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SYNTHESIS OF NOVEL URETHANE-DIMETHACRYLATE MONOMER CONTAINING TWO QUATERNARY AMMONIUM GROUPS FOR APPLICATIONS IN DENTISTRY

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Theoretical background

Dental composite restorative materials that are used in dentistry are mainly composed of dimethacrylate resins due to their good physico-chemical, mechanical and esthetical characteristics. Among them the most commonly used are bisphenol A glycerolate dimethacrylate (Bis-GMA), an ethoxylated Bis-GMA derivative (Bis-EMA), triethylene glycol dimethacrylate (TEGDMA) and urethane-dimethacrylate (UDMA).

However, these materials do not exhibit antibacterial activity. Through that, the amount of bacteria that accumulate on their surfaces is significantly higher, in comparison to the surfaces of tooth tissues. This issue is closely related to the polymerization shrinkage of the dimethacrylate dental composites, which values ranges from 2 to 5% and which is responsible for formation of marginal gaps, in which bacteria accumulate. As a result of bacteria metabolism, secondary caries, which is regarding as the main reason of dental restoration failure occur.

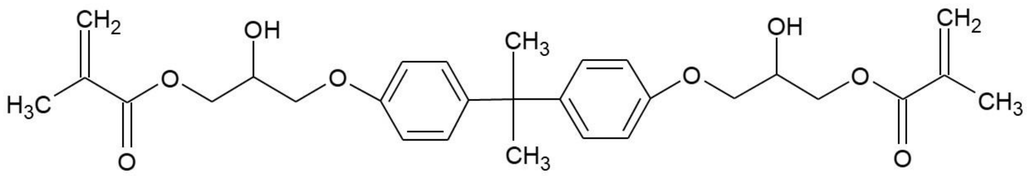
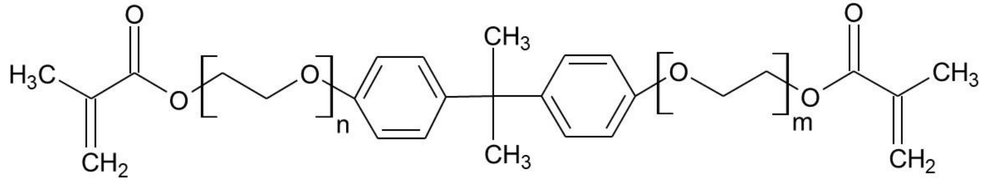


Figure 1. Chemical structure of Bis-GMA.



$n + m = 4$

Figure 2. Chemical structure of Bis-EMA.

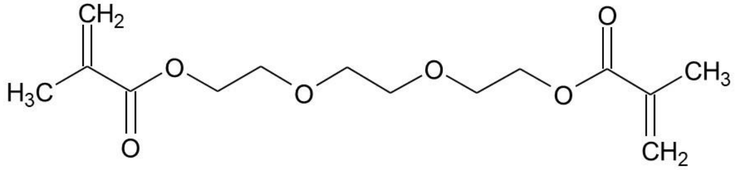


Figure 3. Chemical structure of TEGDMA.

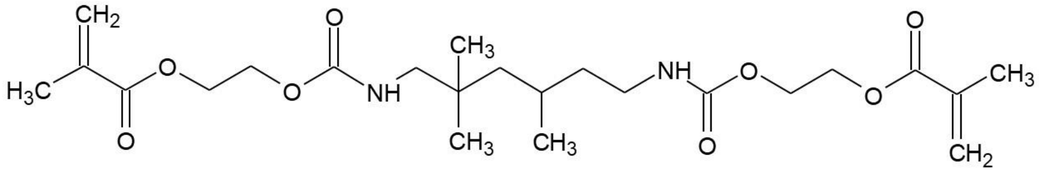


Figure 4. Chemical structure of TEGDMA.

Theoretical background

One of the current trends in the field of dental composite materials is to obtain materials of antibacterial properties, maintaining satisfactory physico-chemical and mechanical characteristics. Up to now, various organic and inorganic compounds have been physically admixed to dental composites.

ANTIBACTERIAL AGENTS

INORGANIC	ORGANIC
zinc oxide	antibiotics
titanium dioxide	chlorhexidine
calcium phosphate	furanone
gold	ursolic acid
silver	benzalkonium chloride
	triclosan
	chitosan
	quaternary ammonium polyethylenimine derivatives nanoparticles

The main shortcoming associated with the use of those antibacterial agents is that they usually negatively affect the macromolecular structure of the dimethacrylate matrix, and thus mechanical properties of the composites.

As an alternative to them, antibacterial agents that can be chemically bonded with the composite matrix were developed.

Aim of our study

The aim of our study was to obtain a novel urethane-dimethacrylate monomer containing two methacrylate groups and two quaternary ammonium groups.

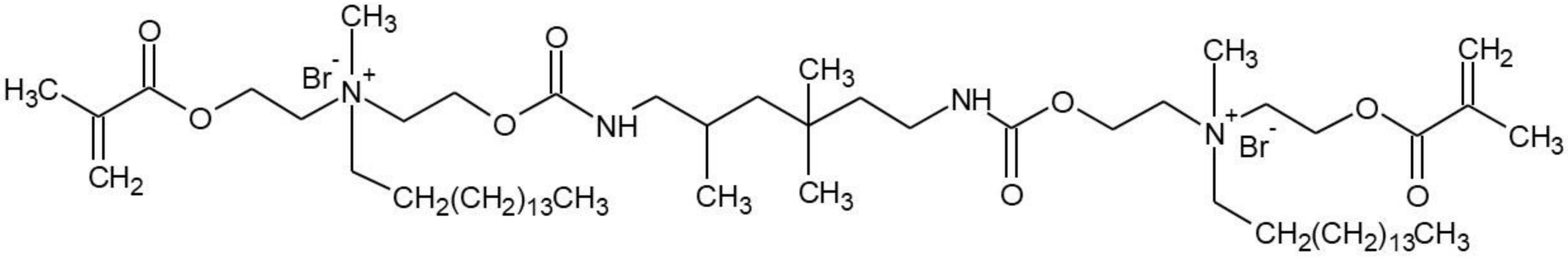


Figure 5. Chemical structure of novel urethane-dimethacrylate monomer – QHAMA-C16-TMDI.

Synthesis of intermediate product HAMA

HAMA was synthesized from methyl methacrylate (MMA, Acros Organics) and N-methyldiethanolamine (MDEA, Acros Organics) in a mole ratio 1.33 : 1. K_2CO_3 (potassium carbonate, Chempur) was used as reaction catalyst. PTZ (phenothiazine, Sigma-Aldrich) was used as an inhibitor to prevent the spontaneous polymerization of the methyl methacrylate group. The reaction was carried out in toluene in a round-bottomed flask equipped with a Vigreux distillation column. The reaction was terminated when the temperature measured at the head of the column reached 100◦C, which was achieved after 2,5 h. Reaction mixture was cooled, filtered and three times washed with distilled water in a 2:1 volume ratio. Then the aqueous layer was extracted three times with chloroform in a 3:1 volume ratio. The chloroform fraction was dried overnight with magnesium sulphate ($MgSO_4$), and then the solvent was removed under the reduced pressure. The crude product was distilled under vacuum (2 mbar), taking boiling fraction of HAMA at 120 – 130 ◦C. The final product yield was 19%.

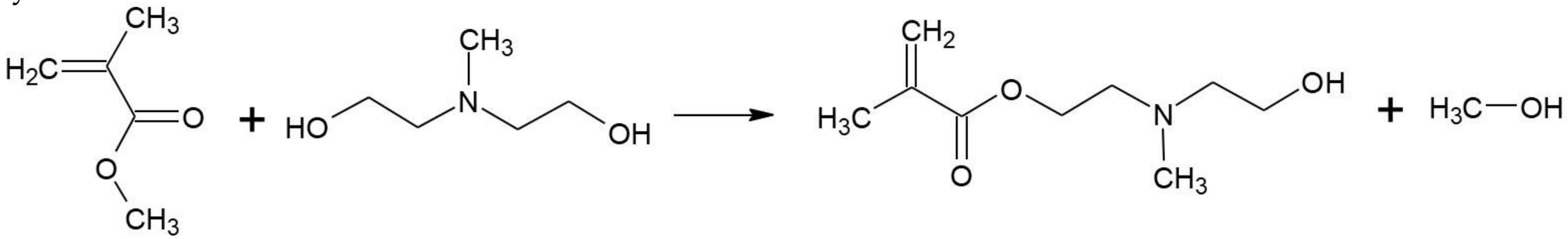


Figure 6. Synthesis of intermediate product - HAMA.

Synthesis of intermediate product QHAMA-C16

QHAMA-C16 was synthesized from HAMA and 1-bromohexadecane (Acros Organics) in a mole ratio 1 : 1. Reaction was carried out for 96 h at 82 ◦C. Crude product was washed several times with diethyl ether in order to remove the unreacted 1-bromohexadecane and HAMA. Then the product was dried under vacuum at 40◦C. The product was obtained with a 90% yield.

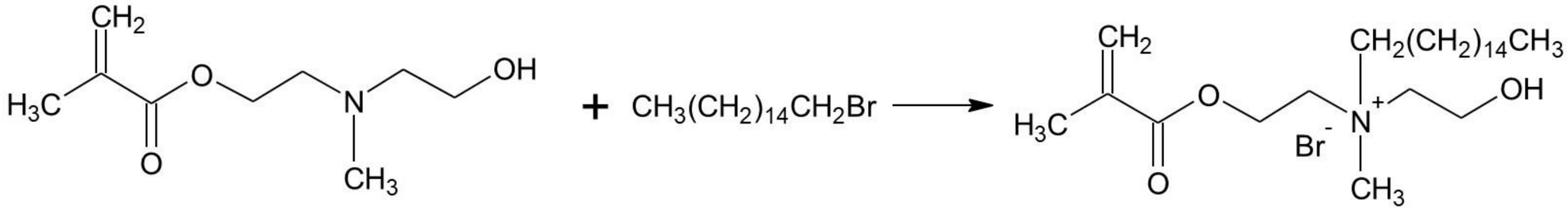


Figure 7. Synthesis of intermediate product – QHAMA-16C

Synthesis of urethane-dimethacrylate monomer QHAMA-C16-TMDI

QHAMA-16C-TMDI was synthesized from QHAMA-C16 and 2,4,4-trimethylhexamethylene diisocyanate (TMDI, TCI) in a mole ratio 2 : 1. Dibutylin dilaurate (DBTDL, Fluka) was used as reaction catalyst. PTZ was used as an inhibitor. The 50 wt.% solution of QHAMA-C16 in methylene chloride was heated to 40 ◦C, and the 50 wt.% solution of TMDI in methylene chloride was added dropwise for 30 minutes, maintaining the temperature at 40 ◦C. The reaction was continued for 3.5 h at 40 ◦C. After cooling, the methylene chloride was evaporated under vaccum. QHAMA-C16-TMDI was obtained with 100% yield.

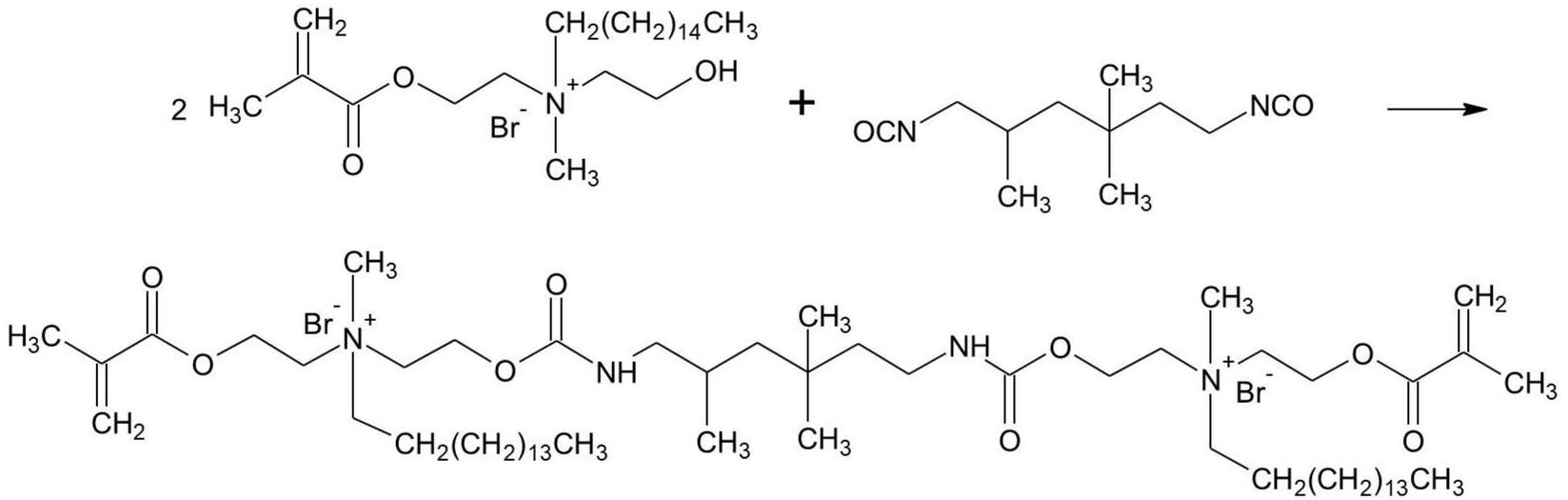


Figure 8. Synthesis of urethane-dimethacrylate – QHAMA-C16-TMDI.

Monomer analysis

Nuclear Magnetic Resonanse (NMR)

^{1}H NMR and ^{13}C NMR spectra of the monomers were recorded in the $CDCl_3$ solution, using TMS as an internal standard. A 300 MHz NMR spectrometer (UNITY/INOVA, Palo Alto, CA, USA) and a 600 MHz NMR spectrometer (Varian, Palo Alto, CA, USA) were employed for these experiments.

Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FT IR)

ATR-FT IR spectra were recorded utilizing a Spectrum Two (Perkin-Elmer, Waltham, MA, USA) spectrometer. Products were tested in a form of a thin layer placed on the diamond crystal. The spectra of products were recorded with 128 scans at a resolution of 1 cm^{-1}.

Results

Novel urethane-dimethacrylate monomer containing two quaternary ammonium groups – QHAMA-C16-TMDI was obtained in a three steps route. First, intermediate product HAMA was obtained via the transesterification reaction of MMA with the use of MDEA. It resulted in formation of tertiary amine with methacrylate group. Then, HAMA was reacted with 1-bromohexadecane in order to transform the tertiary amine group into the quaternary ammonium group via the Menschutkin reaction. Finally, QHAMA-C16-TMDI was obtained in the addition reaction of the hydroxyl group of QHAMA-C16 (which was obtained in the previous step) to the isocyanate groups of TMDI.

Chemical structure of intermediate and final products have been confirmed by ^{1}H NMR, ^{13}C NMR and ATR-FT IR analysis.

^{1}H NMR spectra analysis

HAMA

^{1}H NMR (300MHz, $CDCl_3$): δ = 1,95 (s, 3H, C$\underline{H}_3$-C=), 2,40 (s, 3H, C$\underline{H}_3$-N<), 2,60 – 2,90 (2m, 4H, -C$\underline{H}_2$-N<), 3,45 (m, 1H, -O$\underline{H}$), 3,55 – 4,40 (2m, -C$\underline{H}_2$-O-), 5,60 i 6,20 (2m, 2H, C$\underline{H}_2$=C-) ppm.

QHAMA-C16

^{1}H NMR (300MHz, $CDCl_3$): δ = 0,90 (t, 3H, C$\underline{H}_3$-$(CH_2)_{13}$-CH_2-CH_2-N+), 1,35 (m, 26H, CH_3-(C$\underline{H}_2$)$_{13}$-CH_2-CH_2-N+), 1,70 (m, 2H, CH_3-$(CH_2)_{13}$-C$\underline{H}_2$-CH_2-N+) 1,95 (s, 3H, C$\underline{H}_3$-C=), 3,45 (s, 3H, C$\underline{H}_3$-N+) 3,60 (m, 2H, CH_3-$(CH_2)_{13}$-CH_2-C$\underline{H}_2$-N+), 3,75 – 4,10 (2m, 4H, -C$\underline{H}_2$-N+), 4,20 (s, 1H, -O$\underline{H}$), 4,25 – 4,70 (2m, 4H, -C$\underline{H}_2$-O-), 5,60 i 6,10 (2m, 2H, C$\underline{H}_2$=C-) ppm.

QHAMA-C16-TMDI

^{1}H NMR (600MHz, $CDCl_3$): δ = 0,80 – 1,00 (m, 15H, C$\underline{H}_3$-$(CH_2)_{13}$-CH_2-CH_2-N+, -NH-CH_2-C(C$\underline{H}_3$)$_2$-CH_2-CH(C$\underline{H}_3$)-CH_2-CH_2-NH-), 1,25 – 1,35 (m, 52, CH_3-(C$\underline{H}_2$)$_{13}$-CH_2-CH_2-N+), 1,60 – 1,85 (m, 9H, -NH-CH_2-C$(CH_3)_2$-C$\underline{H}_2$-C$\underline{H}$(CH_3)-C$\underline{H}_2$-CH_2-NH-, CH_3-$(CH_2)_{13}$-C$\underline{H}_2$-CH_2-N+), 1,95 (s, 6H, C$\underline{H}_3$-C=), 2,70 do 3,20 (m, 4H, -NH-C$\underline{H}_2$-), 3,51 (s, 6H, C$\underline{H}_3$-N+), 3,55 – 3,70 (m, 4H, CH_3-$(CH_2)_{13}$-CH_2-C$\underline{H}_2$-N+), 3,90 – 4,30 (2m, 8H, -C$\underline{H}_2$-N+), 4,50 – 4,80 (2m, 8H, -C$\underline{H}_2$-O-), 5,60 i 6,10 (2m, 4H, C$\underline{H}_2$=), 6,30 – 7,15 (m, 2H, -N$\underline{H}$-C=O) ppm.

^{13}C NMR spectra analysis

HAMA

^{13}C NMR (300MHz, $CDCl_3$): δ = 18 ($\underline{C}H_3$-C=), 42 ($\underline{C}H_3$-N<), 55 – 62 ppm (-$\underline{C}H_2$-N<, -$\underline{C}H_2$-O-), 125 ($\underline{C}H_2$=), 138 (>$\underline{C}$=), 166 ($\underline{C}$=O) ppm.

QHAMA-C16

^{13}C NMR (300MHz, $CDCl_3$): δ = 14 ($C\underline{H}_3$-$(CH_2)_{14}$-CH_2-N+), 18 ($\underline{C}H_3$-C=), 22 – 32 (CH_3-$(\underline{C}H_2)_{14}$-CH_2-N+), 50 ($\underline{C}H_3$-N+), 55 – 64 ppm (-$\underline{C}H_2$-N+, -$\underline{C}H_2$-O, CH_3-$(CH_2)_{14}$-$\underline{C}H_2$-N+), 127 ($\underline{C}H_2$=), 135 (>$\underline{C}$=), 166 ($\underline{C}$=O) ppm.

QHAMA-C16-TMDI

^{13}C NMR (600MHz, $CDCl_3$): δ = 14 ($\underline{C}H_3$-$(CH_2)_{14}$-CH_2-N+), 18 – 32 ($\underline{C}H_3$-C=, CH_3-$(\underline{C}H_2)_{14}$-CH_2-N+, -NH-CH_2-$\underline{C}(\underline{C}H_3)_2$-$CH_2$-$\underline{C}H(\underline{C}H_3)$-$CH_2$-$CH_2$-NH-), 36 – 48 (-NH-$\underline{C}H_2$-$C(CH_3)_2$-$\underline{C}H_2$-$CH(CH_3)$-$\underline{C}H_2$-$\underline{C}H_2$-NH-), 50 ($\underline{C}H_3$-N+), 56 – 63 (-$\underline{C}H_2$-N+, -$\underline{C}H_2$-O-, CH_3-$(CH_2)_{13}$-CH_2-$\underline{C}H_2$-N+), 127 ($\underline{C}H_2$=), 134 (=$\underline{C}$<), 155 (-NH-$\underline{C}$=O), 166 (-$\underline{C}$OO-) ppm.

ATR FT IR spectra analysis

HAMA

ATR-FT IR: 3200–3500 (-OH), 3105 (CH_2=), 2930 (-CH_2-, CH_3-), 1716 (C=0), 1638 (C=C) cm^{-1}.

QHAMA-C16

ATR-FT IR: 3200–3500 (-OH), 3106 (CH_2=), 2935 (-CH_2-, CH_3-), 1716 (C=0), 1636 (C=C) cm^{-1}.

QHAMA-C16-TMDI

ATR-FT IR: 3221 (-NH-), 3105 (CH_2=), 2923 (-CH_2-, CH_3-), 1716 (C=O), 1639 (C=C), 1536 (-NH-) cm^{-1}.

Conclusions

- ✓ We successfully designed synthesis route of novel urethane-dimethacrylate monomer that contains two quaternary ammonium groups.
- ✓ Chemical structure of intermediate and final products have been confirmed by ^{1}H NMR, ^{13}C NMR and ATR-FT IR analysis.
- ✓ The structural analysis confirmed that the monomer structure comprises two quaternary ammonium groups, two methacrylate groups, two urethane-bonds and two side alkyl chains directly attached to the two quaternary nitrogen atoms.
- ✓ Further studies, employing the designed synthesis procedure will involve the synthesis of QHAMA-C16-TMDI analogous with eight, ten, twelve, fourteen and eighteen carbon atoms. All monomers (including QHAMA-C16-TMDI) will be then tested for their physico-chemical characteristic. We will also prepare their compositions with commercially used dimethacrylate resins, and their mechanical characteristic will be done.