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Correlation of the degree of conversion with the amount of elutable substances in nano-hybrid dental composites

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ABSTRACT

Objectives. This study's purpose was to measure and compare the degree of conversion (DC) and the amount of elutable substances from modern resin-based composites (RBCs) as function of polymerization time. One nano-hybrid RBC based on tricyclodecane-(TCD)-urethane (Venus® Diamond) and two conventionally formulated RBCs (TetricEvo Ceram®, Filtek™ Supreme XTE) were considered.

Method. DC ($n = 5$) was investigated in real time for 5 min by Fourier transform infrared spectroscopy (ATR-FTIR) in a filling depth of 2 mm at varied irradiation times (5, 10, 20, 40 s). After storing the specimens in ethanol/water for 7 d at 37 °C the eluates were analyzed by gas chromatography/mass spectrometry. Results were statistically analyzed using a multivariate analysis ($\alpha = 0.05$) an independent *t*-test ($p < 0.05$) and a Pearson correlation analysis.

Results. In all groups increasing curing time resulted in a significant increase in DC. For TetricEvo Ceram® a high significant inverse correlation was found between DC and the amount of eluted camphorquinone (CQ, Pearson correlation coefficient = −0.88), ethylene glycol dimethacrylate (EGDMA, −0.73), 4-N,N-dimethylaminobenzoic acid ethylester (DMABEE, −0.87), triethylene glycol dimethacrylate (TEGDMA, −0.68), Tinuvin P (−0.71) and bisphenol-A-polyetheylene glycol dimethacrylate (BisEMA, −0.84). Unexpectedly DC and the amount of eluted methyl acrylate (MAA) correlated directly (0.72). In the specimens of Venus® Diamond a significant inverse correlation was found between DC and the amount of eluted CQ (−0.69) and TEGDMA (−0.50), whereas in the specimen of Filtek™ Supreme XTE DC correlated with CQ (−0.96), EGDMA (−0.70), DMABEE (−0.87), TEGDMA (−0.92) and MAA (−0.92).

Significance. This study demonstrated a strong inverse correlation between DC and elutable substances in RBCs. Both evaluation methods emphasis the importance of an adequate polymerization (20, 40 s), since short curing-times (5, 10 s) resulted in lower DC and higher amount of eluted substances with toxic potential.

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1. Introduction

Methacrylate based dental restoratives are widely used in practice. For dental use it is very important that methacrylate based monomers have at least two double bonds like the Bowen monomer bisphenol-A-glycidyldimethacrylate (BisGMA) or triethylene glycol dimethacrylate (TEGDMA) to form branched polymers. In contrast to (co)monomers with one double bond which can only build linear polymer chains, (co)monomers with two or more double bonds can build a three-dimensional polymer network [1]. During the polymerization process new single bonds will be built from double bond. Apart from the formation of a three-dimensional network, the degree of conversion (DC) of the (co)monomers is also important in dentistry. The DC of (co)monomers to polymers has influence on the material properties as well as on the biocompatibility of a material (the lower the DC the higher the amount of uncured monomers and additives) [2].

The Fourier transform infrared spectroscopy (FTIR) is an established method to determine remaining double bonds [3]. It must be emphasized that the remaining double bonds are not directly related to the amount of remaining (co)monomers (Fig. 1). For measurements with FTIR both cases from Fig. 1a and b are equal. In the first case (Fig. 1a) both (co)monomers are bound to the polymer chain with a single bond resulting from opening a double bond, the second double bond remains unreacted. In the second case (Fig. 1b) the (co)monomer is not linked to a polymer chain, its two double bonds are unreacted. With FTIR in both cases two unreacted double bond can be measured.

The second case is of toxicological interest because it could be shown that these (co)monomers and other substances can be eluted from polymerized dental methacrylate based materials [4]. Bleaching can degrade the three-dimensional polymer network and therefore the amount of elutable monomers and additives increases [5]. In vitro studies have shown that some of the elutable methacrylate based monomers like BisGMA, TEGDMA, 2-hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA) as well as elutable additives like camphorquinone (CQ) can have estrogenic, mutagenic, teratogenic and genotoxic effects [6–9]. From in vivo studies it is known that during the metabolism of BisGMA, TEGDMA and HEMA epoxides like 2,3-epoxymethacrylic acid will be formed [10–12]. Furthermore elutable substances can cause allergic contact dermatitis and asthma in e.g. dentists and their personal [13].

It is discussed that the amount of elutable substances is depending on a lot of parameters like elution medium, polymerization time and the degree of cure. In earlier studies e.g. the relationship between leachability of polymerization initiator and degree of conversion of visible light-cured artificial

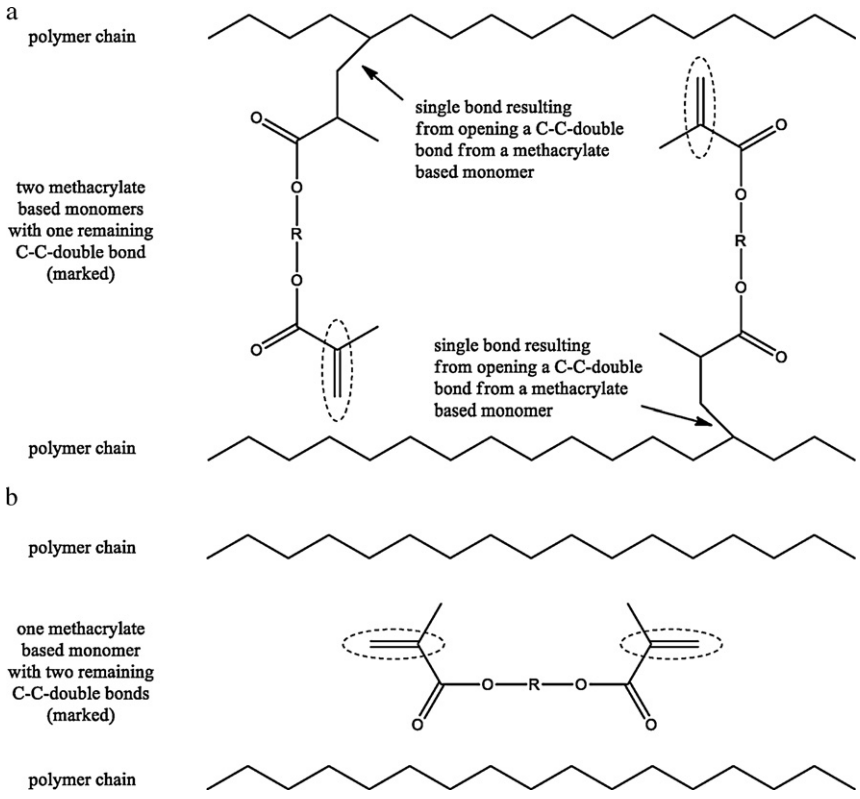

Fig. 1 – With Fourier transform infrared spectroscopy (FTIR) it is possible to detect the amount of unreacted C=C double bonds. In the case of methacrylate based monomers with two C=C double bonds it is not possible to distinguish between two cases with FTIR: (a) only one C=C double bond from the bivalent methacrylate based monomer was involved in the polymer chain formation, the other C=C double bond remains unreacted; (b) none of the C=C double bonds were involved in the polymer chain formation. Like illustrated, in both cases the amount of unreacted C=C double bonds is equal, but the consequences are not. In the second case it is possible that unreacted monomers can be eluted.

Table 1 – Materials, manufacturer, chemical composition of matrix and filler as well as filler content by weight (wt.) and volume (vol.) %.

Nano-hybrid RBCs	Manufacturer/batch	Resin matrix	Filler	Filler (w/v)
Tetric Evo Ceram®	Ivoclar-Vivadent, N30018	BisGMA, UDMA, DMDMA	Ba-glass, YbF_3, MO, PPF	76/54
Venus® Diamond	Heraeus Kulzer, 10036	TCD-DI-HEA, UDMA	Ba–Al–F-glass	81/64
Filtek™ Supreme XTE	3M-ESPE, N163566	BisGMA, BisEMA, UDMA, TEGDMA, PEGDMA	ZrO_2–SiO_2 cluster SiO_2 and ZrO_2 nanofiller	78.5/63.3

Data are provided by manufacturers; *Abbreviations*: BisEMA = bisphenol-A-polyetheylene glycol dimethacrylate; BisGMA = bisphenol-A-diglycidyl dimethacrylate; DMDMA = decamethylendimethacrylate; PEGDMA = poly(ethylene glycol) dimethacrylate; TEGDMA = triethyleneglycol dimethacrylate; TCD-DI-HEA = 2-propenoic acid, (octahydro-4,7 methano-1H-indene-5-diyl) bis(methyleneiminocarbonyloxy-2,1-ethanediyl) ester; UDMA = urethane dimethacrylate; MO = mixed oxide; PPF = pre-polymerized fillers.

resin systems were examined [14]. For our best knowledge up to now, no study from different modern resin-based composites (RBCs) is available comparing the DC and the amount of elutable substances from the same specimen in dependence of the polymerization time.

Therefore the aim of our study was to test if the degree of C=C double bond conversion measured with FTIR correlates with the amount of elutable substances from composites measured with gas chromatography/mass spectroscopy (GC/MS). Moreover the influence of polymerization time on the DC of C=C double bonds and on the amount of elutable substances was measured. The null hypotheses tested in our study were both, DC and the amount of elutable substances would not be influenced by the polymerization time and would not correlate.

2. Methods

All solvents and reagent products were obtained from Merck, Darmstadt, Germany and of highest purity available.

2.1. Preparation of samples

From the light-curable nano-hybrid dental restorative materials Tetric Evo Ceram® (Ivoclar Vivadent, Ellwangen, Germany), Venus® Diamond (Heraeus Kulzer, Hanau, Germany), and Filtek™ Supreme XTE (3M ESPE, Seefeld, Germany, Table 1) specimens of approximately 30 mg (thickness of 2 mm, diameter of 3 mm, color A3, with a resulting surface of 32.99 mm^2 and volume of the cylinder of 14.13 mm^3) were prepared under photolaboratory conditions. The specimens ($n = 5$) were covered with plastic matrix strips (Frasaco, Tettnang, Germany) and polymerized for 5, 10, 20 and 40 s by using an LED light source (Freelight2, 3M-ESPE, 1241 mW/cm^2). The curing unit was directly applied on samples' surface. The irradiance of the curing unit (1241 mW/cm^2) was measured by means of a calibrated fiber optic spectrally resolving radiometer equipped with an integrating sphere (S2000, Ocean Optics, USA).

After preparation specimens were incubated in a mixture of ethanol/water (3:1) at 37 °C for 7 d because after 7 d the major amount of elutable substances were eluted. Caffeine (CF; 0.1 mg/ml) was added to the eluates and each aliquot was analyzed by GC/MS.

2.2. Degree of cure

The measurements of the DC ($n = 5$) were made in real time with an FTIR-Spectrometer with an attenuated total reflectance (ATR) accessory (Nexus, Thermo Nicolet, Madison, USA). Therefore, the un-polymerized composite paste was put directly on the diamond ATR crystal in a mold 2 mm high and with a diameter of 3 mm. The mold was filled in one increment and the curing unit was applied directly on the sample surface. The FTIR spectra were recorded in real time for 5 min on the lower surface of the samples with irradiation for 5, 10, 20 and 40 s. The diameter of the measured surface was 800 μm, the wave number range of the spectrum was 4000–650 cm^{-1} and the FTIR spectra were recorded with two scans/s at a resolution of 8 cm^{-1}.

To determine the percentage of the remained unreacted double bonds, the DC was assessed as the variation of the absorbance intensities peak area ratio of the methacrylate carbon double bond (peak at 1634 cm^{-1}) and those of an internal standard (aromatic carbon double bond; peak at 1608 cm^{-1}) during polymerization, in relation to the uncured material [15]:

$$DC_{\text{Peak height}}(\%) = \left(1 - \frac{(1634\,cm^{-1}/1608\,cm^{-1})_{\text{Peak height after curing}}}{(1634\,cm^{-1}/1608\,cm^{-1})_{\text{Peak height before curing}}}\right) \times 100$$

The samples were then stored for 7 d in ethanol/water (3:1) at 37 °C and re-measured.

2.3. GC/MS analysis

The analysis of the eluates ($n = 5$) was performed on a Finnigan Trace GC ultra gas chromatograph connected to a DSQ mass spectrometer (Thermo Electron, Dreieich, Germany). A FactorFour® capillary column (length 25 m, inner diameter 0.25 mm, coating 0.25 μm; Varian, Darmstadt, Germany) was used as capillary column for GC. The GC oven was heated from 50 °C (2 min isotherm) to 300 °C (5 min isotherm) with a rate of 10 °C/min and 1 μl of the solution was injected with a split of 1:30. Helium was used as carrier gas at a constant flow rate of 1 ml/min. The temperature of the split–splitless injector as well as of the direct coupling to the mass spectrometer was 250 °C. The MS was operated in electron ionization mode

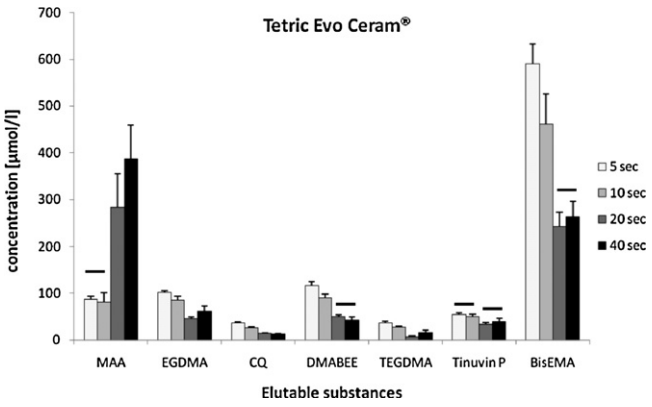

Fig. 2 – Degree of conversion in % of C=C double bonds of the methacryate based monomers measured with Fourier transform infrared spectroscopy (FTIR), in depend on the polymerization time for different dental composites.

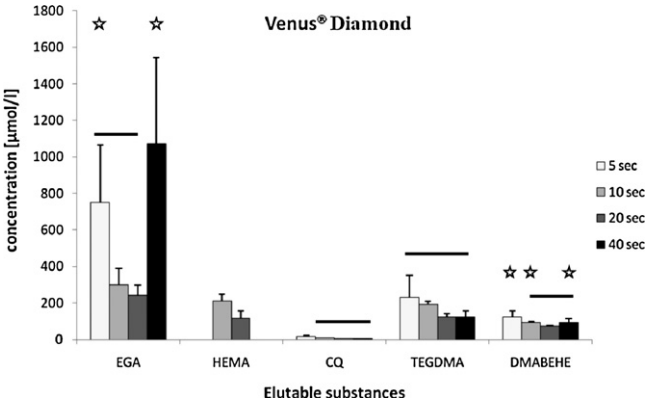

Fig. 3 – Elutable substances from polymerized specimens ($n = 5$) from Tetric Evo Ceram® after 7 d in ethanol/water as elution medium. Lines indicate statistically homogenous subgroups. *Abbreviations*: MAA = methacrylic acid; EGDMA = ethylene glycol dimethacrylate; CQ = camphorquinone; DMABEE = 4-N,N-dimethylaminobenzoic acid ethyl ester; TEGDMA = triethylene glycol dimethacrylate; BisEMA = bisphenol-A-polyetheylene glycol dimethacrylate.

(EI, 70 eV), ion source temperature was 200 °C; only positive ions were scanned. Scan ran over the range *m/z* 50–500 at a scan rate of 1 scan/s for scans operated in full scan mode to qualify analytes. The results were referred to an internal CF standard (0.1 mg/ml CF = 100%), which allows to determine the relative quantities of substances released from various resin-based materials (no further calibration curves were used). All eluates were analyzed five times. The integration of the chromatograms was carried out over the base peak or other characteristic mass peaks of the compounds, and the results were normalized by means of the internal CF standard. Identification of the various substances was achieved by comparison of their mass spectra with those of reference compounds, the NIST/EPA library, literature data and/or by chemical analysis of their fragmentation patterns [16].

2.4. *Calculations and statistics*

The results are presented as means ± standard error of mean (SEM). The statistical significance ($p < 0.05$) of the differences between the experimental groups was tested using the *t*-test, corrected according to Bonferroni-Holm [17]. A Pearson correlation analysis between DC and amount of eluted compounds was performed within each resin-based composite (SPSS Inc., Chicago, IL, USA, Version 19.0).

3. Results

3.1. *Tetric Evo Ceram®-specimens*

The DC is statistical significant increasing from 38.2 ± 2.0% after 5 s of polymerization time to 47.4 ± 2.1% after 40 s of polymerization time (Fig. 2).

A high significant inverse correlation was found between the DC and the amount of eluted CQ (Pearson correlation coefficient = −0.88), EGDMA (−0.73), DMABEE (−0.87), TEGDMA (−0.68), Tinuvin P (−0.71) and BisEMA (−0.84). The DC and the amount of eluted MAA correlated as well (0.72).

The amount of CQ in the elution medium was significantly ($p < 0.05$) decreasing from 35.8 ± 2.6 µmol/l after 5 s of polymerization time to 12.1 ± 1.9 µmol/l after 40 s of polymerization time (Fig. 3). No statistically significant different ($p > 0.05$) amount of CQ in the elution medium was measured after 20 s or 40 s of polymerization time (14.2 ± 1.2 vs. 12.1 ± 1.9 µmol/l) (Fig. 3).

The amount of bisphenol-A-polyetheylene glycol dimethacrylate (BisEMA) in the elution medium was significantly ($p < 0.05$) decreasing from 590.8 ± 42.1 µmol/l after 5 s of polymerization time to 263.5 ± 31.9 µmol/l after 40 s of polymerization time (Fig. 3). No statistical significant different ($p > 0.05$) amount of BisEMA in the elution medium was measured after 20 s or 40 s of polymerization time (243.0 ± 30.8 vs. 263.5 ± 31.9 µmol/l) (Fig. 3).

3.2. *Venus® Diamond-specimens*

The DC is statistical significant increasing from 30.6 ± 2.1% after 5 s of polymerization time to 46.8 ± 1.2% after 40 s of polymerization time (Fig. 2).

A significant inverse correlation was found between the DC and the amount of eluted CQ (−0.69) and TEGDMA (−0.50).

The amount of CQ in the elution medium was significantly ($p < 0.05$) decreasing from 17.0 ± 5.0 µmol/l after 5 s of polymerization time to 6.6 ± 2.1 µmol/l after 40 s of polymerization time (Fig. 3). No statistical significant different ($p > 0.05$) amount of CQ in the elution medium was measured after 10 s, 20 s or 40 s of polymerization time (10.3 ± 2.0 vs. 6.1 ± 0.5 vs. 6.6 ± 2.1 µmol/l) (Fig. 4).

The amount of TEGDMA in the elution medium was decreasing from 229.6 ± 123.6 µmol/l after 5 s of polymerization time to 123.0 ± 34.7 µmol/l after 40 s of polymerization time (Fig. 4).

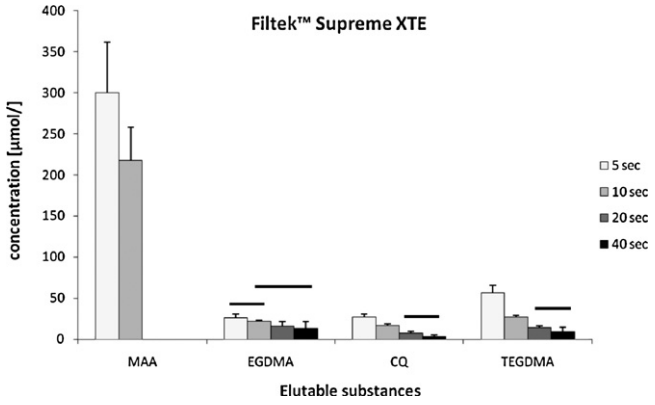

Fig. 4 – Elutable substances from polymerized specimens ($n = 5$) from Venus® Diamond after 7 d in ethanol/water as elution medium. Lines and stars indicate statistically homogenous subgroups. *Abbreviations*: EGA = ethylene glycol acrylate; HEMA = 2-hydroxyethyl methacrylate; CQ = camphorquinone; TEGDMA = triethylene glycol dimethacrylate; DMABEHE = 4-dimethylaminobenzoic acid 2-ethylhexyl ester.

3.3. *Filtek™ Supreme XTE-specimens*

The DC is statistical significant increasing from 22.4 ± 1.9% after 5 s of polymerization time to 46.5 ± 2.6% after 40 s of polymerization time (Fig. 2).

A high significant inverse correlation was found between the DC and the amount of eluted CQ (−0.96), EGDMA (−0.70), TEGDMA (−0.92) and MAA (−0.92).

The amount of CQ in the elution medium was significantly ($p < 0.05$) decreasing from 26.4 ± 4.3 µmol/l after 5 s of polymerization time to 3.7 ± 1.1 µmol/l after 40 s of polymerization time (Fig. 5). No statistical significant different ($p > 0.05$) amount of CQ in the elution medium was measured after 20 s or 40 s of polymerization time (7.6 ± 1.9 vs. 3.7 ± 1.1 µmol/l) (Fig. 5).

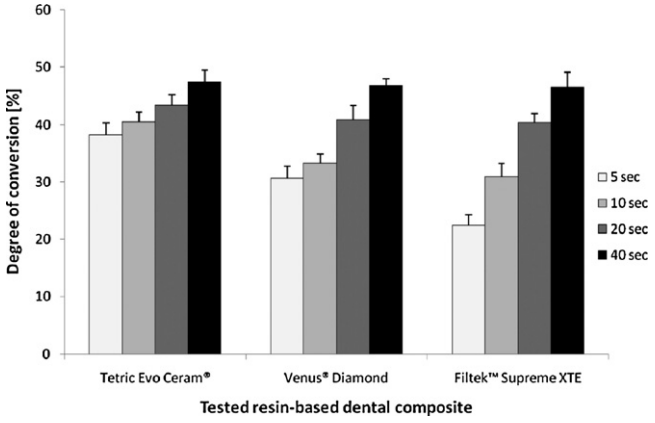

Fig. 5 – Elutable substances from polymerized specimens ($n = 5$) from Filtek™ Supreme XTE after 7 d in ethanol/water as elution medium. Lines indicate statistically homogenous subgroups. *Abbreviations*: MAA = methacrylic acid; EGDMA = ethylene glycol dimethacrylate; CQ = camphorquinone; TEGDMA = triethylene glycol dimethacrylate.

The amount of TEGDMA in the elution medium was significantly ($p < 0.05$) decreasing from 56.3 ± 9.3 µmol/l after 5 s of polymerization time to 11.3 ± 2.0 µmol/l after 40 s of polymerization time (Fig. 4). No statistical significant different ($p > 0.05$) amount of CQ in the elution medium was measured after 20 s or 40 s of polymerization time (13.7 ± 2.1 vs. 11.3 ± 2.0 µmol/l) (Fig. 5).

4. Discussion

Apart from esthetical levels and mechanical properties, the biocompatibility of dental restoratives is of great importance as well. Our null hypotheses tested in this study that, DC and the amount of elutable substances would not be influenced by the polymerization time and would not correlate is rejected. It has been demonstrated that substances released from dental composites can enter the organism [11]. Special attention was given to studies addressing the genotoxic potential of these materials, e.g. DNA strand break induction [9,18]. One reason for the release of substances from polymerized dental composites is the low DC of methacrylate based monomers. The DC of C=C double bond is generally only in the range of 55–65% [19]. However, this does not mean that 35–45% of the monomers are uncured. It means that 35–45% of the C=C double bonds are uncured. It is possible, that monomers like TEGDMA which have two C=C double bonds can react with one of their C=C double bonds, the other remains unreacted (Fig. 1a). In this case the monomer is fixed in the polymer network and it is unlikely that the monomer can be eluted undestroyed. Modern nano-hybrid RBCs, promoted as materials with improved esthetic and mechanical properties, show a trend in changing not only the filler systems but also the monomer–matrix formulations. Besides traditional monomers like BisGMA, BisEMA, urethane dimethacrylate (UDMA) or TEGDMA, a series of new monomers are either completely replacing the traditional monomers or are only merged into a traditional monomer formulation, thus rising questions with regard to their polymerization behavior. As an example, the TCD-urethane (=tricyclodecane urethane) was incorporated in the tested material Venus® Diamond [20] being a methacrylic acid derivatives, prepared by reaction of hydroxyalkyl (meth)acrylic acid esters with diisocyanates and subsequent reaction with polyols. Due to the low-viscosity of TCD-urethane monomers, no further diluents are need, reducing thus the polymerization shrinkage in comparison to BisGMA-based RBCs [21] but also when compared to the low shrinkage silorane-based RBC [22]. Being an acrylic acid ester, the monomer is described to have a high reactivity, achieving consequently higher degrees of conversion as traditional monomers and also a high biocompatibility [20] which might, besides the hydrophobic nature of the monomer, contribute to a reduction of water uptake when compare to the more hydrophilic BisGMA containing resin-based composites. This statement could however only partly be confirmed by our data, since the DC measured 5 min after photoinitiation shows significant lower values for Venus® Diamond at low polymerization times (5, 10 s) when compared to Tetric Evo Ceram®

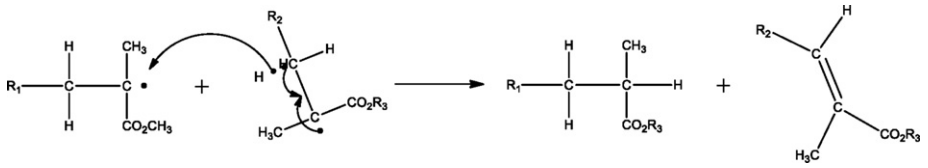

Fig. 6 – For termination the polymerization process of methacrylates disproportionation is important. In this case, one molecule abstracts a hydrogen atom from the other molecule. This molecule forms a C=C double bond. The C=C double bond can be detected by Fourier transform infrared spectroscopy and leads to false low degree of conversion values.

but significantly higher values when compared to Filtek™ Supreme XTE. Only a high polymerization time of 40 s was able to level these differences. Though, a very good mechanical stability was measured for Venus® Diamond also after aging [23,24] demonstrating a good chemical stability, probably as a result of the big molecular size of the TCD-urethane and the absence of diluting agents. As for the material with the highest measured DC, Tetric Evo Ceram®, the mechanical stability was shown to be significantly influenced by aging [25] a behavior that could rather be related to the presence of pre-polymerized fillers, since the bond between pre-polymerized fillers and the polymer matrix is regarded as a weak spot.

To elute most of unpolymerized (co)monomers and additives water or artificial saliva proved to be less effective than ethanol/water 3:1 which was recommended by the United States Food and Drug Administration (US FDA) as a food/oral simulating liquid of clinical relevance [26,27]. In the elution medium of Venus® Diamond HEMA was found. It is possible that HEMA is an impurity from the TCD-urethane synthesis from hydroxyalcyl methacrylates or it was formed during the polymerization process [28].

It could be shown that the amount of CQ in the eluates was decreasing for all tested materials with the polymerization time. This is in good agreement with the understanding of the polymerization process that means that a longer curing time leads to the formation of more activated CQ [29]. More initiating radicals lead to a higher rate of starting the chain growth and create new radicals for further polymerization [30]. The more the number of radicals the higher the probability that two radicals react with each other and the polymerization is stopped. For termination the polymerization process of methacrylates disproportionation plays an important role (Fig. 6) [31]. It should be mentioned that disproportionation leads to the formation of a new C=C double bond which can be measured with FTIR spectroscopy but this C=C double bond does not result from unreacted monomers (Fig. 6). It results from formation during termination of the polymerization process and can therefore lead to false lower DC rates.

The understanding of the influence of polymerization variables is important for the implications for polymer process engineering leading to polymers of well defined properties [32]. The mechanical properties of a polymer depend on chemical as well as on physical aspects like the reaction kinetics (first-order or higher kinetics). The mechanical behavior of a polymer is strongly influenced by the crystallinity of the polymer network [32] as well as the formation of a three dimensional network [33]. The introduction of just one methylene group as an alkyl side chain changes the physical properties e.g. by influencing the chain length [34]. Furthermore the polymerization process and therefore the chain length depends on e.g. the aggregate phase (solid state or fluid state) in which the polymerization occurs [35]. Additionally some monomers (like silorane) can polymerize by ring opening reaction instead of breaking a C=C double bond, also influencing the polymerization process and correlating with the mechanical properties [36].

Lovell et al. [37] demonstrated clearly that small changes in conversion have a pronounced effect on properties, especially modulus.

For Tetric Evo Ceram® it was demonstrated that the amount of elutable BisEMA from polymerized specimen is higher at a polymerization time of 5–10 s compared to 20 or 40 s (Fig. 2). Comparable results were obtained for TEGDMA from specimen from polymerized Filtek™ Supreme XTE.

In eluates from specimen from polymerized Tetric Evo Ceram® it was found that the amount of elutable MAA is increasing with the increase of polymerization time (87.1 μmol/l after 5 s polymerization time compared to 386.5 μmol/l after 40 s). MAA was not detectable with GC/MS in the uncured paste which was dissolved in methanol (data not shown). Moreover MAA was found in the eluates from specimen from polymerized Tetric Evo Ceram® even after 1 d of elution (data not shown). Therefore it cannot be excluded that MAA was formed during the polymerization process (e.g. by chemical reactions or rearrangements in the complex matrix of a composite), or by (possible photo induced) degradation during the process of elution process. The light influence on the polymerization process was studied by He et al. [38]. They found that intra- and intermolecular reactions during the polymerization can influence the polymer network formation. These reactions may lead to reaction products like MAA.

5. Conclusions

All three nano-hybrid composites showed a strong inverse correlation between DC and elutable substances in RBCs. Both evaluation methods emphasize the importance of an adequate polymerization (20 s, 40 s), since short curing-times (5 s, 10 s) resulted in lower DC and in the majority of cases in a higher amount of eluted substances with toxic potential.

Only in the specimen of Tetric Evo Ceram® it was shown that higher amount of MAA was elutable after 40 s of polymerization time compared with 5 s. This can be explained by the formation of MAA as reaction product.

It could be demonstrated that between 20 s and 40 s of polymerization time no significant differences in the DC or amount of elutable substances were found. Especially in the treatment of child a lower polymerization time can lead to better compliance.

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