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Design of Thermoplastic Polyurethanes with Conferred Antibacterial, Mechanical, and Cytotoxic Properties for Catheter Application

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Cite This: https://doi.org/10.1021/acsabm.2c00531 Read Online

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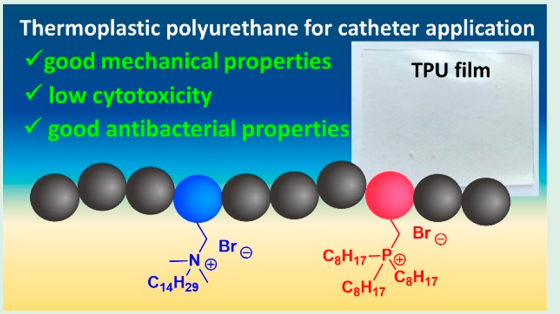
ABSTRACT: Thermoplastic polyurethanes (**TPUs**) are proposed as suitable solution for the fabrication of biocompatible catheters with appropriate mechanical parameters and confirmed antibacterial and cytocompatible properties. For this purpose, a series of quaternary ammonium salts (**QASs**) and quaternary phosphonium salts (**QPSs**) based monomers were prepared followed by the determination of their minimal inhibitory concentrations (MICs) against Gram-positive *Staphylococcus aureus* (*S. aureus*) and Gram-negative *Pseudomonas aeruginosa* (*P. aeruginosa*). A combination of the most active ammonium (**QAS-C$_{14}$**) and phosphonium (**QPS-TOP**) salts led to a MIC down to 2.4 μg/mL against *S. aureus* and 9 μg/mL against *P. aeruginosa*, corroborating the existence of a synergistic effect. These quaternary onium salt (**QOS**) units were successfully incorporated along the polymer chain, as part of a two-step synthesis approach. The resulting **TPU-QOS** materials were subsequently characterized through thermal, mechanical, and surface analyses. **TPU-Mix** (combining the most active **QAS-C$_{14}$** and **QPS-TOP** units) showed the highest antibacterial efficiency, confirming the synergistic effect between both **QOS** groups. Finally, an MTT assay on the SiHa cell line revealed the low cytotoxicity level of these polymeric films, making these materials suitable for biomedical application. To go one step further in the preindustrialization approach, proof of concept regarding the catheter prototype fabrication based on **TPU-QAS/QPS** was validated by extrusion.



KEYWORDS: *biomaterials, biomedical applications, polyurethane, antibacterial, onium salts, catheter*

INTRODUCTION

For years now, bacterial infections have represented a major health concern, responsible for severe complications difficult to cure in clinical practice, as alerted by the World Health Organization and governmental authorities.[1,2] In historical context, since the 1940s, antibiotics have been introduced on a large scale for the treatment of microbial infections. However, their misuse led to a significant rise in antibiotic-resistant bacteria, making the situation even more challenging.[3] As a consequence, Hospital/Healthcare-Acquired Infections (HAIs), namely acquired infections after hospital admission, have emerged as an adverse outcome accompanied by prolongating hospitalization and increasing the related patient costs.[4,5] Medical implantable medical devices, such as catheters, are known to be a subject of operative contamination, accounting for a large proportion of HAIs.[6,7] To address this issue, the fabrication of biocompatible biomaterials with conferred antimicrobial, anti-inflammatory, and/or antifouling properties is subject to intense research from the scientific community.[8] In this context, different concepts and designs were proposed for the fabrication of catheters with incorporated bioactive agents that can be subsequently released such as silver ions, antibiotics, nitric oxide, triclosan, chlorhexidine, and others.[9] However, the leaching of cytotoxic species into the patient's body arises as a major drawback. The second option consists of the fabrication of surface-modified materials, aiming to kill the microorganisms, thus suppressing the development of biofilms on contact. Although antimicrobial enzymes are active against specific pathogens, their production costs and denaturation appear detrimental.[10] Ionic species like quaternary ammonium salts (**QASs**)[11] and zwitterionic species represent another class of very effective antibacterial agents.[12,13] In this vein, quaternary phosphonium salts (**QPSs**) demonstrate much higher biocidal properties with broader spectrum compared to their **QAS** counter-

Received: June 8, 2022
Accepted: October 28, 2022

https://doi.org/10.1021/acsabm.2c00531
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

parts.[14,15] This enhanced antibacterial activity is probably due to the larger radius of the phosphorus atom that induces a stronger polarization effect, facilitating the **QPS** adsorption on a negatively charged bacterial cell wall.[16,17] However, in contrast to the other ionic family members, fewer works investigated the preparation of antibacterial **QPS**-based surfaces.[18]

Based on the daily clinical problematic context and the need of new biomaterials with desired properties, the possibility to fabricate biocompatible thermoplastic polyurethanes (**TPUs**) with incorporated onium salt units for potential catheter application was explored. The **TPU** synthetic pathway was studied in order to fine-tune the working conditions and obtain materials with specific composition and optimal final physicomechanical and biological properties. Therefore, a range of **TPUs** was developed with a great range of mechanical properties. After the successful incorporation of the active agents (0.5 mol %),[19] their antibacterial and cytotoxicity properties were studied. Additionally a mixture of **QAS**/**QPS** in an appropriate molar ratio was tested for the synergistic effect once incorporated in the **TPU** matrix.[20] It can be noted that antibacterial agents combining ammonium and phosphonium groups remain very rare in the literature.[21,22]

RESULTS AND DISCUSSION

For the successful fabrication of the **TPU**-based catheter, a series of quaternary onium salts (**QOSs**) were first synthesized. As a next step, it was of importance to fine-tune the **TPU** physicomechanical properties by taking into account the synthesis conditions and the monomers' molar ratio in order to achieve the materials expected application properties. Prototype feasibility of the catheter was also studied.

Synthesis of Quaternary Onium Salts. The preparation of polymerizable **QOSs** was performed from 3-bromopropane-1,2-diol (**Br-diol**) in the presence of varied tertiary amines or phosphines (Figure 1). These compounds possess short and long alkyl chains (from methyl to hexadecyl) and aryl functional groups for a phosphorus derivative. Indeed, it is well established that positively charged molecules can interact with the negatively charged domains of the bacterial cell wall, whereas long alkyl chains can interact with the bacterial wall and disrupt its architecture.[23] Hence, quaternization of nitrogen of trimethylamine, *N*,*N*-dimethyloctan-1-amine, *N*,*N*-dimethyltetradecan-1-amine, *N*,*N*-dimethylhexadecan-1-amine, and trioctylamine by **Br-diol** in refluxing ethanol gave rise to the corresponding quaternary ammonium salts, namely **QAS-C$_1$**, **QAS-C$_8$**, **QAS-C$_{14}$**, **QAS-C$_{16}$**, and **QAS-TOA** with 78 to 90% yields, respectively (Table 1).

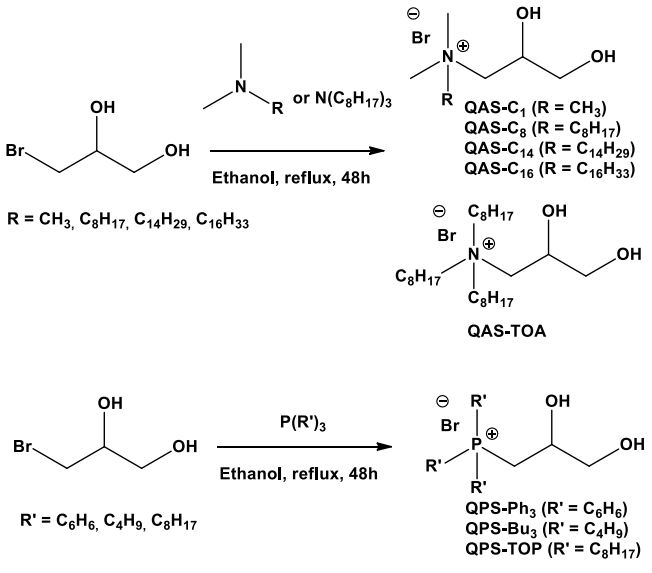


Figure 1. Synthesis of quaternary onium salts (**QOSs**).

Table 1. Reaction Yields of Prepared Quaternary Onium Salts

compound	starting amine or phosphine	reaction yield (%)
QAS-C$_1$	$N(CH_3)_3$	78
QAS-C$_8$	$N(CH_3)_2(C_8H_{17})$	89
QAS-C$_{14}$	$N(CH_3)_2(C_{14}H_{29})$	90
QAS-C$_{16}$	$N(CH_3)_2(C_{16}H_{33})$	87
QAS-TOA	$N(C_8H_{17})_3$	86
QPS-Ph$_3$	$P(C_6H_6)_3$	63
QPS-Bu$_3$	$P(C_4H_9)_3$	72
QPS-TOP	$P(C_8H_{17})_3$	73

Under the same conditions, the reaction between triphenyl-, tributyl-, and trioctylphosphine and **Br-diol** provided the quaternary phosphonium salts, i.e., **QPS-Ph$_3$**, **QPS-Bu$_3$**, and **QAS-TOP**, respectively, in 63 to 73% yields (Table 1).

Synthesis of Modified TPU. As far as the synthesis of (modified) **TPU** is concerned, preliminary results confirmed that a two-step polyaddition method was required to meet the criteria to reach good physical properties of the materials. First, a prepolymer was obtained through the reaction between poly(tetrahydrofuran) (PTHF) and 4,4′-methylenebis(phenyl isocyanate) (MDI) in a ratio of 1:2.2 in DMF at 90 °C. In the second step, a mixture of a prepolymer, MDI, and 1,4-butanediol (BDO) employed in a ratio of 1:2.2:3 led to the successful synthesis of **TPU** as a reference material - **TPUr**. This strategy allowed the production of a polymer with desired structural regularity, mechanical properties, and high molecular weight (M_n of 38 kDa), as evidenced by gel permeation chromatography (GPC). In a step further, the preparation of modified **TPU** (**TPU-QOS**) incorporating ammonium (**TPU-QAS**), phosphonium (**TPU-QPS**), or a mixture of ammonium/phosphonium **TPU-Mix** active moieties was carried out in two steps following the procedure described for the formation of **TPUr** (Figure 2). In that case, ammonium and/or phosphonium units were introduced in the second step of the reaction using only 0.5 mol % compared to the other reagents. Hence, compounds **TPU-QAS-C$_1$**, **TPU-QAS-C$_8$**, **TPU-QAS-C$_{14}$**, **TPU-QAS-C$_{16}$**, and **TPU-QAS-TOA** were composed of ammonium units; **TPU-QPS-Ph$_3$**, **TPU-QPS-Bu$_3$**, and **TPU-QPS-TOP** contained a phosphonium unit, whereas **TPU-Mix** was prepared with an equimolar ratio of **QAS-C14**/**QPS-TOP** targeting a potential synergistic antibacterial effect (This choice will be explained in the section relative to the antibacterial activity of **QAS** and **QPS** monomers.). The modified polymers were isolated in good reaction yields (up to 91%), with a molecular weight in the range from 26 to 36 kDa, as determined by GPC analysis (Table 2). The incorporation of about 0.5 mol % of the ionic species along the polymer macromolecular chain was additionally confirmed by ^{1}H NMR.

Physical Characterization of TPU. The obtained materials were subjected to FT-IR spectroscopic analysis. For

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ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

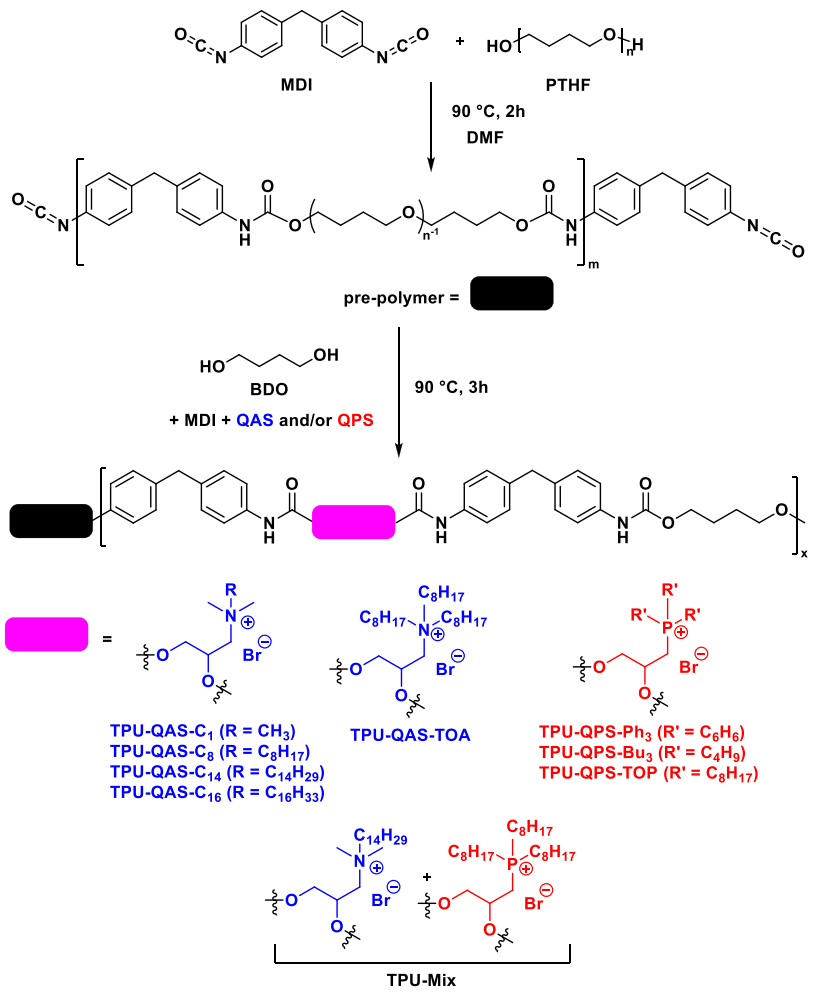

Figure 2. Synthesis of modified **TPU** (**TPU-QOS**) incorporating an ammonium (**TPU-QAS**) or a phosphonium (**TPU-QPS**) unit or a mixture of **QAS-C14**/**QPS-TOP** in a 1:1 ratio.

Table 2. Chemical Composition, Reaction Yields, and M_n of the Synthesized TPUr and TPU-QOS

	TPU composition (molar ratio): PTHF (1)/MDI (4.4)/BDO/QOS			
compound	BDO	QOS (salt)	reaction yield (%)	M_n (kDa)
TPUr	3	0	91	38
TPU-QAS-C$_1$	2.96	0.04 (**QAS-C$_1$**)	90	36
TPU-QAS-C$_8$	2.96	0.04 (**QAS-C$_8$**)	89	32
TPU-QAS-C$_{14}$	2.96	0.04 (**QAS-C$_{14}$**)	90	30
TPU-QAS-C$_{16}$	2.96	0.04 (**QAS-C$_{16}$**)	91	27
TPU-QAS-TOA	2.96	0.04 (**QAS-TOA**)	88	29
TPU-QPS-Ph$_3$	2.96	0.04 (**QPS-Ph$_3$**)	87	26
TPU-QPS-Bu$_3$	2.96	0.04 (**QPS-Bu$_3$**)	90	27
TPU-QPS-TOP	2.96	0.04 (**QPS-TOP**)	91	29
TPU-Mix	2.96	0.02 (**QAS-C$_{14}$**)+ 0.02 (**QPS-TOP**)	87	28

all samples, the formation of urethane functionalities was evidenced by the vanishing of the NCO characteristic band at 2270 cm^{-1} and the appearance of an absorption band at 3300 cm^{-1}, 1700−1730 cm^{-1}, and 1450−1530 cm^{-1}, characteristic for N−H, C═O, and C−N bonds, respectively. In addition, the presence of other typical bands for MDI (C═C stretching vibration at 1500−1700 cm^{-1}), PTHF, and BDO (bending vibration of C−H at 2850−2940 cm^{-1} and C−O−C strong absorption at 1100 cm^{-1}) confirms the successful polymerization. As an example, FT-IR spectra of **TPUr**, **TPU-QAS-C$_{14}$**, and **TPU-QPS-TOP** are presented in Figure 3.

Thermal Analysis of TPU. It was of particular interest to investigate the materials' thermal stability by thermogravimetric analysis (TGA), as well as the thermal transitions by modulated differential scanning *calorimetry* (*MDSC*). TGA obtained thermograms revealed three stages of thermal degradation, where the greater weight loss was observed during the first degradation temperature (T_d) taking place around 300 °C (Figure 4). The T_d's around 300−350 °C and 400−450 °C are characteristic for urethane and ether functional groups, respectively.[24] An exception is the **TPU-QAS$_{14}$** sample, where the weight loss at lower temperatures (onset values around 100 °C) could be assigned to the lower thermal stability of the samples and the occurrence of the Hofmann elimination reaction of the quaternary ammonium group, usually occurring at a temperatures higher than 150 °C.[25] In contrast, phosphonium groups are known to be stable up to 300 °C.[26] For some of the specimens, a third T_d was observed around 550 °C. Overall, all compounds were characterized with good thermal stability, making them suitable for catheter application.

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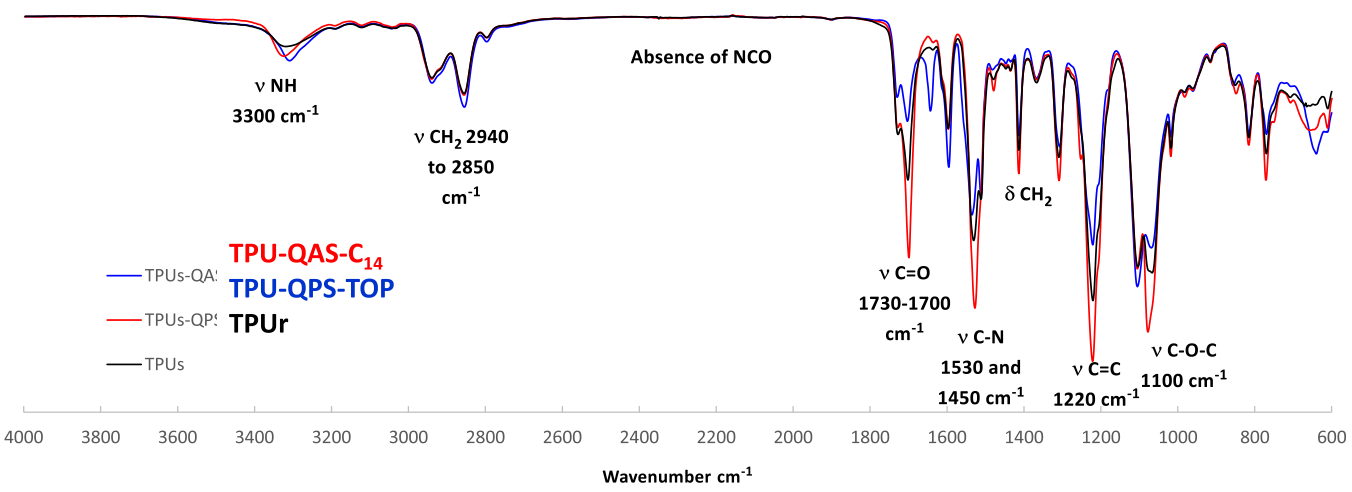

Figure 3. FT-IR spectra of **TPUr** (black), **TPU-QAS-C$_{14}$** (red), and **TPU-QPS-TOP** (blue).

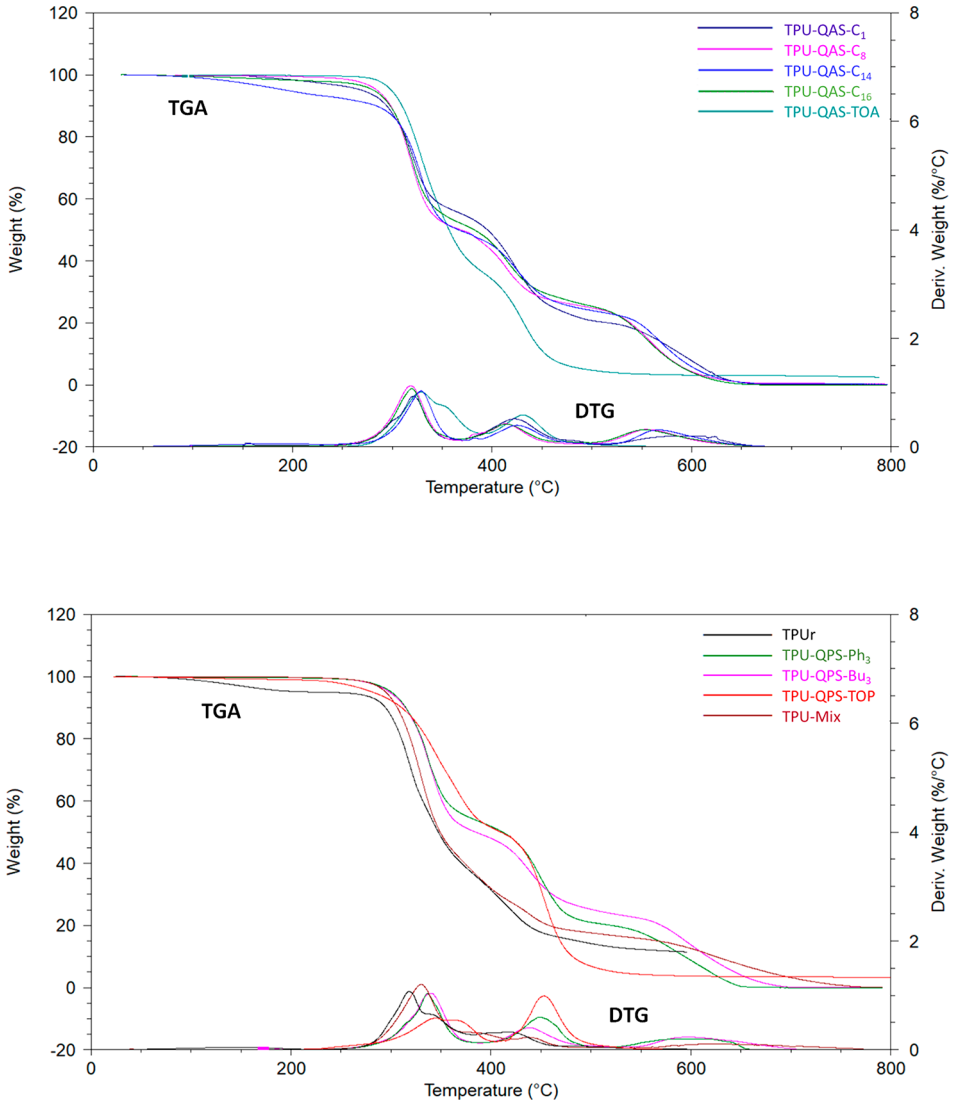

Figure 4. TGA thermograms of **TPUr** and **TPU-QOS** and the corresponding derivative thermogravimetry (DTG) curves showing the decomposition rate.

Based on the *MDSC* analysis, it was noticed that the glass transition temperature (T_g) of **TPU-QOS** increases, from −35 to −10 °C, after the incorporation of the ammonium and phosphonium units. This can be explained with the greater macromolecular chain mobility toward a greater degree of order after the addition of the active moieties, as part of the

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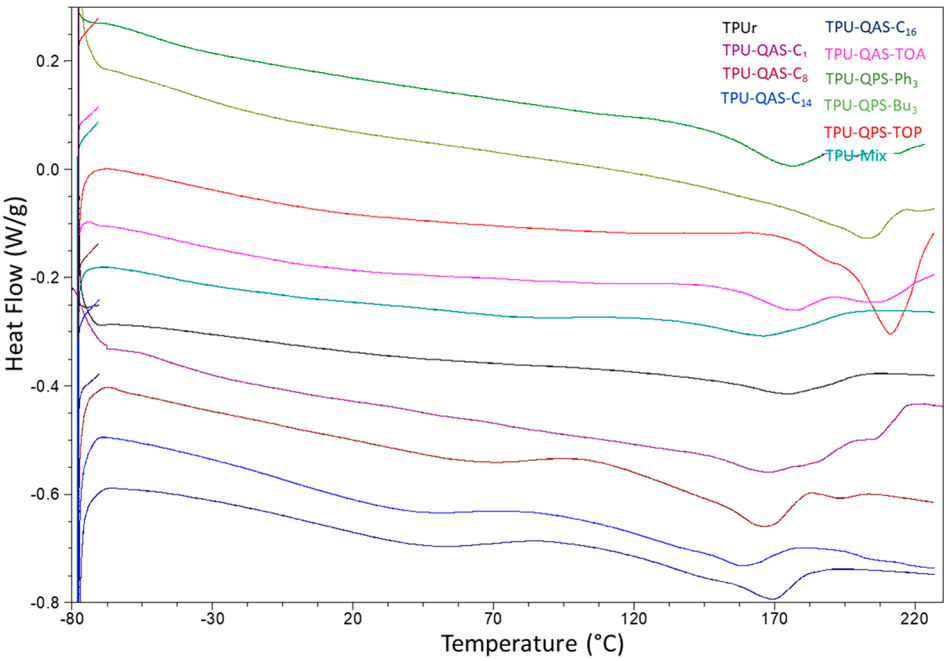

Figure 5. DSC thermograms (2nd heating cycle) of **TPUr** and **TPU-QOS**.

hard segment.[27] Thermal transitions relative to the materials soft segment melting temperature (T_m) can be observed in the range of 156 to 170 °C, explained with the high hard segment content.[28] The decrease in T_m values, from 189 °C for **TPUr** to 145 °C for **TPU-QPS-TOP**, was explained with the addition of the ionic moieties, reflecting again the greater polymer chains mobility and less thermally stable crystalline domains (Figure 5). Both results related to the increase in T_g and the decrease in the T_m values after the incorporation of the active moieties reflected the lower molecular weight as seen in the GPC results for **TPU-QOS**.

Mechanical Tests of TPU. One of the most important properties of the present materials is their physicomechanical properties, presenting a key element for the **TPU** potential use as catheters. Therefore, the synthesized materials subjected to stress−strain tests are presented in Figure 6. The mean values of the Young's modulus are presented in Figure 7. From the obtained data it was concluded that the mechanical properties of the **TPU**-based materials depended on the materials' chemical composition, even at only 0.5 mol % of the incorporated QOS. It was found that the incorporation of **QAS-C$_{14}$** presented an optimal solution to preserve the rigidity of **TPUr**, while conferring biological properties: **TPU-QAS-C$_{14}$** Young's modulus was 302 MPa, slightly lower in values compared to **TPUr** (324 MPa).

It is worth mentioning that Young's modulus lower values were also obtained in the case of the incorporation of **QAS-C$_1$**, **QAS-C$_8$**, and **QAS-C$_{16}$**, but they are still in the acceptable strength range for catheter designing (Figure 7).[29]

TPU-QAS-C$_{14}$ was characterized with a slightly low strain at break (162%) compared to **TPUr** (230%), due to the lower Mn of the **TPU-QAS** sample (Table 2). On the other hand, the lower Young's values for **TPU-QAS-C$_8$** were responsible for the elastomeric properties of the material, where the strain at break was 312%. **TPU-QAS-C$_{16}$** presented lower strain at break values (106%), in accordance with the low Young's modulus value (116 MPa). In the case of the **QPS** incorporation, a drop in the **TPUs**' Young's modulus was also observed. However, the **TPU-QPS**-based materials were still considered with suitable mechanical properties: the obtained Young's modulus was 231 MPa, 175, and 162 MPa for **TPU-QPS-Ph$_3$**, **TPU-QPS-Bu$_3$**, and **TPU-QPS-TOP**, respectively. In this series of materials, only **TPU-QPS-TOP** presented strain at break close to **TPUr** (250%), while **TPU-QPS-Ph$_3$** and **TPU-QPS-Bu$_3$** had lower values: 162% and 208%, respectively. The obtained data were in accordance with the lower Mn referenced to the **TPU-QPS**-based samples.

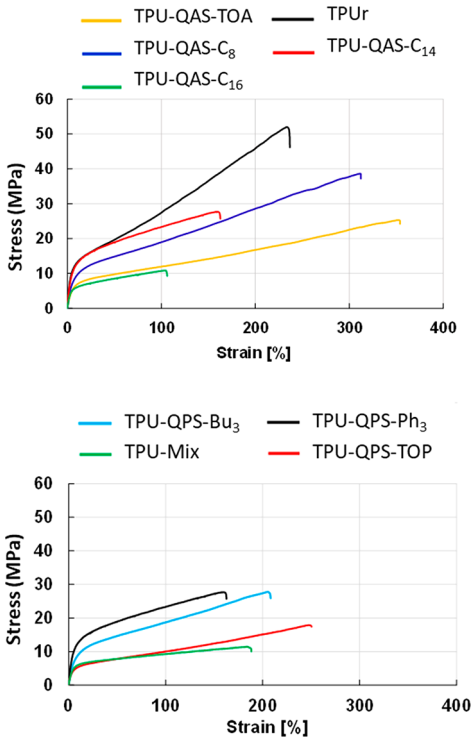

Figure 6. Stress−strain curves of **TPUr** and **TPU-QAS** (up) and **TPU-QPS** and **TPU-Mix** (down).

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ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

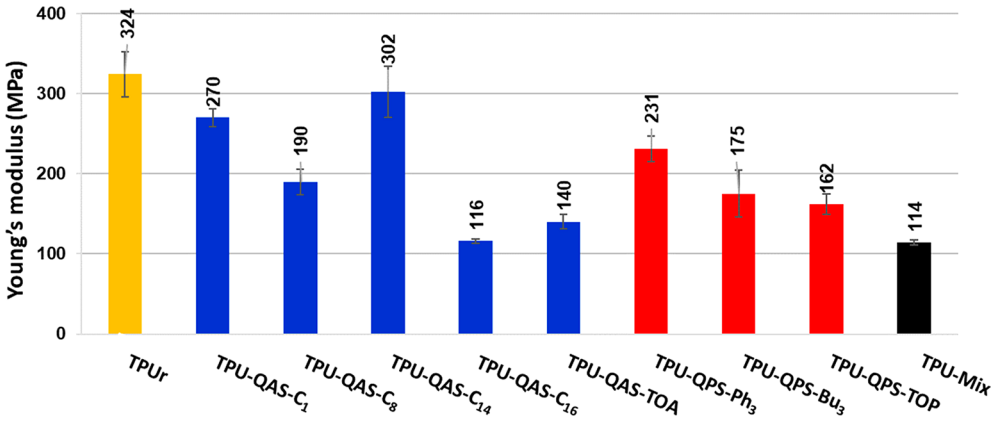

Figure 7. Young's modulus values of **TPUr** and **TPU-QOS**.

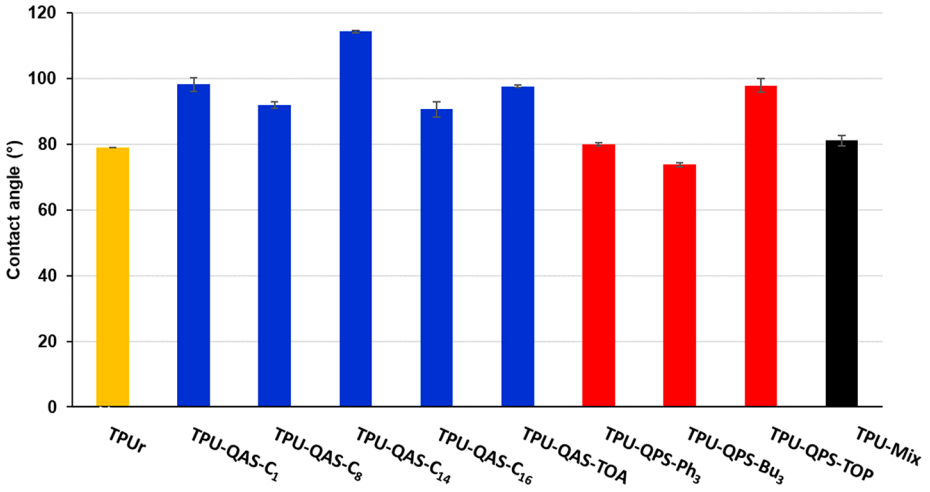

Figure 8. Contact angle values of **TPUr** and **TPU-QOS**.

From a materials point of view, it was promising to combine the mechanical properties of **TPU-QAS-C_{14}** for its good Young's modulus values and **TPU-QPS-TOP** for its good elongation at break. Finally, the **TPU-Mix** sample presented lower Young's modulus values (114 MPa) and increased elongation at break (188%) compared to **TPU-QAS-C_{14}**. In accordance with the literature, **TPU-QAS** and **TPU-QPS** presented slightly low mechanical properties due to the presence of pendant groups, as referenced to **TPUr**.[30] The material DMTA results can be consulted in the SI (Figure S1).

When considering catheter application, two important mechanical factors must be taken into consideration: 1) flexibility of the material to ensure applicable and comfort insertion and removal of the catheter and 2) material strength to ensure the ability to withstand pressure during injection of fluids. Kucinska-Lipka et al. studied the mechanical properties of neat and (1% and 2%) L-ascorbic acid-modified **TPU** designed for medical applications.[31] The results of performed studies showed a tensile strength between 7.5 and 6 MPa and 174% and 170% elongation at break.

Based on the findings presented above, the developed **TPU-QOS**-based materials present interesting mechanical properties, competitive with the available and already used ones in clinical practice materials. For example, intravenous catheters present various mechanical properties as PVC catheters (Vialon) are characterized with Young's modulus around ~34 MPa and PVC- and Teflon-based catheters (FEP 100 Silastic) are characterized with Young's modulus values around ~25 MPa. Silicon catheters (Silastic), as soft material, have Young's modulus around ~1.5 MPa, and PU materials (single-lumen peripherally inserted central venous catheters) have stiffness in the range from 14 to 74 MPa.[32,29]

Surface Analysis of TPU. Taking into account the application field and the high-water content in living organisms, we evaluated the contact angle of the materials. The measurements confirmed the hydrophobicity of the synthesized **TPU-QAS**, and values of 80° were obtained for **TPUr** and slightly increased for **TPU-QAS** (values between 90 and 150°), due to the presence of the alkyl chain in the **QAS** chemical structure (Figure 8). Surface analysis of **TPU-QPS** revealed angle values (80−100°) close to **TPUr**. **TPU-Mix** presented similar to the reference specimen angle values (80°). In a recent work, a **TPU** having the Tecoflex composition, namely **TPU** used for catheter fabrication, showed a contact angle value of 92°.[33]

X-ray photoelectron spectroscopy (XPS) analysis of the specimens (elemental surface composition) is presented in Table S2. The atom percentages for C, N, and O in the samples were in the following range: 58.82−68.96%, 1.31−3.02%, and 21.11−25.61%, respectively (The presence of P atoms was not detected with the used technique.). The **TPU-QAS** deconvoluted C 1s spectra revealed a slight increase in the surface area characteristic for C−H/C−C bonds (285 eV) in comparison to **TPUr** (Figure S2). This surface enrichment

https://doi.org/10.1021/acsabm.2c00531
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with C−H/C−C bonds (direct impact of the QAS incorporation) was responsible for the higher contact values of the TPU-QAS samples. This effect was less pronounced in the case of **TPU-QPS**. The incorporation of the active moieties led to a decrease in the C−O−C/C−N (286 eV) and O═C−O (289 eV) bone specific surface area. In the case of **TPUs-QPS-Ph$_3$** and **TPUs-QPS-Bu$_3$**, the C−H/C−C and C−O−C/C−N bond surface areas in the deconvoluted XPS spectra remained close in value to **TPUr**, explaining the close contact values of the specimens.

QOS Antibacterial Activities. The antibacterial properties of the synthesized active moieties, i.e., ammonium and phosphonium monomers, were first evaluated by determining their minimal inhibitory concentrations (MICs). The ionic compounds were tested against Gram-positive *Staphylococcus aureus* (*S. aureus*) and Gram-negative *Pseudomonas aeruginosa* (*P. aeruginosa*) bacteria (Table 3). These strains were selected

Table 3. MIC of the Synthesized Moieties of QOSs against *S. aureus* and *P. aeruginosa*

	MIC (μg/mL)	
compound	*S. aureus*	*P. aeruginosa*
QAS-C$_1$	>2500	>2500
QAS-C$_8$	310	2500
QAS-C$_{14}$	4.88	78
QAS-C$_{16}$	<2.44	156
QAS-TOA	310	2500
QPS-Ph$_3$	2500	>2500
QPS-Bu$_3$	2500	>2500
QPS-TOP	39	1250
QPS-TOP+QAS-C$_{14}$	2.4	9

considering *S. aureus* is one of the five most common causes of hospital-acquired infections, while *P. aeruginosa* shows a high resistance to many biocides.[34] Therefore, compounds able to target these strains could be good candidates for antibacterial catheter manufacturing. Concerning the **QASs**, the antibacterial effect was improved when the alkyl chain length increases, as observed for **QAS-C$_1$** to **QAS-C$_{16}$**.[35] Hence, MIC values drop from >2500 to 2.4 μg/mL against *S. aureus* and 78 μg/mL against *P. aeruginosa* (for **QAS-C$_{14}$**). Interestingly, **QAS-TOA** and **QAS-C$_8$** exhibit the same activity against both strains (MIC = 310 μg/mL against *S. aureus* and no activity against *P. aeruginosa*). On the other hand, both **QPS-Ph$_3$** and **QPS-Bu$_3$** did not show any antibacterial activity (MIC > 2500 μg/mL), whereas **QPS-TOP** has a significant antibacterial effect against *S. aureus* (MIC = 39 μg/mL) and is inactive against *P. aeruginosa* (MIC = 1250 μg/mL). This slight difference of activity between **QAS** and **QPS** could be attributed to the molecular structure of the salts and the intrinsic properties of the quaternized atoms. Phosphorus has a larger atom radius than nitrogen, and thus, it exhibits a lower electronegativity. As aforementioned, **QPSs** are weaker associated cations and have a stronger polarization effect compared to **QASs** making their adsorption onto negatively charged bacterial membranes easier.[36,37] From these results, **QOSs** show higher antibacterial activity against Gram-positive bacteria than Gram-negative ones, probably due to the existence of the phospholipid bilayer on the latter one rendering them more difficult to penetrate.[38]

Finally, the most active onium salts, namely **QAS-C$_{14}$** and **QPS-TOP**, were combined and dissolved in water. As a result, their MIC reached 2.4 μg/mL against *S. aureus* and 9 μg/mL against *P. aeruginosa*, corroborating the existence of a synergistic effect. Indeed, **QAS** integrates through its hydrophobic tail (when the alkyl chain length is longer than C8) into the lipid layers of the bacterial cell membrane and damages it by forming pores and disrupting membrane functions.[39] **QPS**, on the other hand, forms defects on the bacterial cell wall leading to aberrant septation.[39,40] Therefore, when combining these agents, **QAS** helps with creating pores into the surface, due to its longer alkyl chain, and **QPS** becomes even more potent due to the reduced cell permeability. **QAS-C$_{14}$** and **QPS-TOP** were thereby chosen for the preparation of **TPU-Mix**.

Contact Antibacterial Activity of TPU-QOS. Another aspect to be evaluated was the **TPU-QOS** antibacterial activity in a contact antimicrobial assay, as previously communicated.[19] Indeed, these polymeric ionic compounds are expected to possess a contact killing behavior toward both Gram-positive and Gram-negative bacteria.[15] As the active moieties are covalently bonded to the TPU, no growth inhibition is to be expected when testing the films' antibacterial activity. Nevertheless, the number of surviving bacteria in this contact assay decreased (Figure 9) concomitantly with the **QAS** alkyl chain length, in agreement with their specific antibacterial activity (Table 4). Similarly, for **QPSs**, a slight antibacterial activity and surviving bacteria log reduction were only observed with **QPS-TOP**, further stressing the importance of the alkyl chain length. **TPU-Mix** revealed the most efficient antibacterial activity (3 log CFU reduction) confirming the desired/aimed synergistic effect between the two active moieties. This antibacterial polymeric material exhibits high activity toward both Gram-positive and Gram-negative bacteria compared to efficient antibacterial materials used for biomedical applications.[41−43] The same hypothesis for the synergistic effect, as in the case of the MIC, holds for these polymeric materials. For short-chain salts, such as **QPSs** having a higher adsorption potency, the antimicrobial activity relies solely on the positively charged group coupling with the negatively charged bacterial cell wall to disrupt membrane functions, to alter membrane potential, to reduce protein activity, and to damage bacterial DNA.[44] Whereas long-chain salts, such as **QAS-C$_{14}$**, not only can destabilize the bacteria cell wall through their positive charges (yet lower than **QPSs**) but also can be inserted into the bacterial membrane, resulting in physical disruption.[23] Another hypothesis can be that in the **TPU-Mix**, **QOS** distribution and/or availability could be improved compared to other modified **TPUs**. However, no characterization test was performed to verify this suggestion.

Cytotoxicity Analysis. *IC_{50} Determination of Dissolved Polymers.* The IC_{50} of **TPUr** and **TPU-QOS** (dissolved in DMSO) was evaluated in an MTT assay after 24, 48, and 72 h of incubation. The results of the cytotoxicity assay on the SiHa cell line are shown in Figure S7, and the IC_{50} values are listed in Table 4 and Table S3. A dose-dependent decrease in viability was similarly observed for all the samples. It is worth mentioning that cationic carriers exhibit a toxic effect on cells. They tend to disturb the cell membrane integrity and decrease their metabolic activity.

Therefore, a low amount of charged groups is advised to be incorporated in polymers for the sake of cytocompatibility.[45−47] A comparison of the IC_{50} values indicated that the inhibitory effect on cell proliferation is on the same order of magnitude for all compounds.

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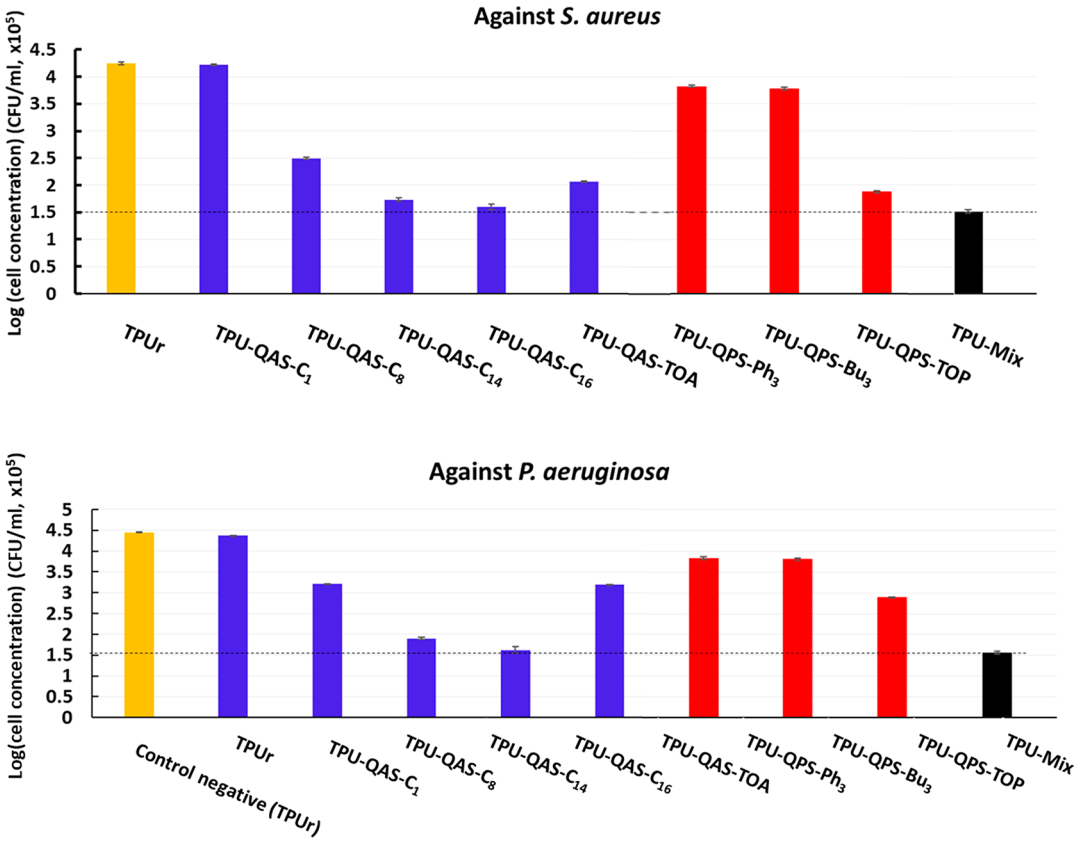

Figure 9. Antibacterial activity of **TPUr** and **TPU-QOS** against *S. aureus* (top) and *P. aeruginosa* (bottom).

Table 4. IC_{50} Values of TPUr and TPU-QOS against the SiHa Cell Line

compound	IC_{50} (μg/mL)
TPUr	17
TPU-QAS-C_1	19
TPU-QAS-C_8	11
TPU-QAS-C_{14}	18
TPU-QAS-C_{16}	15
TPU-QAS-TOA	26
TPU-QPS-Ph_3	20
TPU-QPS-Bu_3	19
TPU-QPS-TOP	22
TPU-Mix	22

The IC_{50} values proved that the synthesized salts are toxic to the cells. However, once covalently incorporated in the polymer this difficulty is overcome since the active moieties are now part of the **TPU-QAS** polymer macromolecular chain. Therefore, a cytotoxicity study on the polymer (in a solid form) was subsequently performed.

Cytotoxicity of Polymer Films. The cytotoxic effect of **TPUr** and **TPU-QOS** films was also studied on the SiHa cell line for a 24-, 48-, or 72-h cell exposure, following a 24-h preincubation in cell culture medium. This procedure was realized in accordance with ISO 10993-5. Afterward, an MTT tetrazolium assay was carried out to determine the % cell viability after exposure to the ionic compounds compared to control samples. Materials are usually defined as toxic when cell viability is reduced by more than 30% and slightly toxic for values between 60% and 90%.[48] The formazan product reflecting the number of living SiHa cells had slightly decreased after 24 and 48 h compared to the control (Figure 10). After 72 h, about 80% of cell viability was observed without a significant difference between the polymeric compounds. **TPU-QOS** thus demonstrated a slight cytotoxicity reaching an acceptable value for biomedical application in comparison with other biomaterials.[49,50]

Having the **QOSs** covalently bonded to the polymer and in a very low percentage probably helps to maintain a low cytotoxicity level, leading to a safe material for biomedical applications. According to the available literature, latex urinary catheters are considered highly toxic.[51] A study done by Ruutu et al. brought to attention the highly toxic effect of the latex catheter eluate on various human cell cultures.[52] Additionally, Pariente et al. advised removing the latex used in catheters after proving their high toxicity on human urothelial cells for both indirect and direct contact tests.[53]

Catheter Fabrication. As a final step, catheter prototype fabrication based on the most promising compound **TPU-Mix** was carried out through an extrusion process (parallel twin-screw extruder), as described in our previous study.[19] Based on the morphological analysis, the resulting material presented a homogeneous compact polymer matrix and confirmed the thermal stability (absence of color change and thermo-oxidative degradation) and the processing feasibility of the material (Figure 11).

Further tests on the catheter should be performed in the presence of human blood in order to evaluate blood cell viability, adhesion, and coagulation impact. An additive manufacturing approach, such as fused deposition modeling − 3D printing, should additionally be explored for the concept and design of personalized catheters with complex shapes for implants with antibacterial and cytocompatibility properties.

https://doi.org/10.1021/acsabm.2c00531
ACS Appl. Bio Mater. XXXX, XXX, XXX−XXX

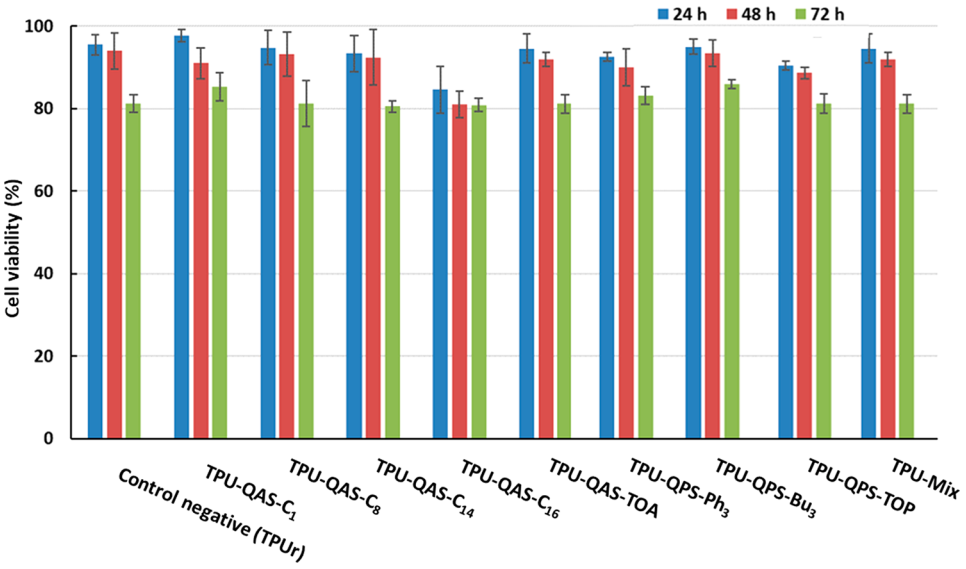

Figure 10. Percentage of cell viability of SiHa cells after being exposed 24, 48, and 72 h to **TPUr** and **TPU-QOS**.

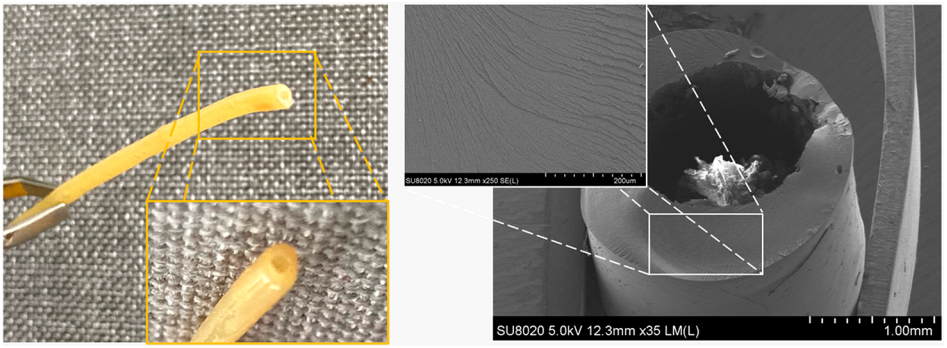

Figure 11. Digital photo and SEM micrograph of the **TPU-Mix** prototype catheter.

CONCLUSIONS

In summary, **TPUs** endowed with suitable mechanical, antibacterial, and cytotoxic properties for potential catheter application were designed. A series of modified polymeric materials were obtained, containing ammonium and/or phosphonium salt units as antibacterial agents. The resulting stress−strain curves evidenced mechanical properties competitive with the available on the market catheters already used in clinical practice, making the **TPU-QOS** suitable for the required application. Moreover, the materials demonstrated good thermal stability and T_m far above 100 °C, making them acceptable for sterilization procedures in clinical practice. In addition to the material hydrophobic characteristics, their antibacterial behavior against Gram-positive *S. aureus* and Gram-negative *P. aeruginosa* was confirmed by incorporating only 0.5 mol % of the **QAS** and **QPS** in the polymer. The combination of **QAS-C$_{14}$** and **QPS-TOP** acted synergistically, leading to a MIC lower than 9 μg/mL against both strains. This trend was corroborated through contact antimicrobial assays of corresponding polymers. A comparison of **TPUr** and **TPU-QOS** confirmed that the presence of onium units bearing long alkyl chains dramatically decreased the number of living *S. aureus* and *P. aeruginosa*. Moreover, **TPU-Mix** (combining 0.5 mol % of **QAS-C$_{14}$** and **QPS-TOP** units) had the most efficient antibacterial activity, confirming the synergistic effect between the two active onium groups. Finally, an MTT assay on the SiHa cell line confirmed the low cytotoxicity level of **TPUr** and **TPU-QOS** films, making these polymers suitable materials for biomedical application. First prototypes were also developed revealing the great potential of the proposed polymer systems. With the present research, combining polymer synthesis and processing techniques and materials biological evaluation, an ambitious multidisciplinary solution was proposed to go one step further in the fabrication of next generation biologically active biomaterials, such as personalized biocompatible catheters.

EXPERIMENTAL METHODS

Materials. The following compounds were used: poly(tetrahydrofuran) (PTHF, 1000 g/mol, Merck), 4,4′-methylenebis(phenylisocyanate) (MDI, 250.25 g/mol, Alfa-Aesar), 1,4-butanediol (BDO, 90.12 g/mol, Sigma-Aldrich), *N,N*-dimethylformamide anhydrous (DMF, Sigma-Aldrich), 1,1-dimethylethylenediamine (amine, 88.15 g/mol), 3-bromo-1,2-propanediol 97% (Br-diol, 154.99 g/mol, Sigma-Aldrich), 2-(dimethylamino)ethyl acrylate (acrylate, 143.18 g/mol, Sigma-Aldrich), trimethylamine (TMA, 59.11 g/mol, Sigma-Aldrich), *N,N*-dimethyloctylamine (DMOA, 157.30 g/mol, Sigma-Aldrich), trioctylamine (TOA, 353.67 g/mol, Sigma-Aldrich), *N,N*-dimethyltetradecylamine (DMTDA, 241.46 g/mol, Sigma-Aldrich), *N,N*-dimethylhexadecylamine (DMHDA, 269.51 g/mol, Sigma-Aldrich), tributylphosphine (TBP, 202.32 g/mol, Sigma-Aldrich), triphenylphosphine (TPP, 262.29 g/mol, Sigma-Aldrich), trioctylphosphine (TOP, 370.64 g/mol, Sigma-Aldrich), 1-bromo-3-propanol (138.99 g/mol, Sigma-Aldrich), and 2,2-bis(bromomethyl)-1,3-

https://doi.org/10.1021/acsabm.2c00531
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propandiol (261.94 g/mol, Sigma-Aldrich). Acetonitrile (ACN), ethanol (EtOH), methanol (MeOH), dichloromethane (DCM), acetone, tryptic soy broth (TSB), and Mueller-Hinton broth (MHB) were purchased from VWR. All materials were used as-received without further purification.

Characterization. ^{1}H NMR and Fourier transform infrared (FT-IR) spectroscopies, thermal gravimetric analysis (TGA), modulated differential scanning calorimetry (MDSC), X-ray diffraction (XRD), dynamic mechanical thermal analysis (DMTA), and X-ray photoelectron spectroscopy (XPS) analyses were carried out using equipment and conditions previously reported.[19,54,55]

Synthesis. *Synthesis of QOSs.* **QASs** were prepared through the reaction of Br-diol (1.2 equiv) with TMA, DMOA, TOA DMTDA, or DMHDA. The reaction was carried out at 80 °C for 48 h in absolute ethanol. After cooling, the mixture was poured in diethyl ether, leading to the precipitation of the salt. The resulting compound was filtered off and dried to give **QAS-C$_1$**, **QAS-C$_8$**, **QAS-TOA**, **QAS-C$_{14}$**, and **QAS-C$_{16}$**. Likewise, **QPSs** were synthesized using Br-diol (1.2 equiv) with TBP, TPP, or TOP, under the same conditions; however, the reaction was kept running for 72 h at 60 °C in bulk producing **QPS-Bu$_3$**, **QPS-Ph$_3$**, and **QPS-TOP**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.26 (m, −CH−), 3.65−3.42 (m, $-CH_2-$), 3.22 (s, N−CH_3), 1.22 (m, $-CH_2-$), 0.87 (t, J = 6.8 Hz, $-CH_3$).

*3-(Trimethyl-λ^4-azaneyl)propane-1,2-diol Bromide (**QAS-C$_1$**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.94 (m, −CH−), 3.77−3.49 (m, $-CH_2-$), 2.86 (s, $-CH_3$).

*N-(2,3-Dihydroxypropyl)-N,N-dimethyloctan-1-aminium Bromide (**QAS-C$_8$**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.99 (s, −OH), 4.48 (s, −OH), 4.40 (m, −CH−), 3.74−3.67 (m, $-CH_2-$), 3.50 (m, N−CH_3), 3.30 (s, $-CH_3$), 1.74 (m, $-CH_2-$), 1.33 (m, $-CH_2-$), 0.85 (m, $-CH_3$).

*N-(2,3-Dihydroxypropyl)-N,N-dioctyloctan-1-ide-1-aminium Bromide (**QAS-TOA**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.26 (m, −CH−), 3.65−3.42 (m, $-CH_2-$), 3.22 (m, $-CH_2-$), 1.22 (m, $-CH_2-$), and 0.83 (m, $-CH_3$).

*N-(2,3-Dihydroxypropyl)-N,N-dimethyltetradecan-1-ammonium Bromide (**QAS-C$_{14}$**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.26 (m, −CH−), 3.65−3.42 (m, $-CH_2-$), 3.22 (s, N−CH_3), 1.22 (m, $-CH_2-$), 0.87 (t, J = 6.8 Hz, $-CH_3$).

*1-((2,3-Dihydroxypropyl)dimethyl-l4-azaneyl)hexadecane-pentadecaylium Bromide (**QAS-C$_{16}$**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.09 (s, −OH), 4.95 (s, −OH), 3.80 (m, −CH−), 3.69−3.51 (m, $-CH_2-$), 3.34 (s, $-CH_3$), 1.74 (m, $-CH_2-$), 1.24 (m, $-CH_2-$), 0.87 (m, $-CH_3$).

*2,3-(Dihydroxypropyl)triphenylphosphonium Bromide (**QPS-Ph$_3$**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (m, −CH-arom), 7.66 (m, −CH-arom), 4.05 (m, $-CH_2-$), 3.83−3.72 (m, P-CH_2), and 3.44 (m, −CH−).

*2,3-(Dihydroxypropyl)tributylphosphonium Bromide (**QPS-Bu$_3$**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.26 (m, −CH−), 3.70 (m, $-CH_2-$), 2.64 (m, $-CH_2-$), 2.33 (m, P-CH_2), 2.53 (m, $-CH_2-$), and 0.97 (m, $-CH_3$).

*2,3-(Dihydroxypropyl)trioctylphosphonium Bromide (**QPS-TOP**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (s, OH), 3.93 (m, $-CH_2-$), 3.72−3.67 (m, −CH−), 3.47−2.62 (m, $-CH_2-$), 2.30 (m, $-CH_2-$P), 1.25 (m, $-CH_2-$), and 0.87 (m, $-CH_3$).

*Synthesis of **TPUr**.* **TPUr** was synthesized using PTHF/MDI/BDO in a ratio of 1/4.4/3, respectively. In the first step, PTHF (3 g; 3 mmol) was solubilized in DMF (28 mL; 25% w/v) followed by dropwise addition of MDI (1.65 g; 6.59 mmol). The reaction was heated at 90 °C for 2 h. In the second step, MDI (1.65 g; 6.59 mmol) and BDO (0.8 g; 8.87 mmol) were added to the stirring solution, and the reaction was kept at 90 °C for 3 h.

At the end of the reaction, the solvent was evaporated using a ventilated oven overnight at 60 °C, followed by 12 h of drying in a vacuum oven at 60 °C. For purification, Soxhlet extraction was carried out for 48 h at 40 °C using chloroform as a solvent.

Size exclusion chromatography was performed under conditions identical to those previously reported.[19]

^{1}H NMR (500 MHz, THF-d_8): δ 8.59 (s, −NHC═O), 7.35−7.02 (m, H arom.), 4.12 (m, $COOCH_2$), 3.82 (s, Ar−CH_2−Ar), 3.36 (m, $-CH_2-$O), and 1.58 (m, $-CH_2$).

FTIR (in cm^{-1}): 3300 (N−H), 2940−2850 (C−H), 1730−1700 (C═O), 1600 (C−N), 1550−1500 (C═C), and 1100 (C−O−C).

*Synthesis of **TPU-QOS**.* **QOS**-containing **TPUs** were synthesized following the synthesis path of **TPUr**. **QOSs** were incorporated in the second step giving **TPU-QOS**, and the yields and M_n were measured.

*Typical Procedure: **TPU-QAS-C$_{14}$**.* **TPU-QAS-C$_{14}$** was synthesized using PTHF/MDI/BDO/**QAS-C$_{14}$** in a molar ratio of 1/4.4/2.96/0.04, respectively. In the first step, PTHF (3 g; 3 mmol) was solubilized in DMF (28 mL; 25% w/v) followed by dropwise addition of MDI (1.65 g; 6.59 mmol). The reaction was heated at 90 °C for 2 h. In the second step, MDI (1.65 g; 6.59 mmol), BDO (0.8 g; 8.87 mmol), and **QAS-C$_{14}$** (0.047 g; 0.118 mmol) were added to the stirred solution, and the reaction was kept at 90 °C for 3 h.

TPU-QAS-C$_1$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.5 (s, −NHC═O), 7.33−7.07 (m, H arom.), 4.09 (m, $COOCH_2$), 3.88 (s, Ar−CH_2−Ar), 3.4 (m, −CH−), 3.35 (m, O−CH_2), 1.69−1.48 (m, CH_2), 1.29 (m, CH_2), and 0.85 (m, CH_3).

TPU-QAS-C$_8$. ^{1}H NMR (500 MHz, THF-d_8): δ 8.81 (s, −NHC═O), 7.37−7.03 (m, H arom.), 4.13 (m, $COOCH_2$), 3.88 (s, Ar−CH_2−Ar), 3.4 (m, −CH−), 3.35 (m, O−CH_2), 1.69−1.48 (m, CH_2), 1.29 (m, CH_2), and 0.85 (m, CH_3).

TPU-QAS-TOA. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.91 (s, −NHC═O), 7.34−7.07 (m, H arom.), 4.44 (m, −CH−), 4.08 (m, $COOCH_2$), 3.82 (s, Ar−CH_2−Ar), 3.37 (m, $-CH_2-$), 1.58 (m, CH_2), 1.22 (m, CH_2), and 0.84 (m, CH_3).

TPU-QAS-C$_{14}$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.5 (s, −NHC═O), 8.5 (s, −NHC═O), 7.33, 7.07 (m, H arom.), 4.09 (m, $COOCH_2$), 3.88 (s, Ar−CH_2−Ar), 3.4 (m, −CH−), 3.35 (m, O−CH_2), 1.69−1.48 (m, CH_2), 1.29 (m, CH_2), and 0.85 (m, CH_3).

TPU-QAS-C$_{16}$. ^{1}H NMR (500 MHz, THF-d_8): δ 8.69 (s, −NHC═O), 7.37−7.03 (m, H arom.), 4.12 (m, $COOCH_2$), 3.82 (s, Ar−CH_2−Ar), 3.72 (m, −CH−), 3.58 (m, O−CH_2), 3.37 (m, CH_2), 1.58 (m, CH_2), 1.28 (m, CH_2), and 0.85 (m, CH_3).

TPU-QPS-Ph$_3$. ^{1}H NMR (500 MHz, THF-d_8): δ 8.64 (s, −NHC═O), 7.67−7.60 (m, H arom.), 7.37−7.03 (m, H arom.), 4.12 (m, $COOCH_2$), 3.82 (s, Ar−CH_2−Ar), 3.72 (m, −CH−), 3.24 (m, CH_2), 2.6 (m, CH_2), and 1.36 (m, CH_3).

TPU-QPS-Bu$_3$. ^{1}H NMR (500 MHz, THF-d_8): δ 8.62 (s, −NHC═O), 7.36−7.04 (m, H arom.), 4.12 (m, $COOCH_2$), 3.93 (m, CH_2), 3.76 (s, Ar−CH_2−Ar), 3.36 (m, −CH−), 3.23 (m, O−CH_2), 2.95 (m, CH_2), 2.56 (m, CH_2), 1.46 (m, CH_2), and 0.95 (m, CH_3).

TPU-QPS-TOP. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.49−8.50 (s, −NHC═O), 7.33−7.07 (m, H arom.), 4.09 (m, $COOCH_2$), 3.77 (s, Ar−CH_2−Ar), 3.33 (m, $-CH_2-$), 3.29 (m, CH_2), 1.48 (m, CH_2), 1.23 (m, CH_2), and 0.85 (m, CH_3).

TPU-Mix. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.52−8.53 (s, −NHC═O), 7.35−7.08 (m, Ar−H), 3.77 (s, Ar−CH_2−Ar), 4.09 (m, O−CH_2−, 8H), 3.34 (m, O−CH−), 3.6 (s, $-CH_3-$), 1.97 (m, P-CH_2-), 1.48−1.69 (m, $-CH_2-$), 1.23 (m, $-CH_2-$), and 0.85 (m, $-CH_3$).

Biological Tests. Minimum inhibitory concentration (MIC), contact antibacterial activity of polymers, and IC_{50} determination of polymers were determined through the procedures described in a previous study.[19] **Catheter prototyping.** The catheter fabrication was performed through extrusion according to the procedure described in a previous study.[19]

■ ASSOCIATED CONTENT

Supporting Information

. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsabm.2c00531.

Additional experimental details: Thermal values of **TPUr** and **TPU-QOS**; C, O, and N elemental percentages of **TPUr** and **TPU-QOS**; Evaluation of % cell viability and IC_{50} of synthesized **TPU** at different

https://doi.org/10.1021/acsabm.2c00531
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concentrations; E' (storage modulus), E'' (loss modulus), and Tan δ of **TPUr** (black), **TPU-QAS-C$_{14}$** (blue), and **TPU-QPS-TOP** (red); Deconvoluted C1 spectra of **TPUr** and **TPU-QOS**; MIC of **QPS-TOP**, Tween 80, and **TPUr** (control negative) against Gram-positive and Gram-negative bacteria; MIC of **QAS-C14** and **TPUr** against Gram-positive and Gram-negative bacteria; Evaluation of % cell viability of synthesized **TPU** at different concentrations (PDF)

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Conceptualization, F.M. and J.-M.R.; methodology, F.M., J.-M.R., R.A.N., J.V., A.T., and V.F.; validation, F.M., J.-M.R., A.T., and V.F.; formal analysis, F.M., J.-M.R., R.A.N., J.V., A.T., and V.F.; investigation, F.M., J.-M.R., R.A.N., J.V., A.T., and V.F.; resources, F.M., J.-M.R., A.T., and V.F.; data curation, F.M., J.-M.R., R.A.N., J.V., A.T., and V.F.; writing—original draft preparation, F.M., J.-M.R., A.T., and V. F; writing—review and editing, F.M. and J.-M.R.; supervision, F.M. and J.-M.R.; project administration, F.M. and J.-M.R.; funding acquisition, J.-M.R.

Funding

The research was financially supported by the PROSTEM project, the COST action CA15114 "AMiCI" (Antimicrobial Coating Innovations to Prevent Infectious Diseases), and the COST action TD1305 "iPROMEDAI" (Improved PROtection of MEdical Devices Against Infection). SMPC is grateful to the Region Wallonne support in the case of LCFM-BIOMAT.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

J.M.R. is a senior research associate at FRS-FNRS.

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