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Proceeding Paper

Antibacterial Properties of Dental Copolymer Modified with Monomers Possessing Quaternary Ammonium Groups †

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Abstract: Dental caries are treated using dental composite restorative materials (DCRM). However, commercial DCRMs lack antibacterial activity. This research aimed to analyze the in vitro antibacterial activity of a series of copolymers consisting of a urethane–dimethacrylate monomer (UDMA), bisphenol A glycerolate dimethacrylate (Bis-GMA), triethylene glycol dimethacrylate (TEGDMA) and urethane–dimethacrylate monomer with two quaternary ammonium groups and a 1,3-bis(1-isocyanate-1-methylethyl)benzene core (QAn+TMXDI, where n = 8, 10, or 12 is the number of carbon atoms in the N-alkyl substituent). QAn+TMXDI contents in copolymers were 20 and 40 wt.%. The results of the *Staphylococcus aureus* and *Escherichia coli* adhesion test demonstrated that the logCFU/mL decreased as the length of the N-alkyl chain decreased and QAn+TMXDI content increased. The copolymers of QA8+TMXDI 40 wt.%, Bis-GMA 40 wt.%, and TEGDMA 20 wt.% showed the highest antibacterial activity, with a logCFU/mL of 2.39 for *S. aureus* and no viable *E. coli* cells.

Keywords: quaternary ammonium; urethane–dimethacrylate; antibacterial properties

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1. Introduction

The pathogenic bacteria occurring in the biofilm that forms on teeth and mouth surfaces may cause dental caries [1,2]. This biofilm is also found in the marginal gap between dental fillings and the tooth surface, causing secondary caries [3].

Typical dental fillings are made of dental composite restorative materials (DCRM), which are composed of a silica filler dispersed in a dimethacrylate polymer matrix, and they do not have antibacterial activity. Research aiming to prevent secondary caries by providing DCRMs with antibacterial activity is being conducted worldwide [4–6]. One of these approaches is based on the modification of existing dimethacrylate DCRM adhesives through copolymerization with bioactive comonomers. Promising examples of such compounds are monomethacrylate (QAMMA) and dimetchacrylates (QADMAs), which possess quaternary ammonium groups [6]. QADMAs are a better alternative because, unlike QAMMAs, they do not reduce the crosslink density in the DCRM matrix. Several types of QADMAs are known from the literature. They include derivatives of (i) *N*-methyldiethanolamine (MDEA) [7–9], (ii) *N*,*N*-dimethyloaminoethyl methacrylate (DMAEMA) [10], (iii) UDMA based on diisocyanates, such as isophorone diisocyanate [11] or 1,6-diisocyanato-2,2,4-trimethylhexane [12], 1,3-bis(1-isocyanato-1-methylethyl)benzene [13], and (iv) Bis-GMA [14,15]. The incorporation of quaternary ammonium monomers into common dental copolymers usually leads to increased antibacterial activity but a decreased physico-mechanical performance. Therefore, they are interesting research objects, whose use in

DCRM matrices allows for materials to be obtained with properties that are at least no worse compared to the materials currently available.

In our previous study, we synthesized and characterized two novel urethane-dimethacrylate monomers with two quaternary ammonium groups and a 1,3-bis(1-isocyanato-1-methylethyl)benzene-derived core: QA10+TMXDI and QA12+TMXDI. They were subjected to copolymerization with UDMA, Bis-GMA, and TEGDMA, at 20, 20, 40, and 20 wt.%, respectively. The obtained copolymers, 20(QA10+TMXDI) and 20(QA12+TMXDI), demonstrated very good physicochemical and mechanical properties and certain antibacterial activity. The latter manifested in a reduction in the minimum bactericidal concentration (*MBC*) and minimum inhibitory concentration (*MIC*) against *S. aureus* and *E. coli* in comparison to the reference polymer (UDMA 40 wt.%, Bis-GMA 40 wt.%, and TEGDMA 20 wt.% (40(UDMA)). The results also showed that a decrease in the *N*-alkyl chain in QAn+TMXDI resulted in an increase in copolymer antibacterial activity [13]. Therefore, the aim of this work was to continue the research on the antibacterial activity of copolymers containing QAn+TMXDI to assess their potential as chemically bonded biocides in dental dimethacrylate copolymers. For this purpose, another new QAn+TMXDI monomer with the N-octyl substituent (QA8+TMXDI) was synthesized. This was introduced at 20 wt.% in the copolymer with UDMA 20 wt.%, Bis-GMA 40 wt.%, and TEGDMA 20 wt.% (20(QA8+TMXDI)) and, additionally, at 40 wt.% in a copolymer with Bis-GMA 40 wt.% and TEGDMA 20 wt.% (40(QA8+TMXDI)). The antibacterial properties of the obtained copolymers were characterized using logCFU/mL values in adhesion tests against *S. aureus* and *E. coli*. The copolymers presented in the previous work [13], the copolymer with QA10+TMXDI 40 wt.% (40(QA10+TMXDI)), and the 40(UDMA) reference polymer were also obtained for comparison purposes.

2. Materials and Methods

2.1. Materials

Octyl bromide (OB), decyl bromide (DB), dodecyl bromide (DDB), *N*-methyldieth anolamine (MDEA), and methyl methacrylate (MMA) were purchased from Acros Organics, Geel, Belgium. 1,3-bis(1-isocyanato-1-methylethyl)benzene (TMXDI), phenothiazine (PTZ), camphorquinone (CQ), *N*,*N*-dimethylaminoethyl methacrylate (DMAEMA), bisphenol A-glycidyl dimethacrylate (Bis-GMA), triethylene glycol dimethacrylate (TEGDMA), urethane–dimethacrylate (UDMA), and tetramethylsilane (TMS) were purchased from Sigma-Aldrich, St. Louis, MO, USA. Dibutyltin dilaurate (DBTDL) was purchased from Fluka, Charlotte, NC, USA. Deuterated dichloromethane (CD_2Cl_2) and deuterated trichloromethane ($CDCl_3$) were purchased from Deutero GMBH, Kastellaun, Germany. Magnesium sulfate ($MgSO_4$) and potassium carbonate (K_2CO_3) were purchased from Chempur, Piekary Śląskie, Poland. Toluene, trichloromethane, and dichloromethane were purchased from Stanlab, Lublin, Poland. All chemicals were used as received. Tryptic soy broth (TSB) was purchased from Biomaxima, Lublin, Poland. TSB was dissolved in sterile water following the information posted on the packaging.

2.2. Monomer Synthesis

The monomers were synthesized according to a procedure known from the literature [12] (Figure 1). The first step in the synthesis involves the transesterification of MMA. MMA 1.00 mol (100.12 g), and MDEA 0.67 mol (79.85 g), a catalyst, K_2CO_3 8 wt.% (14.40 g), a polymerization inhibitor, PTZ 0.05% wt.% (0.09 g), and toluene 400 cm^3 were introduced into a 1000 mL, single-necked, round-bottom flask equipped with a distillation kit. The reaction was carried out until the temperature at the column head reached 100 °C. The cooled and filtered solution was washed three times with distilled water in a 1:2 volume ratio. The aqueous fractions were washed three times with trichloromethane in a 1:3 volume ratio. Then, trichloromethane was evaporated on a rotary evaporator under reduced pressure (30 mbar). The crude product (HAMA) was subjected to vacuum distillation (3 mbar), collecting a boiling fraction from 110 to 130 °C. In the second step, HAMA 0.107 mol (20.00 g),

alkyl bromide 0.107 mol (OB 20.66 g, DB 23.66 g, and DDB 26.67 g), and PTZ 0.05 wt.% (0.020, 0.022, and 0.023 g, respectively, in the reactions with OB, DB, and DDB) were introduced into a 250 mL, three-necked, round-bottom flask equipped with a reflux condenser, thermometer, and mechanical stirrer. The reaction was carried out at 80 °C for 90 h. The reaction yielded 100% 2-(methacryloyloxy)ethyl-2-hydroxyethylmethyloctylammonium bromide (QAHAMA-8), 2-(methacryloyloxy)ethyl-2-decylhydroxyethylmethylammonium bromide (QAHAMA-10), and 2-(methacryloyloxy)ethyl-2-dodecylhydroxyethylmethylammonium bromide (QAHAMA-12).

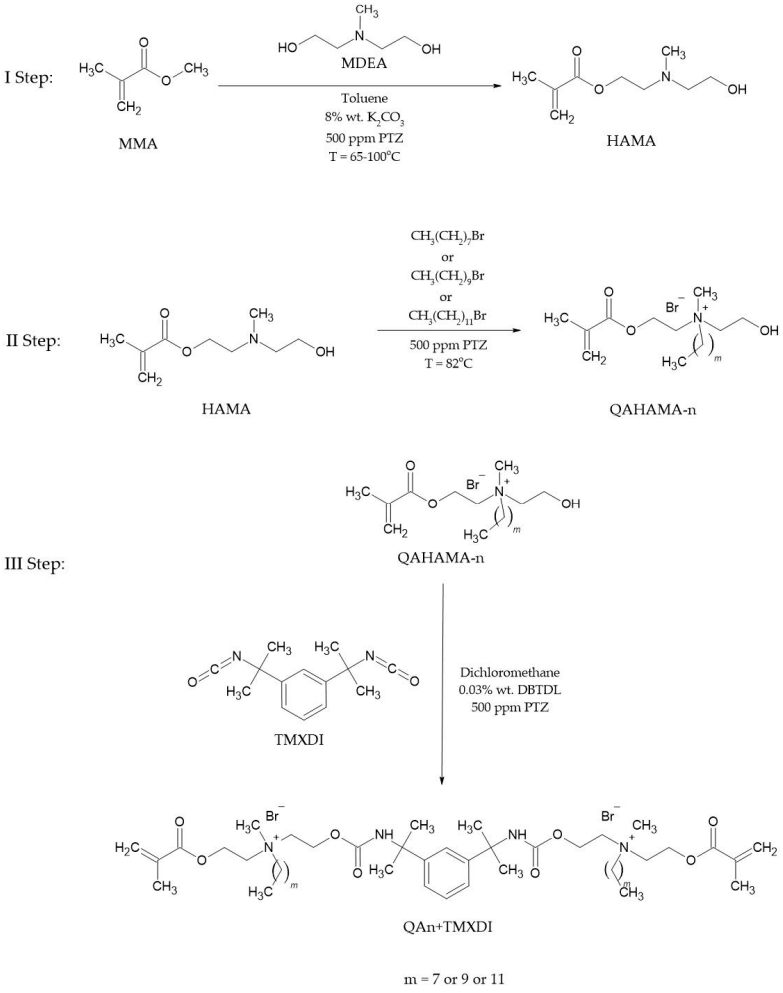


Figure 1. Synthesis route of novel urethane–dimethacryalte monomers—QAn+TMXDI.

In the final step (Figure 1), a 50% solution of QAHAMA-n 0.070 mol (QAHAMA-8 26.67 g, QAHAMA-10 28.60 g, and QAHAMA-12 30.55 g), a catalyst, DBTDL 0.035 wt.% (0.013 g), and a solvent, dichloromethane 21 cm^3, were introduced into a 250 mL, three-necked, round-bottom flask equipped with a dropping funnel, reflux condenser, and thermometer. A 50% solution of TMXDI 0.035 mol (8.55 g) in 6.5 cm^3 dichloromethane was dropped into the flask. After the reaction mixture was brought to a boil (approximately 42 °C), a TMXDI solution was added to the flask dropwise for 1.5 h. The reaction was carried out for 5 h, maintaining the temperature in the flask. The solvent was removed using a rotary evaporator under reduced pressure (30 and then 3 mbar) and the products were stored in the laboratory dryer (SLW 53 STD, POL-EKO, Wodzisław Śląski, Poland) at 40 °C for 24 h. The products were light yellow, viscous, liquid resins. The reaction yield for all products was 100%.

The chemical structures of the final products and semi-products were confirmed via Nuclear Magnetic Resonance Spectroscopy (^{1}H and ^{13}C NMR).

2.3. Curing Procedure and Sample Preparation

Five liquid monomer compositions were prepared using mechanical stirring at 50 °C. The first series consisted of QAUDMA (QA8+TMXDI, QA10+TMXDI and QA12+TMXDI) 20 wt.%, UDMA 20 wt.%, Bis-GMA 40 wt.%, and TEGDMA 20 wt.%; the second series was composed of QAUDMA (QA8+TMXDI and QA10+TMXDI) 40 wt.%, Bis-GMA 40 wt.%, and TEGDMA 20 wt.%. The reference composition was also prepared; it consisted of UDMA 40 wt.%, Bis-GMA 40 wt.%, and TEGDMA 20 wt.%. The photopolymerization-initiating system components, CQ 0.4 wt.% and DMAEMA 1 wt.%, were introduced into homogeneous monomer mixtures and stirred until CQ dissolved. The compositions achieved in this way were poured into the molds, covered with PET foil to minimize oxygen inhibition, and exposed to UV–VIS irradiation at room temperature for 1 h utilizing the Ultra Vitalux 300 lamp (Osram, Munich, Germany). Each obtained cast was polished with fine sandpaper before the experiments.

2.4. Nuclear Magnetic Resonance Spectroscopy (NMR)

In the study, the NMR 300 MHz spectrometer (UNITY/INOVA, Varian, Palo Alto, CA, USA) was used. The spectrometer collected 256 scans for ^{1}H spectra and 40,000 scans for ^{13}C NMR spectra. CD_2Cl_2 and $CDCl_3$ were used as deuterated solvents, and TMS was used as an internal standard.

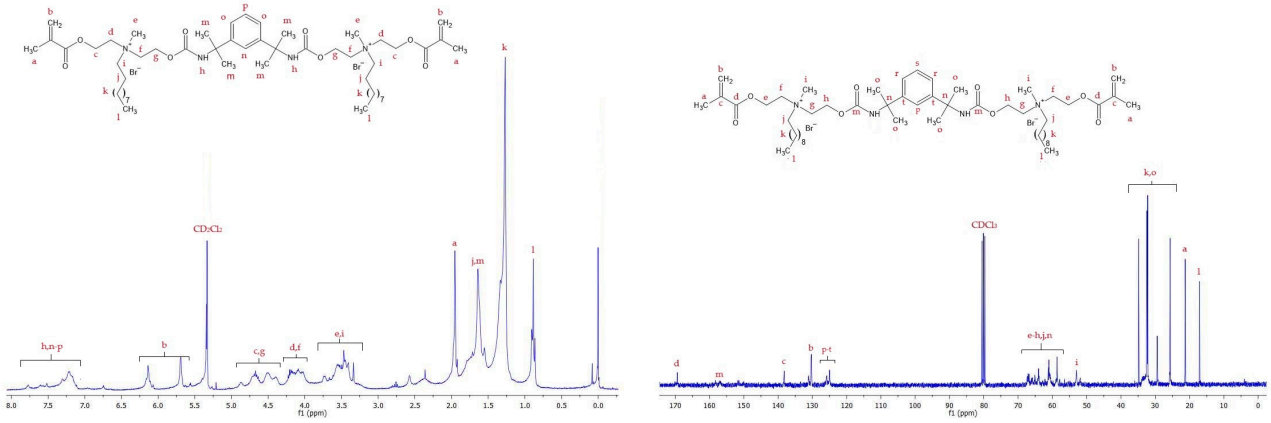
2.5. Bacterial Adhesion

The bacterial adhesion of *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (ATCC 25922) was tested with copolymer disc-like samples (10 mm diameter and 3 mm thickness). Each sample was placed in a 25 mL test tube and immersed in 1 mL of bacterial suspension (~5×10^6 CFU/mL). After incubation, carried out at 37 °C for 18 h, the bacterial suspensions were removed from the tubes and copolymer samples were washed with sterile water. Washed samples were moved to new test tubes, impressed in 1 mL of sterile water, and vortexed at 3000 rpm for 1 min to remove the bacteria that had adhered to the surface of the samples. Next, 100 µL of the obtained bacteria suspensions was mixed with 0.9% NaCl at the following concentrations: 1:10, 1:100, 1:1000, 1:10,000, 1:100,000, and 1:1 000,000. Then, 100 µL of those solutions was speared on agar plates (Müller-Hinton agar, Diag-Med, Warsaw, Poland). The bacteria incubation lasted for 18 h at 37 °C. After that point, bacterial colonies were counted.

3. Results

3.1. ^{1}H and ^{13}C Spectroscopy Analysis

Figure 2 shows the exemplary ^{1}H and ^{13}CNMR spectrum of QA10+TMXDI.



(**a**) (**b**)

Figure 2. NMR spectrum for QA10+TMXDI: (**a**) ^{1}H NMR and (**b**) ^{13}C NMR.

Table 1 shows the ^{1}H NMR signals for QAn+TMXDI monomers and their chemical shifts.

Table 1. ^{1}H NMR signals of QA8+TMXDI, QA10+TMXDI, and QA12+TMXDI monomers.

Signal Symbol	Hydrogen Atom	Multiplicity	Number of Protons	Chemical Shift [ppm]
a	$C\underline{H}_3$-C=	S	6	1.95
b	=$C\underline{H}_2$	2m	4	5.70 and 6.14
c	-O-$C\underline{H}_2$-CH_2-N^+-	m	4	4.33–4.91
d	-O-CH_2-$C\underline{H}_2$-N^+-	m	4	4.00–4.26
e	-N^+-$C\underline{H}_3$	s	6	3.30–3.77
f	-O-CH_2-$C\underline{H}_2$-N^+-	m	4	4.00–4.26
g	-O-$C\underline{H}_2$-CH_2-N^+-	m	4	4.33–4.91
h	-N$\underline{H}$-C=O	m	2	7.10–7.80
i	-N^+-$C\underline{H}_2$-CH_2-$(CH_2)_{5(or\ 7\ or\ 9)}$-CH_3 [1]	m	4	3.30–3.77
j	-N^+-CH_2-$C\underline{H}_2$-$(CH_2)_{5(or\ 7\ or\ 9)}$-CH_3 [1]	m	4	1.49–1.88
k	-N^+-CH_2-CH_2-$(C\underline{H}_2)_{5(or\ 7\ or\ 9)}$-$CH_3$ [1]	m	20/28/36 [2]	1.16–1.47
l	-N^+-CH_2-CH_2-$(CH_2)_{5(or\ 7\ or\ 9)}$-$C\underline{H}_3$ [1]	m	6	0.82–1.00
m	$C\underline{H}_3$-C-$C\underline{H}_3$	m	12	1.49–1.88
n	-C$\underline{H}$- (Ar)	m	1	7.10–7.80
o	-C$\underline{H}$- (Ar)	m	2	7.10–7.80
p	-C$\underline{H}$- (Ar)	m	1	7.10–7.80

[1] $-(CH_2)_5-$ corresponds to QA8+TMXDI; $-(CH_2)_7-$ corresponds to QA10+TMXDI; $-(CH2)_9-$ corresponds to QA12+TMXDI; [2] 20 corresponds to QA8+TMXDI; 28 corresponds to QA10+TMXDI; 36 corresponds to QA12+TMXDI.

Table 2 shows the ^{13}C NMR signals for the QAn+TMXDI monomers and their chemical shifts.

Table 2. ^{13}C NMR signals of QA8+TMXDI, QA10+TMXDI, and QA12+TMXDI monomers.

Signal Symbol	Carbon Atom	Chemical Shift [ppm]
a	$\underline{C}H_3$-C=	21
b	=$\underline{C}H_2$	130
c	CH_3-$\underline{C}$=CH_2	138
d	-O-$\underline{C}$=O	169
e–h	-CH_2-	59–67
i	-N^+-$\underline{C}H_3$	53
j	-N^+-$\underline{C}H_2$-$(CH_2)_{6(or\ 8\ or\ 10)}$-$CH_3$ [1]	59–67
k	-N^+-CH_2-$(\underline{C}H_2)_{6(or\ 8\ or\ 10)}$-$CH_3$ [1]	26–35
l	-N^+-CH_2-$(CH_2)_{6(or\ 8\ or\ 10)}$-$\underline{C}H_3$ [1]	17
m	-NH-$\underline{C}$=O	157
n	-NH-$\underline{C}$-	59–67
o	>C-$\underline{C}H_3$	26–35
p–s	-CH= (Ar)	124–126
t	>C= (Ar)	

[1] $-(CH_2)_6-$ corresponds to QA8+TMXDI; $-(CH_2)_8-$ corresponds to QA10+TMXDI; $-(CH_2)_{10}-$ corresponds to QA12+TMXDI.

3.2. Bacterial Adhesion

An adhesion test for 20(QA8+TMXDI) showed that both logCFU/mL values (for *S. aureus* and *E. coli*) were lower than those for 20(QA10+TMXDI) and 20(QA12+TMXDI) (Table 3 and Figure 3). Compared to 40(UDMA), no significant differences were observed for 20(QA10+TMXDI) and 20(QA12+TMXDI). It was also observed that the logCFU/mL values for 40(QAn+TMXDI) were lower than those for 20(QAn+TMXDI) and 40(UDMA) (Table 3 and Figure 3). In summary, 40(QA8+TMXDI) demonstrated the highest antibacterial activity, as shown by the lowest logCFU/mL of 2.39 observed for *S. aureus* and the lack of colonies observed for *E. coli*.

Table 3. The results of the adhesion test of *S. auresus* and *E.coli*.

Sample	*Staphylococcus aureus* (logCFU/mL)	*Escherichia coli* (logCFU/mL)
Experimental copolymers		
20(QA8+TMXDI)	4.97 ± 0.28	3.94 ± 0.97
20(QA10+TMXDI)	6.41 ± 0.03	5.57 ± 0.73
20(QA12+TMXDI)	6.32 ± 0.17	6.26 ± 0.23
40(QA8+TMXDI)	2.39 ± 0.62	Not observed
40(QA10+TMXDI)	5.41 ± 0.27	1.76 ± 0.67
Reference copolymer		
40(UDMA)	6.21 ± 0.21	6.26 ± 0.51
Control		
Sterile water	11.42 ± 0.05	11.01 ± 0.25

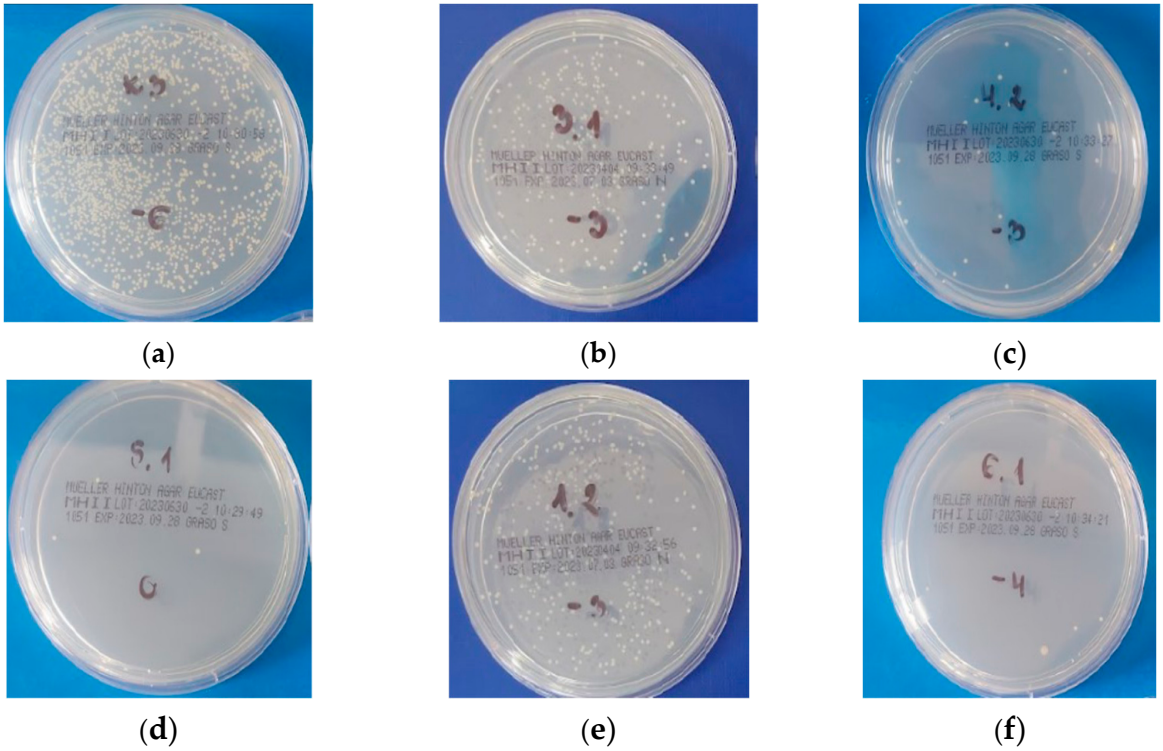


Figure 3. *S. aureus* colonies on Petri dishes after the adhesion test: (**a**) sterile water; (**b**) 40(UDMA); (**c**) 20(QA8+TMXDI); (**d**) 40(QA8+TMXDI); (**e**) 20(QA10+TMXDI); (**f**) 40(QA10+TMXDI).

4. Discussion

In this study, three QAn+TMXDI monomers were synthesized utilizing a procedure known from the literature [12]. The synthesis was carried out to obtain monomers with two quaternary ammonium groups and a core derived from 1,6-diisocyanato-2,2,4-trimethylhexane (QAn+TMDI). The three-step process involved the synthesis of HAMA and QAHAMA-n semi-products, and the final synthesis of QAn+TMDI. We replaced TMDI with TMXDI, and QA8+TMXDI, QA10+TMXDI, and QA12+TMXDI (Figure 1) were obtained. Two of these products, QA10+TMXDI, and QA12+TMXDI, were described in our previous work [13], while QA8+TMXDI is new and presented in the literature for the first time.

The bacteria adhesion test demonstrated that the antibacterial activity depended on the length of the N-alkyl chain. As the logCFU/mL values for 20(QA8+TMXDI) and 40(QA8+TMXDI) were lower than those for 20(QA10+TMXDI), 20(QA12+TMXDI), and

40(QA10+TMXDI), it can be concluded that the shorter the N-alkyl substituent, the higher the antibacterial activity of the copolymer (Table 3). The mechanism of antibacterial action of the quaternary ammonium (QA) compound, leading to bacteria death, indicates that the N-alkyl substituent should have a specific length to allow for effective interaction between the cationic QA group, which contains negatively charged compounds forming the bacteria cell wall [16]. According to Gilbert et al., effective antibacterial action can be achieved for N-alkyl substituents constituting from 4 to 18 carbon atoms. This is due to the similar length of the N-alkyl substituent and the number of carbon atoms in the alkyl chains present in the compounds used to build bacteria cell walls [17]. The present study showed that the highest antibacterial activity was achieved for 20(QA8+TMXDI) and 40(QA8+TMXDI), indicating that the N-octyl substituent was the most efficient. This finding is in agreement with the finding of Yudovin-Farber, who observed the highest antibacterial activity in quaternary ammonium polyethyleneimine nanoparticles quantized with octyl bromide [18]. Another parameter that influences the antibacterial properties is the concentration of QAn+TMXDI in copolymers. We found that the logCFU/mL values for 20(QA8+TMXDI) and 20(QA10+TMXDI) were higher than those for 40(QA8+TMXDI) and 40(QA10+TMXDI), leading to the conclusion that the higher the QAUDMA content in the copolymers, the higher their antibacterial activity.

5. Conclusions

In comparison to copolymers based on QAn+TMDI, the use of QAn+TMXDI for the synthesis of copolymers with Bis-GMA, UDMA, and TEGDMA can improve the physico-chemical and mechanical properties but decreases the antibacterial activity of copolymers. This study showed that antibacterial activity increased with an increase in the length of the N-alkyl substituent and an increase in the QAn+TMXDI content in the copolymer. As the 40(QA8+TMXDI) copolymer had the highest antibacterial activity, further studies should focus on an analysis of the physico-mechanical properties and cytotoxicity of this copolymer and its derivatives. Antibacterial activity studies should also be extended to the *Streptococcus mutans* strain, the most common pathogenic bacteria present in the human mouth.

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