fraction of 70% Bis-GMA and a mass fraction of 30% TEGDMA (typical dental resin mixture) was also activated with the same equimolar amounts of CQ and 4E. These mixtures are referred to herein as formulations with 'equimolar polymerization initiator'.

Formulations with constant molar polymerization initiator concentrations

Mixtures containing a combined mass fraction of 56% MCD and 44% TEGDMA and a combined mass fraction of 70% Bis-GMA and 30% TEGDMA were each activated with a combined constant mole fraction of 12.56% polymerization initiator. Although the sum of the concentrations of the two activators was constant, i.e. mol fraction (%) CQ + mol fraction (%) 4E = 12.56 mol fraction (%), various polymerization initiator proportions were used: (0.3 + 12.26, 1.8 + 10.76, 3.3 + 9.26, 4.8 + 7.76, 6.28 + 6.28, 7.8 + 4.76 or 9.3 + 3.26) mol fraction (%) CQ + mol fraction (%) 4E, respectively. These are referred to as formulations with 'constant-molar sum polymerization initiator'.

The various composite formulations were prepared by hand spatulation of one part by mass of the activated liquid resin mixture with three parts by mass of glass filler (silanated, milled barium oxide-containing glass, Caulk Dentsply, Milford, DE, USA). The homogenized composite formulations were kept under vacuum (530 mm Hg) overnight to eliminate air entrained during mixing.

Flexural strength and degree of conversion

Specimens ($n = 6$) for three-point flexural strength were prepared by curing the composite in (2 mm \times 2 mm \times 25 mm) stainless-steel molds. The molds were faced with Mylar (0.06 mm, du Pont, Wilmington, DE, USA), covered on either side with a microscope slide, and clamped together. These specimens were light-cured using three 8 mm diameter tips aligned together side by side light source (Max 100, Caulk Dentsply, Milford, DE, USA) at 400 mW/cm^2 in intensity for 1 min on each side, and then immersed in water at 37 $^\circ\text{C}$ for 24 h. The flexural strength was measured with a computer-controlled universal testing machine (Model 5500, Instron Corporation, Canton, MA, USA) at a cross-head speed of 0.5 mm/min. The degree of conversion in MCD-based resin formulations was measured with a differential photocalorimeter (Model 2920-modulated DSC, TA Instruments, New Castle, DE, USA) under nitrogen with a light intensity at 100 $\mu\text{W/cm}^2$ and an exposure time of 60 min.

Statistics

Multiple comparisons were made using one-way ANOVA and Tukey's post hoc test. Unless stated otherwise, \pm indicates one standard deviation and is assumed to be the estimate of the standard uncertainty.

Results

Characterization and estimation of the average number of methacrylate groups in MCD

The ^1H NMR of MCD showed peaks corresponding to vinyl protons at 6.06 and 5.69 ppm; the methyl protons of the methacrylate groups appeared at 1.88 ppm, with a standard uncertainty of 0.05 ppm. Fig. 1 is a schematic representation of one member of the MCD family having seven unreacted hydroxyl groups. The elemental analysis of MCD corresponded to an average of about 16 methacrylate groups per MCD molecule. The results of the elemental analyses of MCD were C = 56.67% mass fraction, H = 6.19% mass fraction, O = 36.11% mass fraction, and N = 0.27% mass fraction as compared to the calculated values for fully methacrylated MCD that are C = 59.01% mass fraction, H = 6.05% mass fraction, and O = 34.94% mass fraction. Also, the bromination technique indicated an average of 16.6 (± 2.0) methacrylate double bonds per molecule of MCD. Thus, the method of synthesis described above did not esterify all of the 21 hydroxyl groups of BCD.

The major peaks of a MALDI-TOF-MS spectrum of a sample indicated an average of about 14 methacrylate groups per MCD molecule, with a measurement uncertainty estimated to have

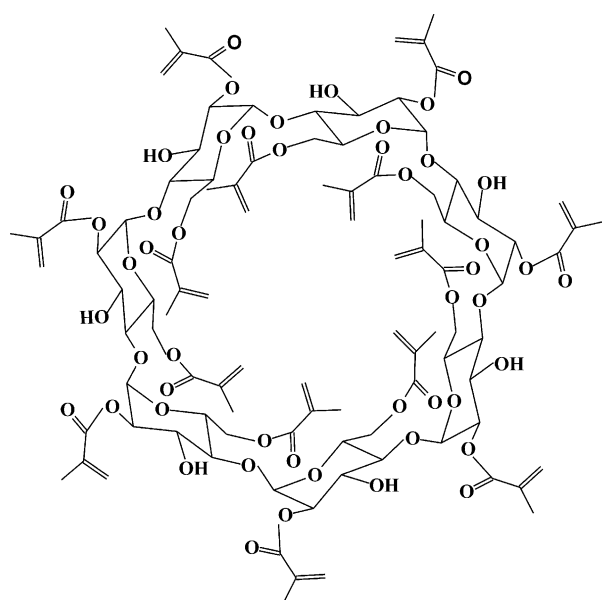


Figure 1 Schematic representation of a partially methacrylated beta-cyclodextrin; the method of synthesis did not esterify all of the 21 hydroxyl groups of β -cyclodextrin (BCD). The drawing shows the characteristic 'hollow' configuration of such compounds. The methacrylated cyclodextrin (MCD) products formed in this study retained nearly a third of their original hydroxyl groups.

a standard deviation of about two mass units.²⁶ How residual pyridine, which was observed in the MALDI-TOF-MS analysis of the MCDs, may have affected polymerization and subsequent physical properties of the MCD formulations, is not presently known. From the above methods of analysis, the number of methacrylate double bonds per molecule of MCD was between 16.6 and 14. And, for the purpose of this study the number of methacrylate double bonds per molecule of MCD used was 16.

Complexation of polymerization initiators with MCDs

In the TLC analysis, the R_f values of the MCDs complexed with CQ and 4E differed significantly from those of the free components. The calculated R_f values were approximately as follows: uncomplexed MCDs, 0.54; CQ, 0.81; 4E, 0.9; MCD/CQ, 0.48; and MCD/4E, 0.49. These semiquantitative data suggest that the MCDs formed inclusion complexes with CQ and with 4E. Fig. 2 displays a computer-generated model of CQ complexed as a 'guest' within the 'host' space of an MCD molecule.

Flexural strength and degree of conversion

Equimolar polymerization initiator compositions

Fig. 3 shows the relationship between flexural strength and total mol fraction (%) of polymerization initiator in MCD/HEMA-based composites at equimolar polymerization initiator compositions. Also shown in the same plot is the degree of conversion versus total mol fraction (%) of polymerization initiator of the unfilled MCD/HEMA-based resin mixtures with equimolar polymerization initiator compositions. The flexural strength and degree of conversion increased significantly ($p < 0.05$) with increasing polymerization initiator concentrations in the formulations. Fig. 4 shows flexural strength versus varied total mol fraction (%) polymerization initiator for MCD-based and Bis-GMA-based composites with equimolar polymerization initiator compositions. The flexural strength of the MCD/TEGDMA-based composites increased significantly ($p < 0.05$) when the equimolar polymerization initiator concentrations were increased. In contrast, for Bis-GMA/TEGDMA-based composites, the flexural strength did not increase significantly with increasing equimolar polymerization initiator concentrations ($p = 0.06$).

Constant molar sum polymerization initiator compositions

Based on the previous set of experiments with equimolar polymerization initiator concentrations,

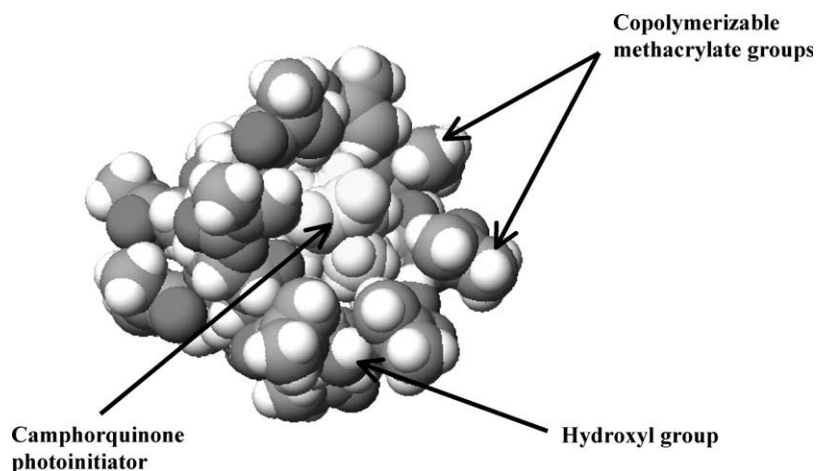


Figure 2 The 'hollow' configuration of BCD and its derivatives allows for formation of three-dimensional inclusion complexes with suitably sized 'guest' molecules. The space-filling scale model depicted here demonstrates that camphorquinone (CQ), a polymerization initiator, can be complexed within MCD molecules. This and analogous complexation of the copolymerization initiator ethyl-4-dimethylaminobenzoate (4E) within MCD monomers could understandably influence rates of photo-initiated polymerization.

it was decided that 6.3 mol fraction (%) CQ + 6.3 mol fraction (%) 4E seemed to give the highest flexural strength for MCD/TEGDMA-based composites. In search of an optimum concentration ratio of CQ-to-4E, the mol fraction (%) CQ and mol fraction (%) 4E were varied in such a way as to give a sum of about 12.6 mol fraction (%) of these polymerization initiators in the formulations. These were the formulations with 'constant molar sum polymerization initiator', for which the flexural strength values were measured. Fig. 5 shows the flexural strength of MCD-based composites at constant molar sum polymerization initiator compositions. The mean flexural strength values increased as the mol fraction (%) CQ in the total

polymerization initiator increased, and passed through a maximum (94.0 ± 10.0 MPa) in the region of 7.8 mol fraction (%) CQ + 4.76 mol fraction (%) 4E. One-way ANOVA showed significant differences that existed between the groups ($p < 0.05$). However, for constant molar sum polymerization initiator compositions containing 3.3 mol fraction (%) CQ and more, the mean flexural strength values of MCD-based composites were not significantly different. The mean flexural strength values of Bis-GMA-based composites with constant molar sum polymerization initiator were higher than those of the MCD-based composites and in contrast to the MCD-based composites, did not vary significantly ($p = 0.159$) with the varying mol fraction (%) CQ.

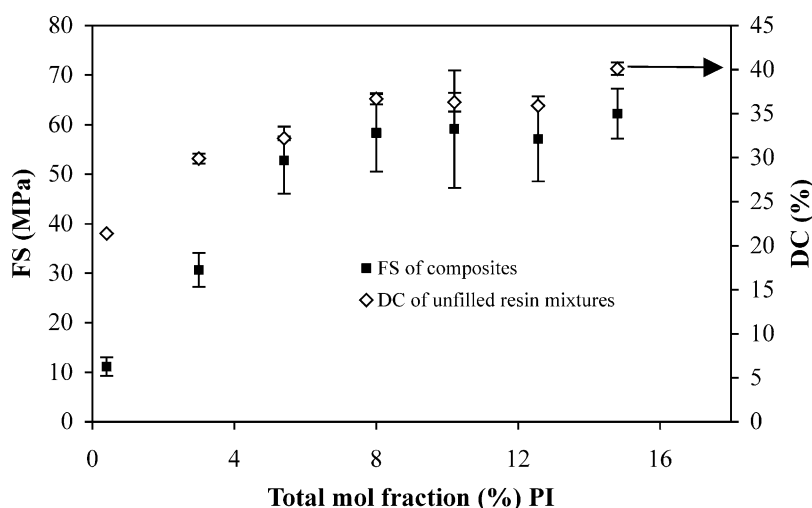


Figure 3 Flexural strength (FS) and degree of conversion (DC) of various compositions versus their respective total equimolar concentrations of polymerization initiators (PI) in MCD/HEMA-based formulations, ($n = 6$).

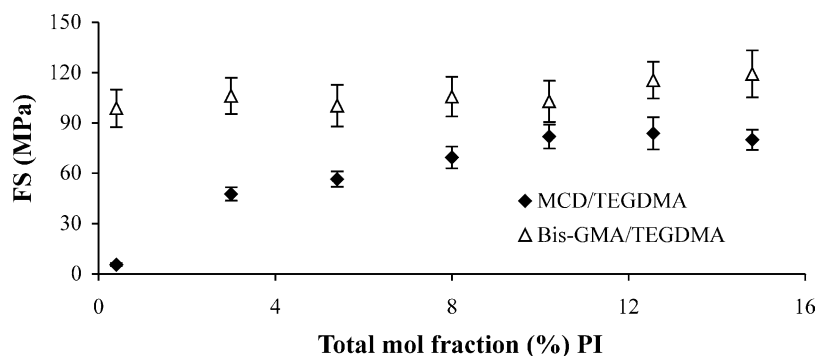


Figure 4 Flexural Strength (FS) of compositions versus total equimolar concentrations of polymerization initiators (PI) in MCD/TEGDMA and Bis-GMA/TEGDMA-based composites, ($n = 6$).

The degree of conversion (Fig. 6) in MCD and Bis-GMA-based composites with constant molar sum polymerization initiator compositions was found to vary significantly with the mol fraction (%) CQ ($p < 0.05$) at lower levels of CQ and not at higher CQ levels.

Discussion

From the TLC results, MCDs appeared to form stable inclusion complexes with CQ; no free CQ was observed along with the MCD/CQ complex. In contrast, some free 4E was observed on the TLC plate along with the MCD/4E complex, suggesting that, if all of the 4E was complexed when applied to the TLC plate, the MCD/4E complex was less stable

in the migrating toluene-methanol solvent mixture.

Calculated values of $\log P$ (octanol/water partition coefficient), which estimate the degree of hydrophobicity of molecules, indicated CQ as less hydrophobic ($\log P = 0.75$) than 4E ($\log P = 2.89$). ($\log P$ values were calculated by the online KowWin program developed by the Syracuse Research Corporation, North Syracuse, NY, USA). If other factors were assumed to be equal, CQ would be expected to form a less stable complex with MCD in a water environment than would 4E. However, this relationship was not seen in the TLC results where toluene plus methanol was the migrating solvent. With cyclodextrins, inclusion-complex formation and stability are not totally governed by classical hydrophobic interactions but by favorable enthalpy and entropy, among other factors that include

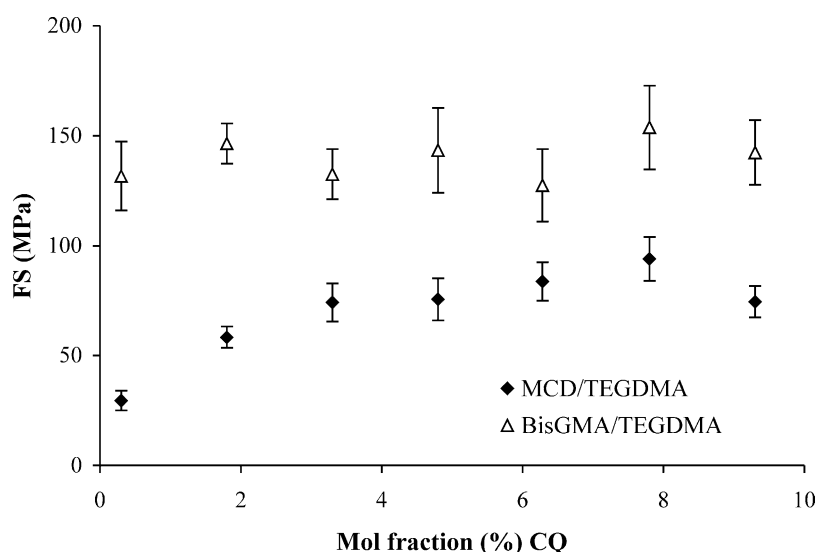


Figure 5 Flexural Strength (FS) of compositions versus mol fraction (%) CQ in MCD/TEGDMA and Bis-GMA/TEGDMA-based composites, ($n = 6$) with 'constant molar sum' polymerization initiators.

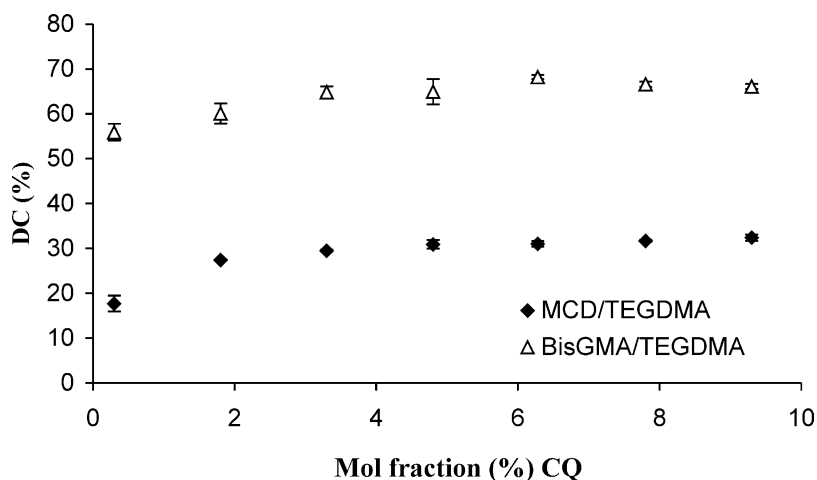


Figure 6 Degree of conversion (DC) of compositions versus mol fraction (%) CQ in MCD/TEGDMA and Bis-GMA/TEGDMA-based unfilled resin mixtures, ($n = 3$) with 'constant molar sum' polymerization initiators.

hydrogen bonding between the guest and the hydroxyl groups of cyclodextrin.² Perhaps hydrogen bonding of the CQ carbonyl oxygens with unreacted hydroxyl groups of MCD and/or a better 'fit' account for the apparently greater complex stability of CQ in comparison with 4E.

Although the R_f values of uncomplexed CQ and 4E differed considerably from those of their complexes with MCD, the difference in the R_f values of uncomplexed MCD and complexed MCD were small, which is usually the case with complexes of cyclodextrin derivatives.²⁸

The trend of flexural strength and degree of conversion values increasing with increasing equimolar polymerization initiator concentrations (MCD/HEMA data shown in Fig. 3) could be understood as analogous to steric hindrance of the polymerization initiators, to the extent of their complexation coefficient constants with the cavities of the MCD molecules. At higher polymerization initiator levels, there may have been sufficient amounts of uncomplexed initiator available to give better polymerization and higher conversion.

As seen in Fig. 4, the flexural strength values of MCD/TEGDMA-based composites with equimolar polymerization initiator compositions followed the same trend as MCD/HEMA-based composites (Fig. 3). At higher polymerization initiator levels (from 5.4 mol fraction (%) polymerization initiator and higher) increasing amounts of probably uncomplexed polymerization initiator did not produce a significant difference in the flexural strength values. In the Bis-GMA/TEGDMA-based composites the flexural strength values did not vary significantly with increasing equimolar polymerization initiator concentrations because Bis-GMA and

TEGDMA are monomers that cannot complex the polymerization initiators, and the smaller concentrations of CQ and 4E were adequate to initiate polymerization. Rueggeberg et al.²⁹ measured various properties of unfilled light-cured resin formulations containing 50 mol fractions each of Bis-GMA and TEGDMA but with differing polymerization initiator concentrations. Although their DC and some other properties changed with differing polymerization initiator concentrations, their biaxial flexural strength values for light-cured only groups remained unaffected.

MCD/TEGDMA-based composites with equimolar polymerization initiator compositions showed the maximum flexural strength of 83.8 ± 9.6 MPa at a polymerization initiator level of 6.28 mol fraction (%) CQ and 6.28 mol fraction (%) 4E (Fig. 4). This polymerization initiator level was chosen and kept constant (constant-molar-sum polymerization initiator), while proportions of CQ and 4E were varied in the MCD/TEGDMA and Bis-GMA/TEGDMA-based composites. For the MCD/TEGDMA-based composites, flexural strength varied with the amount of CQ and reached a maximum at 93.9 ± 10 MPa. This, however, was not observed with the Bis-GMA/TEGDMA-based composites (Fig. 5), indicating that complexation of polymerization initiator with MCD can affect the properties of composites.

For a given constant molar sum polymerization initiator concentration the degree of conversion in MCD/TEGDMA unfilled resin formulation was lower than that of the corresponding Bis-GMA-TEGDMA unfilled resin formulation. The degree of conversion increased by about 10% in the MCD-based resin formulations when the CQ was increased from 0.3 to 1.8 mol fraction (%) compared to an increase of

only about 4% in the case of Bis-GMA/TEGDMA-based resin formulation (Fig. 6). The larger increase in conversion for the MCD-based formulation could be attributed to relatively more uncomplexed initiator being available for polymerization at higher polymerization initiator levels. An increase in conversion with polymerization initiator concentration in contrast to flexural strength in light cured Bis-GMA/TEGDMA has also been observed by Rueggeberg et al.²⁹ It is interesting to note that although the average degree of conversion in MCD/TEGDMA-based resin formulations is about 30%, the average flexural strength of the corresponding composites is comparatively high (about 80 MPa). This could be due to the fact that MCDs, being bulky molecules with high molecular weights ranging from about 1750–2290 g/mol as sampled with MALDI-TOF-MS provide a stiff center core, which was able to form a solid polymeric network, even if only relatively few of the available double bonds on MCD had polymerized. Future studies of the network formation in MCD formulations by photo differential scanning calorimetry and by dynamic mechanical analysis are in progress.

Conclusions

CQ and 4E polymerization initiators have been shown to form inclusion complexes with methacrylated β -cyclodextrin molecules. While incorporated within MCDs, CQ and/or 4E may have been less effective in initiating polymerization of the MCD formulations. This could account for the relationships between the polymerization initiator concentrations, the flexural strengths, and the degrees of conversion in these MCD-based formulations. Hence, the proportions of polymerization initiators should be taken into consideration when formulating MCD-based composites in order to achieve the best properties for viable dental applications.

Disclaimer

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