Vinyl carbonate photopolymers with improved mechanical properties for biomedical applications

Andreas Mautner, Barbara Steinbauer, Günter Russmüller, Roman Lieber, Thomas Koch, Jürgen Stampfl & Robert Liska

To cite this article: Andreas Mautner, Barbara Steinbauer, Günter Russmüller, Roman Lieber, Thomas Koch, Jürgen Stampfl & Robert Liska (2016) Vinyl carbonate photopolymers with improved mechanical properties for biomedical applications, Designed Monomers and Polymers, 19:5, 437-444, DOI: 10.1080/15685551.2016.1169378

To link to this article: http://dx.doi.org/10.1080/15685551.2016.1169378

Published online: 11 Apr 2016.

Submit your article to this journal

Article views: 145

View related articles

View Crossmark data
Vinyl carbonate photopolymers with improved mechanical properties for biomedical applications

Andreas Mautner\textsuperscript{a,b}, Barbara Steinbauer\textsuperscript{b}, Günter Russmüller\textsuperscript{c}, Roman Lieber\textsuperscript{d}, Thomas Koch\textsuperscript{e}, Jürgen Stampfle\textsuperscript{e} and Robert Liska\textsuperscript{b}

\textsuperscript{a}Institute for Materials Chemistry & Research, Polymer & Composite Engineering (PaCe) Group, University of Vienna, Vienna, Austria; \textsuperscript{b}Institute for Applied Synthetic Chemistry, Vienna University of Technology, Vienna, Austria; \textsuperscript{c}Department of Cranio-Maxillofacial and Oral Surgery, Medical University of Vienna, Vienna, Austria; \textsuperscript{d}Institute of Biomedical Research, Medical University Vienna, Vienna, Austria; \textsuperscript{e}Institute of Materials Science and Technology, Vienna University of Technology, Vienna, Austria

\textbf{ABSTRACT}

Recently, vinyl carbonates have been demonstrated to be a versatile alternative to acrylates and methacrylates in biomedical applications as they exhibit photoreactivity and mechanical properties on a level or even above (meth)acrylates. Furthermore, much lower cytotoxicity as well as degradation via a surface erosion mechanism qualify them for medical use. However, it is highly desirable to improve the mechanical properties of vinyl carbonates to reach the performance of PLA. Thus, the main focus of this study lies on designing vinyl carbonates with suitable functional groups that are capable of augmenting mechanical properties of vinyl carbonates, e.g. cyclic structures or urethane groups, and implementing them into the vinyl carbonate structures. Resulting monomers were tested regarding their photoreactivity and cytotoxicity. Furthermore, cured specimens were investigated concerning their mechanical properties. In addition, the thiol-ene reaction was utilized to further improve photoreactivity. The new vinyl carbonates exhibit excellent biocompatibility and photoreactivity that can be significantly enhanced through the addition of thiols onto the level of highly photoreactive acrylates. Most importantly, results showed that the mechanical properties could be improved onto the level of PLA and above.

\textbf{1. Introduction}

Treatment of injuries of the skeletal system in human bodies and thus intervention in a complex and sensitive biological system is one of the major challenges in tissue engineering with a number of prerequisites that have to be fulfilled to make this intervention successful.[1] Biocompatibility is obviously mandatory, degradability is eligible, whereby degradation products must not be toxic, and the mechanical properties of the biomaterial should match the ones of the tissue to be replaced.[1,2] (Meth)acrylates for non-resorbable fixation techniques like bone cements or resorbable polycondensates such as poly(lactic acid) (PLA) are currently state-of-the-art materials for the treatment of injured bone.[3,4] Unfortunately, for both types of materials there are limitations present regarding their utility.

Methacrylate bone cements, successfully applied in many surgical applications,[5–8] were already introduced in 1960 by Sir John Charnley.[9] However, serious drawbacks such as thermal necrosis of bone tissue due to the exothermic polymerization reaction, chemical necrosis caused by the release of unreacted monomer, large volumetric shrinkage and certain brittleness and weakness limit their usability.[10–15] Processing of bone cements into custom-made scaffolds e.g. by means of additive manufacturing technologies (AMT) is not possible as well. To circumvent these drawbacks, switching the structure from thermoplastics to thermoset networks was proposed by making use of dimethacrylates.[16–22] These materials usually consist of a urethane dimethacrylate (UDMA) and bisphenol A diglycidyl methacrylate (BisGMA) together with a viscosity modifier (D3MA). Advantageous of this approach is the significantly lower polymerization exotherm compared to MMA resulting in considerably lower peak temperatures reducing the chance to suffer a necrosis. Furthermore, these compounds exhibit decreased volumetric shrinkage along significantly increased stiffness. [17,23] Responsible for improved mechanical properties are the aromatic ring system and the urethane groups of these resins, whereas due to the difunctionality,
the amount of unreacted monomer is reduced.[24,25] Improved handling properties (e.g., possibility to manufacture custom-made scaffolds by means of AMT) are further advantages. However, methacrylates lack biodegradability and can be irritant and cytotoxic.[26,27] Degradable biopolymers are also applied in bone regeneration therapies,[3] whereby synthetically produced biopolymers, e.g., PLA or PCL, offer predictable degradation behavior and mechanical properties as well as low risk of immunoresponse or infections.[28] However, as PLA and PCL are thermoplastics, their utility is inherently limited.[1] To enable the manufacture of custom-made shapes, biopolymers were developed that are produced or further utilized via photopolymerization techniques, exemplarily modification with photopolymerizable groups, e.g., (meth)acrylate groups.[29,30] However, toxicity issues [26,27] of (meth)acrylates are present also for these materials. In addition, upon degradation poly[(meth)acrylic acid] is among the degradation products,[31,32] which, in combination with the predominant autocatalytic bulk erosion mechanism of the biopolymer,[33,34] constitute large amounts of free acid of high Mw that can lead to inflammatory response and ultimately fracture due to implant failure.[35,36] Consequently, a different degradation mechanism with non-problematic degradation products together with reduced cytotoxicity and irritancy is desirable. Low-cytotoxic and non-irritant vinyl carbonates (VCs) have recently been introduced as versatile alternative to (meth)acrylates in bone tissue engineering applications.[37,38] The degradation products of poly(vinyl carbonates) are nontoxic poly(vinyl alcohol), already utilized in biomedical applications and approved by the US Food and Drug Administration (FDA), along with low Mw dialcohols that can be easily conveyed away from the implant site. However, the mechanical properties of these polymers do not yet challenge state-of-the-art PLA in terms of mechanical performance.[37,38]

We here present two new vinyl carbonate compounds that are proposed to exhibit increased mechanical properties as compared to conventional vinyl carbonates. The aim was to identify suitable functional groups that are capable of improving the mechanical properties of poly(vinyl carbonates) to gain degradable, low-cytotoxic materials suitable for the application as bone replacement materials. Standard protocols for the synthesis of vinyl carbonates were utilized together with new precursor molecules, resulting in novel compounds that were tested regarding their cytotoxicity and photoreactivity. Cured specimens produced of these monomers were analyzed for their mechanical properties. Finally, the impact of the thiol-ene reaction onto the photoreactivity of the new vinyl carbonates was studied, as thiols were recently shown [39] to be able to boost the photoreactivity of vinyl carbonates onto the level of acrylates.

Figure 1. Structures of monomers of dental methacrylate formulation $MA = UDMA : Bis-GMA : D3MA (1:1:1 \text{ M})$.

2. Experimental

2.1. Materials

2,2,4-Trimethyl-1,6-diisocyanatohexane (TMDI; Sigma), tin(II) 2-ethylhexanoate (Sigma), vinyl chloroformate (VCF, Aldrich), and dianhydro-D-glucitol (Aldrich) were used as received. Ethylene glycol and all other solvents were redistilled before use. Pentaerythritol tetra-3-mercaptopropionate (TT) was kindly donated by Bruno Bock. 2-Hydroxy-1-[4-(2-Hydroxyethoxy)phenyl]-2-methyl-1-propanone (Irgacure 2959) was received as a gift from BASF. O,O′-(7,7,9-Trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl) dimethacrylate (urethane dimethacrylate, UDMA), [2-Hydroxy-3-[4-[2-[4-[2-hydroxy-3-(2-methylprop-2-enoyloxy)prop-oxy]phenyl]prop-2-enyl]phenoxy]propyl] 2-methyl-prop-2-enoate (bisphenol A diglycidyl methacrylate, Bis-GMA), and 1,10-decanediol dimethacrylate (D3MA) were kindly supplied by Ivoclar Vivadent. A 1:1:1 equimolar formulation (Figure 1) of UDMA, Bis-GMA, and D3MA was used as reference material referred to as ‘MA.’ Tetra(ethylene glycol) dimethacrylate (TTeGDMA, ≥ 90%) was obtained from UCB.

2.2. Synthesis of the monomers

2.2.1. Synthesis of bis(2-(((vinlyloxy)carbonyl)oxy)ethyl) (2,2,4-trimethylhexane-1,6-diyldicarbamate (UDVC)

For the synthesis of UDVC, first the precursor bis(2-hydroxyethyl) (2,2,4-trimethylhexane-1,6-diyldicarbamate (UD) was synthesized. Therefore, freshly distilled ethylene glycol (55.91 g, 900 mmol) was dissolved under argon atmosphere in 345 mL of dry dioxane. Tin(II) 2-ethylhexanoate (100 mg) was added and the solution heated to 75 °C. Afterwards, freshly distilled 2,2,4-trimethyl-1,6-diisocyanatohexane (9.47 g, 45 mmol) was dissolved in 10 mL dioxane and added to the solution via a dropping funnel. The reaction was heated for 24 h at 75 °C. Afterwards, dioxane was...
evaporated and the excess of ethylene glycol removed by distillation to give 14.3 g of bis(2-hydroxyethyl) (2,2,4-trimethylhexane-1,6-diyldicarbamate (urethane diol, UD). The crude product was purified by column chromatography using CDCl3 as a solvent (grade of deuteration of at least 99.5%). The solvent signal was used as a reference.

A solution of the precursor UD (2.11 g, 6.3 mmol) and pyridine (1.1 g, 13.1 mmol) in CH2Cl2 (16 mL) was cooled to 0 °C and purged with argon. Vinyl chloroformate (1.35 g, 12.7 mmol) was added dropwise over a period of 10 min using a syringe. After stirring for 30 min, the reaction was allowed to warm up to room temperature and stirred for additional 24 h. The reaction was hydrolyzed with 1 N HCl solution (15 mL), the organic layer dried over Na2SO4, and filtered. After evaporation of the volatile compounds, the crude product was purified by column chromatography to give UDVC as colorless, highly viscous liquid.

Yield: 43%. TLC (PE:EE = 1:1): Rf = 0.59; 1H-NMR (200 MHz, CDCl3): δ (ppm) = 7.08 (dd, 2H, J1 = 13.8 Hz, J2 = 6.3 Hz, CH=CH–), 4.94 (dd, 2H, J = 13.8 Hz, J2 = 2.0 Hz, CH=O–O–trans), 4.60 (dd, 2H, J1 = 6.2 Hz, J2 = 2.1 Hz, CH2–CH=O–cis), 4.37 (s, 8H, –O–CO–CH2–CH2–O–) 3.22–2.90 (m, 4H, –nH–CH2–), 1.50–0.89 (m, 14H, –C(CH3)2–CH2–CH(CH3)–CH2–); 13C-nMR (50 MHz, CDCl3): δ (ppm) = 156.0 (–O–CO–nH–), 152.5 (CH=CH–O–CO–), 142.5 (CH=O–O–trans), 98.1 (CH=CH–O–), 66.8 (–CO–O–CH2–CH2–O–CO–NH–), 62.2 (–CO–O–CH2–CH2–O–CO–NH–), 48.6 (–O–CO–NH–CH2–C(=CH2)–), 46.4 (–C(CH3)2–CH2–CH(CH3)–CH2–), 39.4 (–C(CH3)2–CH2–CH(CH3)–CH2–), 37.3 (–C(CH3)2–CH2–CH(CH3)–CH2–), 27.4 (–C(CH3)2–CH2–CH(CH3)–CH2–), 25.1 (–C(CH3)2–CH2–CH(CH3)–CH2–), 22.3 (–C(CH3)2–CH2–CH(CH3)–CH2–); elemental analysis: C21H34N2O10: calculated: C: 53.16%, H: 7.22%, N: 5.90%, O: 44.72%; found: C: 50.39%, H: 4.73%, O: 44.88%.

### 2.2.2. Synthesis of hexahydrofuro[3,2-b]furan-3,6-diyldivinyl dicarbonate (GDVC)

A solution of dianhydro-D-glucitol (1.53 g, 10.4 mmol) and pyridine (1.73 g, 21.9 mmol) in CH2Cl2 (16 mL) was cooled to 0 °C and purged with argon. Vinyl chloroformate (1.92 g, 21.1 mmol) was added dropwise over a period of 10 min using a syringe. After stirring for 30 min, the reaction was allowed to warm up to room temperature and stirred for additional 24 h. The reaction was hydrolyzed with 1 N HCl solution (25 mL), the organic layer dried over Na2SO4, and filtered. After evaporation of the volatile compounds, the crude product was purified by column chromatography to give GDVC as white solid.

Yield: 95%. 1H-NMR (200 MHz, CDCl3): δ (ppm) = 5.64–5.26 (m, 2H, –NH–), 3.70 (m, 4H, –CH3–OH), 3.59 (br s, 2H, OH), 3.18–2.76 (m, 4H, –NH–CH2–), 1.73–0.74 (m, 14H, –C(CH3)2–CH2–CH(CH3)–CH2–), 39.4 (–C(CH3)2–CH2–CH(CH3)–CH2–CH2–); 13C-nMR (50 MHz, CDCl3): δ (ppm) = 151.9 (CH=CH–O–CO–), 142.4 (CH=CH–O–), 98.4 (CH2 = CH–O–), 85.79 (–CH–O–), 81.5 & 80.9 (VC–CH–), 73.1 & 70.6 (–CH–O–); elemental analysis: C12H14O6 calculated: C: 50.35%, H: 4.93%, O: 44.72%, found: C: 50.39%, H: 4.73%, O: 44.88%.

### 2.2.3. Synthesis of butane diol divinyl carbonate (4VC)

A solution of 3.91 g of 1,4-butanediol (43.4 mmol) and 7.56 g of pyridine (95.6 mmol) in CH2Cl2 (25 mL) was cooled to 0 °C and purged with argon. 9.25 g of vinyl chloroformate (86.9 mmol) was added dropwise over a period of 10 min using a syringe. After stirring for 30 min, the reaction was allowed to warm up to room temperature and stirred for additional 24 h. The reaction was hydrolyzed with 1 N HCl solution (25 mL), the organic layer dried over Na2SO4, and filtered. After evaporation of the volatile compounds the crude product was purified by column chromatography to give 4VC as colorless liquid.

Yield: 96%. TLC (PE:EE = 3:1): Rf = 0.77; 1H-NMR (200 MHz, CDCl3): δ (ppm) = 7.08 (dd, 2H, J1 = 13.9 Hz, J2 = 6.3 Hz, CH=CH–), 4.92 (dd, 2H, J = 13.9 Hz, J2 = 2.2 Hz, CH=CH–O–trans), 4.58 (dd, 2H, J1 = 6.3 Hz, J2 = 2.0 Hz, CH=CH–O–cis), 4.24 (m, 4H, –CH2–VC), 1.82 (m, 4H, –CH2–CH2–).

### 2.3. Characterization of the monomers

NMR spectra (200 MHz for 1H and 50 MHz for 13C, respectively) were recorded with a Bruker AC 200 spectrometer, using CDCl3 as a solvent (grade of deuteration of at least 99.5%). The solvent signal was used as a reference. Elemental microanalysis was carried out with an EA 1108 CHN–S–O analyzer from Carlo Erba at the microanalytical laboratory of the Institute for Physical Chemistry at the University of Vienna.

#### 2.3.1. Cell culture experiments

For Alamar Blue assays, 1 M solutions of the new vinyl esters in DMSO (HYBRI-MAX®, Sigma) were prepared. Each solution was diluted with Dulbecco's Modified Eagles Medium (DMEM, Sigma), 10% fetal calf serum (FCS, PAA), 100 U ml−1 Penicillin (Invitrogen), and 100 μg ml−1 streptomycin (Invitrogen), to acquire solutions with seven different concentrations of the monomers (10, 5, 2.5, 1.25, 0.63, 0.31, and 0.16 mM). Osteoblasts cells [strain C57BL/6 of mus musculus (ATCC Catalog no. CRL-2593, MC3T3-E1, Subclone 4)] were cultured in 100 μl DMEM medium supplemented with 10% FCS, 100 U ml−1 penicillin and 100 μg ml−1 streptomycin, in 96-well plates at a density of 6.4 × 103 cells per well for 24 h in humidified air (95% relative humidity) with 5% CO2 at 37 °C. The next day, the
cells were treated with 100 μL of the different concentrations of the test substances for 5 days in triplicates. 10 μL of resazurin were added and the cells incubated for 4 h at 37 °C. The fluorescence intensity was measured for excitation at 570 nm and emission at 585 nm and compared to untreated cells (cells + medium). As control groups cells treated with 1% DMSO solution, a blank value, and PBS buffer were used. The results represent the mean with standard deviations of triplicate assays (n = 3). The concentration at which more than 50% of cells survived (LC50) was used to compare results.

### 2.3.2. Photo-DSC

Photo-DSC measurements were conducted on a Netzsch Photo-DSC 204 F1 Phoenix. The photoreactivity was analyzed with formulations containing 2 wt.% of 2959 as photoinitiator (PI). For each measurement accurately 10 ± 1 mg of the respective formulation was weighed into an aluminum pan; an empty pan was used as reference. Samples were purged with nitrogen and thermostatted at 25 or 70 °C for 3 min and subsequently irradiated (filtered UV light (280–500 nm), double light guide (OmniCureVR 2000), light intensity of 3 W cm−2) from a distance of 25 mm calculated starting from the slope of the unloading curve's tangent at the maximum force, with u, being the Poisson's ratio of the sample (u = 0.35), v, the Poisson's ratio of the indenter tip (for diamond u = 0.07), E, [MPa] the reduced Young's modulus of the indentation contact, E, = 1140 GPa for diamond, S [N m−1] the contact strength (defined as the resistance of two particles against their mutual displacement), and A, [m2] the projected area of the imprint.

\[
E_i = \frac{1 - (v_i)^2}{1 - (u_i)^2} \left( \frac{1}{E_i} - \frac{1}{E} \right)
\]

(3)

The polymerization rate \( R_p \) can be calculated from the specific heat flow at maximum (= the height of the peak at the peak maximum \( h \) [mW mg⁻¹]), the density (ρ), and the polymerization heat (Δ\( H_p \)) [41]

\[ R_p = \frac{h \cdot \rho}{\Delta H_0} \]

(2)

### 2.4. Mechanical properties

#### 2.4.1. Sample preparation

Specimens prepared by bulk photopolymerization were fabricated in silicone molds of appropriate size. The formulations contained 2 wt.% 2959 as PI. In the case of formulations containing thiols, 0.1 wt.% of pyrogallol as inhibitor was added. For poly-GDVC samples, the monomer/PI mixture was melted, subsequently casted and quickly cured before solidification could occur. For nanoindentation, cylindrical platelets (diameter 5 mm, height 1 mm) were produced.

Photopolymerization was carried out in a ventilated UV-chamber (Uvitrin UV 1080 Flood Curing System with Uvitrin Intelliray 600 halide lamps, irradiation power 600 W, UV-A: 125 mW cm⁻², and Vis: 125 mW cm⁻², distance from light source: 130 mm, intensity at curing position: 120 mW cm⁻²) with an exposure time of 600 s on both sides of the specimens.

#### 2.4.2. Nanoindentation

Nanoindentation experiments were carried out on a Nanoindenter XP, MTS Systems Inc. For the measurements, platelets (diameter = 5 mm, thickness = 1 mm) were fabricated as described above. The specimens were glued onto an aluminum cylinder with an epoxy-based adhesive and the surface was grinded and polished. The specimens were indented with a rate of 20 nm s⁻¹ until an indentation depth of 2 μm was reached. At least seven measurement points were analyzed. The indentation modulus \( E_i \) was calculated starting from the slope of the unloading curve's tangent at the maximum force. The indentation hardness \( H_i \) was calculated from the maximum force \( F_{max} \).

\[ H_i = \frac{F_{max}}{24.5 \cdot h_c^2} \]

(5)

\[ h_c = h_{max} - \varepsilon \cdot (h_{max} - h_i) \]

(6)

with \( F_{max} \) [N] being the maximum force, \( h_{max} \) [m] the penetration depth at maximum force, \( h_i \) the intersection of the tangent of the unloading curve at maximum load with the x-axis [m], and \( \varepsilon \) an indenter constant.
3. Results and discussion

3.1. Monomer synthesis

The conventional route to vinyl carbonates,[37,38] utilizing vinyl chloroformate and pyridine as acid scavenger and catalyst, could be utilized for the preparation of new vinyl carbonates: a urethane divinyl carbonate (UDVC) and cyclic glucitol divinyl carbonate (GDVC) (Scheme 1). The urethane diol (UD) for the synthesis of UDVC was synthesized from 2,2,4-trimethyl-1,6-diisocyanatohexane (TMDI) and ethylene glycol in the presence of a catalytic amount of tin(II) 2-ethylhexanoate (Scheme 1a). [42] UD was subsequently reacted with vinyl chloroformate in the presence of pyridine. For the synthesis of a glucitol divinyl carbonate (GDVC) (Scheme 1b), dihydro-D-glucitol (DDG) was reacted with vinyl chloroformate in the presence of pyridine. Butanediol divinyl carbonate (4VC) [39] was also synthesized as reference compound. The new VCs were received in moderate yields around 40%.

3.2. Toxicological analysis

Polymers used in biomedical applications potentially release unreacted monomers into their vicinities.[37,38] Therefore, knowledge about the cytotoxicity of these substances is of great importance. Cytotoxicity values were assessed by cell viability measurements (Alamar Blue assays). LC_{50} values (Table 1), the concentration at which 50% of the cells survived after five days, for UDVC and GDVC were 2.5 and 5 mM, respectively, similar to conventional vinyl carbonates which have already proven to exhibit excellent biocompatibility in vivo tests.[37] For (meth)acrylates, e.g. TTeGDMA, this value is usually well below 1 mM.[31,32,39,43] However, the dental formulation MA, which was the blueprint for the new types of vinyl carbonates and is known for its excellent biocompatibility,[22,24,25] was in the same range as the new vinyl carbonates. Thus, these results suggest that the new types of vinyl carbonates exhibit excellent biocompatibility and accordingly usability as bone replacement material as well.

3.3. Photopolymerization tests by photo-DSC

As curing by UV-light is the typical method for the polymerization of vinyl carbonates, the photoreactivity was analyzed for the new monomers. Thereby three parameters are used for the quantification of the photoreactivity: the double bond conversion (DBC), the polymerization rate \( (R_p) \), and the time to reach the maximum of the polymerization exotherm \( (t_{\text{max}}) \). The DBC is the key factor for the application of photomonomers, for only high values of reacted double bonds guarantee minimization of potential leachables and good mechanical properties. Irgacure 2959 was utilized as photoinitiator (PI) as this compound exhibits high photoreactivity and good biocompatibility.[44,45] For GDVC is solid at 25 °C and had to be analyzed at 70 °C, UDVC was tested at 25 °C and also at 70 °C to render the measurements comparable. The results of photo-DSC measurements of UDVC and GDVC compared to 4VC and the dental methacrylate formulation composed of UDMA and Bis-GMA are displayed in Figures 2 and 3.

\[ T_{\text{max}} \] of UDVC was 4.2 and 4.0 s at 25 and 70 °C, respectively, and hence similar to GDVC (4.2 s); both of which were received in moderate yields around 40%.

Table 1. Cytotoxicity (LC_{50} values): new vinyl carbonates compared to methacrylates.

| Substance   | LC_{50} (mM) |
|-------------|--------------|
| 4VC         | >10          |
| GDVC        | 5            |
| UDVC        | 2.5          |
| TTeGDMA     | <0.16        |
| Bis-GMA     | 2.5          |
| UDMA        | 5            |

Scheme 1. Synthesis and structures of divinyl carbonates.
reacting slightly slower compared to 4VC (3.3 s). A DBC (4VC: 73%) of 63% (71% at 70 °C) and 61% for UDVC and GDVC, respectively, was a good result for the application envisioned. The lower DBC was based on the structure and functionality. Large molecules with a rather high viscosity enable lower DBC compared to shorter, low-viscosity compounds. The polymerization rate of both compounds (0.778 mol L⁻¹ s⁻¹ for GDVC and 0.507 (0.589 at 70 °C) mol L⁻¹ s⁻¹ for UDVC, respectively) was on a high level, comparable to 4VC (0.812 mol L⁻¹ s⁻¹). Compared to MA (t_max = 6.6 s, R_p = 0.171 mol L⁻¹ s⁻¹, DBC = 57%), the new monomers exhibited much lower t_max and significantly increased DBC and R_p. This demonstrates that they can easily outperform state-of-the-art methacrylate systems in terms of photoreactivity; improved photoreactivity and lower cytotoxicity qualify these new monomers to be particularly suitable as alternative to methacrylates in bone replacement applications.

To further boost the photoreactivity, nontoxic thiols,[39,43] via the thiol–ene reaction, have recently been demonstrated to be suitable polymerization accelerators for vinyl carbonates.[39] Thus, the influence of thiols onto the photoreactivity of the new vinyl carbonates was analyzed, too (Figure 4). GDVC (m.p. = 65 °C) and mixtures thereof with thiols were analyzed at 70 °C again. As anticipated, the exotherm peak was shifted to shorter times for both compounds indicating an improved photoreactivity. t_max was reduced from 4.2 to 3.1 s and 3.5 s for UDVC and GDVC, respectively, proving that the photoreactivity could be strongly increased with the help of a sufficient amount of thiol (40% based on functional groups), while a lower concentration of TT (20%) resulted in almost unchanged photoreactivity. Eventually, the photoreactivity as expressed by t_max was in the same range as those of acrylates.[43] This acceleration is based upon a combined chain and step-growth polymerization mechanism.[39]

### 3.4. Mechanical characterization by nanoindentation

The mechanical properties of UDVC and GDVC were assessed by means of nanoindentation and compared to
PLA and MA. Nanoindentation is the method of choice when only small amounts of materials are available, as it provides data for the modulus and the hardness of a material in one test. The formulation of GDVC, since it is a solid at room temperature, had to be melted first, quickly placed in the mold, and subsequently irradiated to achieve polymerization before solidification could occur. The results of nanoindentation measurements are displayed in Figure 5.

The sugar-based compound GDVC was able to outperform PLA as well as MA in both modulus and hardness ($E_i$ of 6120 vs. 5680 and 4550 MPa, respectively, and $H_i$ of 450 compared to 210 and 290 MPa, respectively), whereby the hardness of PLA was more than doubled. The urethane vinyl carbonate UDVC (230 MPa) was also able to exceed the hardness of PLA; the hardness of MA and 4VC could almost be matched, too. Additionally, the indentation modulus of UDVC was approximately 25% lower compared to PLA (4380 vs. 5680 MPa) but almost the same as for MA (4550 MPa) and significantly higher than for 4VC (3200 MPa). Responsible for this excellent mechanical performance was the ring system in GDVC, resulting in a stiff polymer network, and the urethane group in UDVC, introducing additional molecular interactions reinforcing the polymer network. For the thiol-ene reaction was demonstrated to boost the reactivity of the new types of vinyl carbonates, the influence of thiols onto the mechanical performance had to be analyzed as well (Figure 5). The typical trend, already found for various types of photopolymers such as (meth)acrylates,[46] vinyl ester,[43] and vinyl carbonates,[39] that the addition of thiols leads to a decrease in both indentation modulus and hardness was found again. This is based on thiols rendering the polymer network more flexible, resulting in reduced stiffness and hardness but increased toughness. In the case of the new vinyl carbonates, the reduction of both parameters was moderate. The modulus was only reduced upon an addition of 40% TT to UDVC and GDVC to 75 and 84%, respectively, of the value of the pure monomer.

4. Conclusions

Vinyl carbonate photopolymers were recently introduced as promising alternatives to methacrylates in bone replacement applications. However, their mechanical performance could so far not match the one of PLA or methacrylate systems, the resorbable and non-resorbable, respectively, state-of-the-art materials for bone tissue engineering applications. Thus, it was envisioned to design vinyl carbonates with functional groups that were anticipated to improve mechanical properties, such as urethane groups or cyclic structures. Therefore, two new types of vinyl carbonates were synthesized. Cytotoxicity tests showed that the new monomers were on the same good level of biocompatibility as conventional vinyl carbonates. The photoreactivity of these monomers was similar to common vinyl carbonates, too, and could be improved through the addition of thiols via the thiol-ene reaction without losing much of the mechanical properties. The mechanical performance, though, in the case of the urethane vinyl carbonate was comparable to and in the case of the glucitol divinyl carbonate superior to conventional vinyl carbonate systems and even capable of outperforming PLA and methacrylate systems, qualifying them to be an alternative to these materials in biomedical applications.

Acknowledgment

We would like to thank Ivoclar Vivadent for providing reference materials.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by Synthes.

ORCID

Andreas Mautner http://orcid.org/0000-0003-0347-8643

References

[1] Nair LS, Laurencin CT. Biodegradable polymers as biomaterials. Prog. Polym. Sci. 2007;32:762–798.
[2] Ratner BD, Hoffman AS, Schoen FJ, et al., editors. Biomaterials science – an introduction to materials in medicine. 2nd ed. San Diego (CA): Elsevier; 2004.
[3] Salgado AJ, Coutinho OP, Reis RL.Bone tissue engineering: state of the art and future trends. Macromol. Biosci. 2004;4:743–765.
[4] Tian H, Tang Z, Zhuang X, et al. Biodegradable synthetic polymers: preparation, functionalization and biomedical application. Prog. Polym. Sci. 2012;37:237–280.
[5] Lewis G. Properties of acrylic bone cement: state of the art review. J. Biomed. Mater. Res. 1997;38:155–182.
[6] Boesel LF, Reis RL. A review on the polymer properties of hydrophilic, partially degradable and bioactive acrylic cements (HDBC). Prog. Polym. Sci. 2008;33:180–190.
[7] Hendriks JGE, van Horn JR, van der Mei HC, et al. Backgrounds of antibiotic-loaded bone cement and prosthesis-related infection. Biomaterials. 2004;25:545–556.
[8] Lewis G. Properties of antibiotic-loaded acrylic bone cements for use in cemented arthroplasties: a state-of-the-art review. J. Biomed. Mater. Res. Part B Appl. Biomater. 2009;89B:558–574.
[9] Charnley J. Anchorage of the femoral head prosthesis to the shaft of the femur. J. Bone Joint. Surg. Br. 1960;42-
B:28–30.

[10] Boesel LF, Mano JF, Reis RL. Optimization of the formulation and mechanical properties of starch based partially degradable bone cements. J. Mater. Sci. Mater. Med. 2004;15:73–83.

[11] Deb S, Aiyathurai L, Roether JA, et al. Development of high-viscosity, two-paste bioactive bone cements. Biomaterials. 2005;26:3713–3718.

[12] Boner V, Kuhn P, Mendel T, et al. Temperature evaluation during PMMA screw augmentation in osteoporotic bone in vitro study about the risk of thermal necrosis in human femoral heads. J. Biomed. Mater. Res. Part B Appl. Biomater. 2009;90B:842–848.

[13] Boesel LF, Fernandes MHV, Reis RL. The behavior of novel hydrophilic composite bone cements in simulated body fluids. J. Biomed. Mater. Res. 2004;70B:368–377.

[14] Kenny SM, Buggy M. Bone cements and fillers: a review. J. Mater. Sci. Mater. Med. 2003;14:923–938.

[15] Lewis G. Fatigue testing and performance of acrylic bone cement materials: state-of-the-art review. J. Biomed. Mater. Res. 2003;66B:457–486.

[16] Kowalski R, Barker D, inventor; Depuy Int Ltd, assignee. Bone cement compositions. WO2007007065A2. 2005 Jul 8.

[17] Yusof RM, Nakamura T, Iida H, et al. Development of bioactive bone cement and its clinical applications. Biomaterials. 1998:19:1479–1482.

[18] Park B-J, Park K, Ahn K-D, et al. Preparation of new bioactive hybrid bone cements containing bis-GMA derivatives as a prepolymer. Macromol. Mater. Eng. 2006;291:684–689.

[19] Kobayashi M, Nakamura T, Okada Y, et al. Bioactive bone cement: comparison of apatite and wollastonite containing glass-ceramic, hydroxyapatite, and beta-tricalcium phosphate fillers on bone-bonding strength. J. Biomed. Mater. Res. 1998;42:223–237.

[20] Kobayashi M, Nakamura T, Tamura J, et al. Bioactive bone cement: comparison of AW-GC filler with hydroxyapatite and beta-TCP fillers on mechanical and biological properties. J. Biomed. Mater. Res. 1997;37:301–313.

[21] Zhang H, Zhang M. Effect of surface treatment of hydroxyapatite whiskers on the mechanical properties of bis-GMA-based composites. Biomed. Mater. 2010;5:054106/1–7.

[22] Kawanabe K, Tamura J, Yamamuro T, et al. A new bioactive bone cement consisting of bis-GMA resin and bioactive glass powder. J. Appl. Biomater. 1993;4:135–141.

[23] Vallo CI, Schroeder WF. Properties of acrylic bone cements formulated with bis-GMA. J. Biomed. Mater. Res. Part B Appl. Biomater. 2005;74B:676–685.

[24] Moszner N, Fischer UK, Angermann J, et al. A partially aromatic urethane dimethacrylate as a new substitute for bis-GMA in restorative composites. Dent. Mater. 2008;24:694–699.

[25] Moszner N, Salz U. New developments of polymeric dental composites. Prog. Polym. Sci. 2001;26:535–576.

[26] Calnan CD. Acrylates in industry. Contact Dermat. 1980;6:53–54.

[27] Andrews LS, Clary JJ. Review of the toxicity of multifunctional acrylates. J. Toxicol. Environ. Health. 1986;19:149–164.

[28] Chandra R, Rustgi R. Biodegradable polymers. Prog. Polym. Sci. 1998;23:1273–1335.

[29] Baroli B. Photopolymerization of biomaterials: issues and potentialities in drug delivery, tissue engineering, and cell encapsulation applications. J. Chem. Technol. Biotechnol. 2006;81:491–499.

[30] Ikkovits JL, Burdick JA. Review: photopolymerizable and degradable biomaterials for tissue engineering applications. Tissue Eng. 2007;13:2369–2385.

[31] Heller C, Schwentenwein M, Russmueller G, et al. Vinyl esters: low cytotoxicity monomers for the fabrication of biocompatible 3D scaffolds by lithography based additive manufacturing. J. Polym. Sci., Part A: Polym. Chem. 2009;47:6941–6954.

[32] Husar B, Heller C, Schwentenwein M, et al. Biomaterials based on low cytotoxic vinyl esters for bone replacement application. J. Polym. Sci., Part A: Polym. Chem. 2011;49:4927–4934.

[33] Burkersroda Fv, Schiedl L, Göpferich A. Why degradable polymers undergo surface erosion or bulk erosion. Biomaterials. 2002;23:4221–4231.

[34] Göpferich A. Mechanisms of polymer degradation and erosion. Biomaterials. 1996;17:103–114.

[35] Hutmacher DW. Scaffolds in tissue engineering bone and cartilage. Biomaterials. 2000;21:2529–2543.

[36] Rezwan K, Chen QZ, Blaker JJ, et al. Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering. Biomaterials. 2006;27:3413–3431.

[37] Heller C, Schwentenwein M, Russmueller G, et al. Vinylcarbonyl and vinylcarbamates: biocompatible monomers for radical photopolymerization. J. Polym. Sci., Part A: Polym. Chem. 2011;49:650–661.

[38] Husar B, Liska R. Vinyl carbones, vinyl carbamates, and related monomers: synthesis, polymerization, and application. Chem. Soc. Rev. 2012;41:2395–2405.

[39] Mautner A, Qin X, Kapeller B, et al. Efficient curing of vinyl carbones by thiol-ene polymerization. Macromol. Rapid Commun. 2012;33:2046–2052.

[40] Fouassier JP. Photochemistry and UV curing: new trends. Research Signpost; 2006.

[41] Ullrich G, Hanster B, Salz U, et al. Photoinitiators with functional groups. IX. Hydrophilic bisacylamidophosphine oxides for acidic aqueous formulations. J. Polym. Sci., Part A: Polym. Chem. 2006;44:1686–1700.

[42] Majumdar KK, Kundu A, Das I, et al. Efficient organotin catalysts for urethanes: kinetic and mechanistic investigations. Appl. Organomet. Chem. 2000;14:79–85.

[43] Mautner A, Qin X, Wutzel H, et al. Thiol-ene photopolymization for efficient curing of vinyl esters. J. Polym. Sci., Part A: Polym. Chem. 2013;51:203–212.

[44] Williams CG, Malik AN, Kim TK, et al. Variable cytocompatibility of six cell lines with photoinitiators used for polymerizing hydrogels and cell encapsulation. Biomaterials. 2005;26:1211–1218.

[45] Schuster M, Turecek C, Weigel G, et al. Gelatin-based photopolymers for bone replacement materials. J. Polym. Sci., Part A: Polym. Chem. 2009;47:7078–7089.

[46] Rydholm AE, Reddy SK, Anseth KS, et al. Controlling network structure in degradable thiol-acrylate biomaterials to tune mass loss behavior. Biomacromolecules. 2006;7:2827–2836.