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Biodegradable Block Copolyelectrolyte Hydrogels for Tunable Release of Therapeutics and Topical Antimicrobial Skin Treatment

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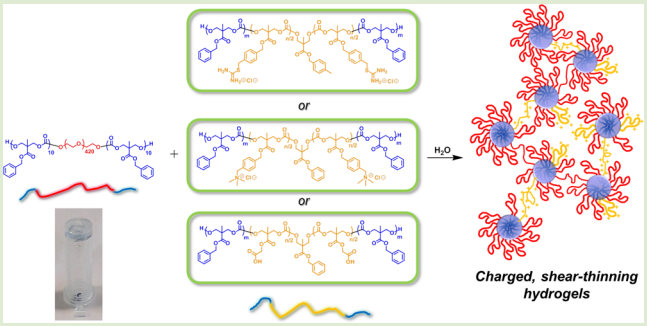
Supporting Information

ABSTRACT: Biodegradable polycarbonate-based ABA triblock copolyelectrolytes were synthesized and formulated into physically cross-linked hydrogels. These biocompatible, cationically, and anionically charged hydrogel materials exhibited pronounced shear-thinning behavior, making them useful for a variety of biomedical applications. For example, we investigated the antimicrobial activity of positively charged thiouronium functionalized hydrogels by microbial growth inhibition assays against several clinically relevant Gram-negative and Gram-positive bacteria. It is noteworthy that these hydrogels exhibited broad spectrum killing efficiencies approaching 100%, thereby rendering these thixotropic materials attractive for treatment of skin and other surface bound infections. Finally, cationic trimethylammonium containing hydrogels and anionic carboxylic acid functionalized hydrogels were utilized to sustain the release of negatively charged (diclofenac) and positively charged (vancomycin) therapeutics, respectively. Collectively, the present work introduces a simple method for formulating charged hydrogel materials that are capable of interacting with various analytes of interest through noncovalent interactions.



Amphiphilic ABA triblock copolymers comprising hydrophobic terminal A blocks flanking a central, hydrophilic B block self-assemble in water to form flower-like micelles above their critical micelle concentration (CMC). At sufficiently high polymer concentration, these micelles can become interconnected with hydrophobic A segments as the anchor points within adjacent micelle cores, leading to a physically cross-linked network of micelles and ultimately resulting in the formation of a water-swollen gel. The viscoelastic properties of such physically cross-linked hydrogels are manipulated through variation of polymer concentration as well as its composition. To this end, advances in controlled polymerization methodologies have not only enabled syntheses of extremely well-defined triblock copolymers in terms of their molecular weight and dispersity, but also have facilitated the introduction of diverse chemical functionality into hydrogel materials, leading to environmentally responsive "smart" hydrogel systems. Such materials exhibit property changes when exposed to external stimuli such as temperature,[1] light,[2] or pH,[3] enabling them to be useful in myriad applications.

Within the context of hydrogel-forming polymers, those which are biocompatible and contain hydrolytically or enzymatically labile linkages (e.g., esters, carbonates, amides) are particularly suited for use in the biomedical application space. Such biodegradable polymers are typically synthesized via controlled ring opening polymerization (ROP) of cyclic monomers, including lactones, carboxyanhydrides, and cyclic carbonates. To this end, several research groups have reported on a number of elegant polycarbonate-based hydrogel systems, though in most cases, covalent cross-links were utilized for gelation.[4−7]

We have recently reported a number of biodegradable physically cross-linked ABA triblock copolymer hydrogel systems realized by controlled ROP of hydrophobic cyclic carbonate monomers from a hydrophilic and telechelic poly(ethylene glycol) (PEG) macroinitiator. By virtue of their shear thinning properties and biocompatibility, the resulting materials were evaluated as injectable hydrogels for sustained subcutaneous delivery of therapeutics such as Herceptin[8] and Avastin,[9] FDA-approved monoclonal antibodies used for the treatment of breast and colorectal cancer, respectively. The most salient feature of the hydrogels was the efficient delivery of both Herceptin and Avastin such that the antimetastatic activity of the antibodies delivered using a one-time injection of the hydrogel was therapeutically as effective as that of 4× weekly intravenous injections of the solution formulations. The reduced number of injections would improve patient compliance.

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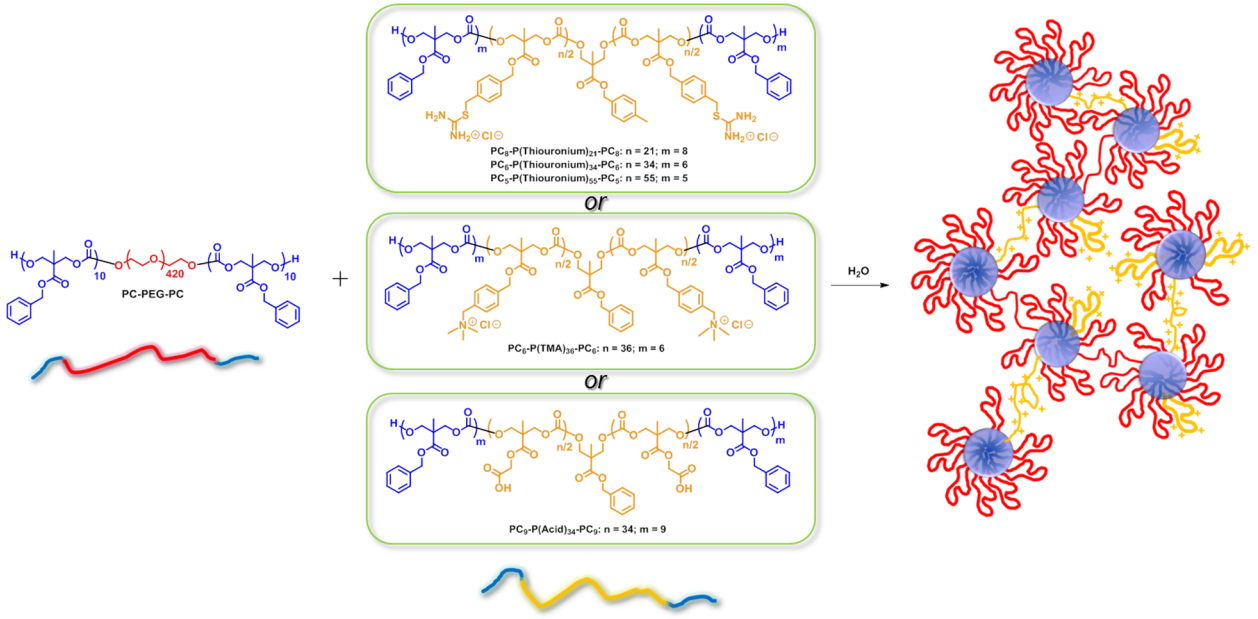
Scheme 1. Formulation of Charged ABA Triblock Copolymer Composite Hydrogels



In the above-mentioned examples, the hydrogel network acted as a diffusion barrier which controlled the release of the analyte (i.e., the therapeutic agent) in a sustained manner to provide a continuous therapeutic effect, where the rate of release depended on the relative proportions of the hydrophilic and hydrophobic segments of the triblock copolymer. On a molecular level, the analyte interacted in a nonspecific manner with the hydrophilic PEG segments of the triblock copolymer (e.g., through hydrogen-bonding, van der Waals forces, and hydrophilic/hydrophobic interactions). Building on this work, we became interested in the synthesis of functional hydrogels capable of chemically interacting with an analyte of interest through specific, noncovalent interactions; a feature that we envisioned should enable an additional level of control over release kinetics of the analyte. Specifically, motivated by recent work on the hydrogelation of block copolyelectrolytes[10−13] and considering that a large number of therapeutics carries a net negative or positive charge at physiological pH, we anticipated that the introduction of appropriately charged functional groups to the hydrophilic segments of the hydrogel-forming polymer should facilitate electrostatic interaction between the hydrogel and the analyte, thereby mediating its release. Furthermore, such block copolyelectrolyte hydrogels may find use in a broader range of applications, such as drug delivery or antimicrobials, where the use of electrostatic interactions is paramount for association of the polymer with charged drugs or microbial membranes, respectively.

To achieve this goal, we designed and synthesized a series of charged polycarbonate-based ABA triblock copolymers wherein the central B blocks contained pendant positively or negatively charged functional groups and coformulated them with a PEG-based ABA triblock copolymer to form block copolyelectrolyte hydrogels. Herein, we disclose our efforts toward the preparation of these hydrogel materials, investigation of their rheological properties, and evaluation of their use as an antimicrobial agent, and as a matrix for the sustained delivery of both anionic (diclofenac) and cationic (vancomycin) cargos.

The charged ABA triblock copolymers used in this study were synthesized by organocatalyzed ROP via sequential addition of cyclic carbonate monomers from a diol initiator (see Supporting Information for details). Briefly, a telechelic benzyl chloride or *tert*-butyl ester functionalized polycarbonate, serving as a precursor to positively or negatively charged B blocks, respectively, was synthesized and chain extended with a short chain of hydrophobic benzyl ester functionalized polycarbonate A blocks. A and B block lengths could be adjusted by varying the initial monomer-to-initiator loading ratios. ABA triblock copolyelectrolytes containing cationic B blocks were generated by the treatment of pendant benzyl chloride groups with thiourea or trimethylamine to afford thiouronium (PC-P(thiouronium)-PC) or trimethylammonium (PC-P(TMA)-PC) containing polymers, respectively. Triblock copolymers containing anionic B blocks (PC-P(acid)-PC) were generated by deprotection of the *tert*-butyl ester groups using trifluoroacetic acid.

To formulate the cationically or anionically charged hydrogels, a charged triblock polymer was mixed with a charge-neutral triblock copolymer (PC−PEG-PC) comprising 18.5 kDa PEG and benzyl ester functionalized polycarbonate as the hydrophilic B and hydrophobic A blocks, respectively, in a given amount of water (Scheme 1). As an illustrative example, solid PC-PEG-PC (130 mg) and PC-P(thiouronium)-PC (10 mg) were added to a glass scintillation vial, and 1000 μL of water was added, such that the composition of the final mixture was 13 wt % PC-PEG-PC and 1 wt % PC-P(thiouronium)-PC. The mixture was subjected to ultrasonication to ensure homogeneity, and gelation was qualitatively confirmed by performing an inverted vial test. It should be noted that no gelation was observed with the polycarbonate-based triblock copolyelectrolytes alone, and it was therefore necessary to coformulate them with PC-PEG-PC, whose gelation properties have been previously established[14] and could serve as a charge-neutral structural scaffold. Oscillatory shear rheology confirmed a similar range of storage (G') moduli for gels formulated using 13 wt % PC-PEG-PC (Table 1, entry 1) and for those coformulated with up to 1 wt % of PC-P(thiouronium)-PC (entries 2−7), indicating that addition of small amounts of the charged triblock to PC-PEG-PC did not considerably affect the

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Table 1. Average Values of G' (Storage Modulus) and G'' (Elastic Modulus) of Positively-Charged ABA Triblock Copolymer PC-PEG-PC Composite Hydrogels Measured at 25 °C, 10−25 rad/s[a]

polymer[b]	amt (wt %)	G' (Pa)	G'' (Pa)
		6242 ± 227	1057 ± 70
PC_5-P(thiouronium)$_{55}$-PC_5	0.1	6328 ± 234	1293 ± 80
PC_5-P(thiouronium)$_{55}$-PC_5	1	6929 ± 306	1666 ± 136
PC_6-P(thiouronium)$_{34}$-PC_6	0.1	6234 ± 219	1125 ± 66
PC_6-P(thiouronium)$_{34}$-PC_6	1	6870 ± 355	1483 ± 144
PC_8-P(thiouronium)$_{21}$-PC_8	0.1	7772 ± 314	2283 ± 175
PC_8-P(thiouronium)$_{21}$-PC_8	1	8127 ± 254	1458 ± 80

[a]Every entry contains 13 wt % PC-PEG-PC. [b]Subscript denotes degree of polymerization (DP).

rheological properties of the hydrogel. The highest gel strength (G') was observed for the composite hydrogels containing PC_8-P(thiouronium)$_{21}$-PC_8, presumably owing to its relatively large hydrophobic A block length among the three cationic triblocks. As shown in Figure 1, the hydrogel formulations also exhibited

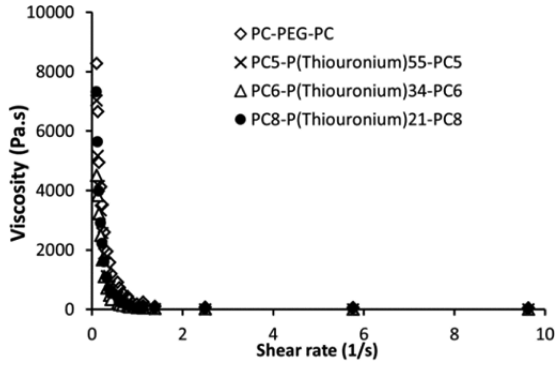

Figure 1. Viscosity as a function of shear rate for PC-PEG-PC (13 wt %) hydrogel loaded with PC-P(thiouronium)-PC (1 wt %) of different DP.

pronounced shear-thinning behavior, facilitating its ability to be spread over surfaces such as skin for topical application, as well as its flow through needles, an essential property that is required for subcutaneous or intramuscular delivery.

Having determined the viscoelastic properties of the charged hydrogels, we turned our attention toward their application as topical antimicrobial agents.[15,16] The misuse and overuse of antibiotics, leading to the emergence of increasing numbers drug-resistant bacterial strains, is threatening to become a global issue in the near future. Outside of the clinical setting, regulatory bodies within the European Union and United States are under pressure to phase out triclosan, an antimicrobial compound that is pervasively used in consumer goods such as cosmetics and personal care products, having been linked to hormone disrupting effects and negative impact on the environment, not to mention bacterial resistance. Altogether, the above-mentioned concerns have prompted significant research efforts into the discovery of new classes of antibacterial compounds. To this end, macromolecular antimicrobials are particularly promising because their mode of action of destabilizing bacterial membranes by inserting into the lipid bilayer is less prone to resistance development. Here, we envisioned that a cationically charged, spreadable (i.e., shear thinning) hydrogel would be an ideal antimicrobial material for the prevention of surface-bound microbial infections, such as those of the skin or an open wound. S-alkylthiouroniums are easily installed by alkylation of thiourea and are structurally similar to guanidinium cations. Guanidinium-rich polymers have been shown to exhibit enhanced cell-penetrating activity[17] and have also recently gained attention as effective macromolecular antimicrobials;[18] hence, we elected to focus on cationic hydrogels featuring PC-P(thiouronium)-PC. Thus, hydrogels containing 13 wt % PC-PEG-PC and varying amounts of PC-P(thiouronium)-PC were formulated and evaluated for their activity against four clinically relevant microbes: *S. aureus* (Gram-positive), *P. aeruginosa* (Gram-negative), *E. coli* (Gram-negative), and *C. albicans*, an opportunistic fungus. The microbial suspension was added to the hydrogel sample in a 96-well plate for incubation of 24 h, and the number of microbes was then obtained by agar plating. The detailed protocol can be found in the Supporting Information. As shown in Figure 2, we observed an increase in killing efficiency with increasing concentrations of PC-P(thiouronium)-PC in the hydrogel formulation. For fixed concentrations of PC-P(thiouronium)-PC, increasing the P(thiouronium) block length led to increasingly potent antimicrobial activity (Figure 2). Notably, the cationic hydrogels exhibited broad spectrum activity against all microbes tested, with killing efficiencies greater than 99.9% for hydrogels containing 1 wt % PC-P(thiouronium)-PC. This demonstrates the expansive functionality of the composite hydrogels that includes antimicrobial performance where the simple mixing of charged and uncharged copolymers can result in biologically active hydrogels that eliminates pathogenic microbes.

We then focused our efforts on mediating the release of therapeutic agents through electrostatic interaction with the charged hydrogels. Diclofenac, a nonsteroidal anti-inflammatory drug containing a carboxylic acid group, is used topically and orally via intravenous or intramuscular injection to reduce inflammation and pain. It has a short half-life in vivo; therefore, frequent administrations are required. In addition, the organic solvent DMSO was used in its topical formulation,[19] which may cause toxicity/irritation to the skin. Diclofenac was chosen as a model compound for negatively charged analytes, and incorporated into ABA triblock copolymer hydrogels (see the Supporting Information for details regarding drug-loaded hydrogel formulation). The time-dependent release of diclofenac from the hydrogel was then studied using PBS (pH 7.4) at 37 °C. As shown in Figure 3, diclofenac release was much more sustained from the cationic composite hydrogel comprising PC-PEG-PC and cationic triblock copolymer PC-P(TMA)-PC (7.5 and 3.75 wt %, respectively) as compared to the PC-PEG-PC (7.5 wt %) gel alone. Specifically, after 30 h, only 40% of diclofenac was released from the cationic composite hydrogel as compared to close to 70% of diclofenac being released from the charge-neutral PC-PEG-PC hydrogel in the same amount of time. A sustained release of diclofenac from the cationic composite hydrogel compared to that from PC-PEG-PC was presumably due to electrostatic interactions between diclofenac and the cationic blocks present in the former. These results demonstrate the potential application of this cationic composite hydrogel as a topical or injectable formulation for diclofenac delivery that can alleviate the use of DMSO and improve patient compliance/therapeutic efficacy, respectively. DMSO is a small molecule which is capable of penetrating deep into the dermal layers. Clinical signs of skin irritation and topical toxicity with repeated exposure of human

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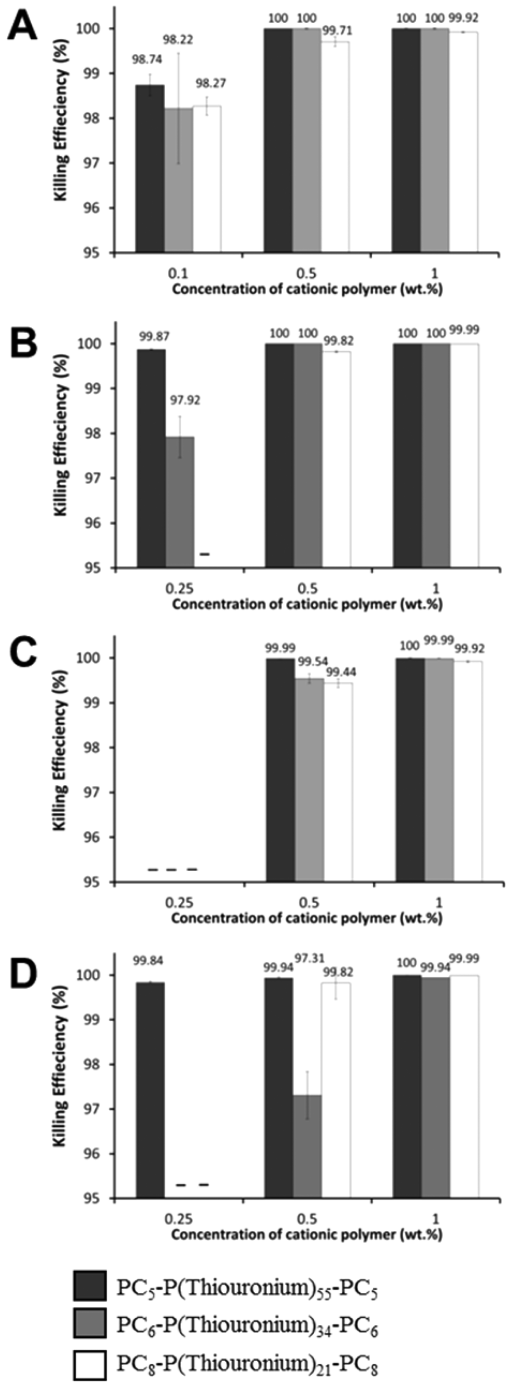

Figure 2. Killing efficiency of composite hydrogels formulated from PC-PEG-PC (13 wt %) on (A) *S. auerus*, (B) *P. aeruginosa*, (C) *E. coli*, and (D) *C. albicans*; "-" represents no observable antimicrobial effects.

subjects to topically applied DMSO have been reported.[20] On the other hand, polymers that make up the structure of the composite hydrogels are unable to penetrate the skin due to their large molecular size. Hence, effects of the hydrogels on the skin are transient and omitted once the gels are removed from the site of application.

Similarly, vancomycin was used as a model drug to evaluate the possibility of mediating the release of positively charged analytes from negatively charged hydrogels. Vancomycin is an antibiotic that is effective against serious infections caused by multidrug-resistant Gram-positive bacteria such as MRSA.

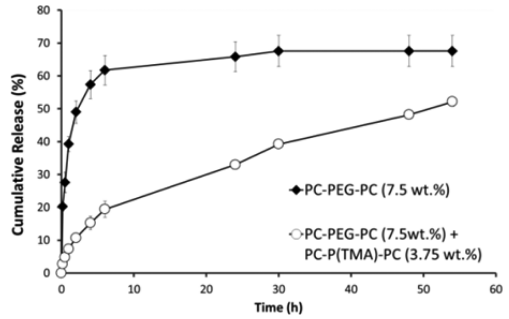

Figure 3. Diclofenac release from hydrogels as a function of time.

However, vancomycin must be administered intravenously for systemic treatment, often requiring multiple injections per day due to its short half-life.[21] A sustained release of vancomycin from a hydrogel matrix deposited under the skin through a one-time injection may therefore be desirable to reduce patients' discomfort and improve compliance. In our study, vancomycin was loaded into a hydrogel comprising PC-PEG-PC as well as that containing the carboxylic acid functionalized PC-P(Acid)-PC. In vitro drug release study was performed using PBS (pH 7.4) at 37 °C. Unlike diclofenac, vancomycin release was sustained from the control PC-PEG-PC hydrogel without cationic charge (Figure 4) due to its larger size (1449 vs 296

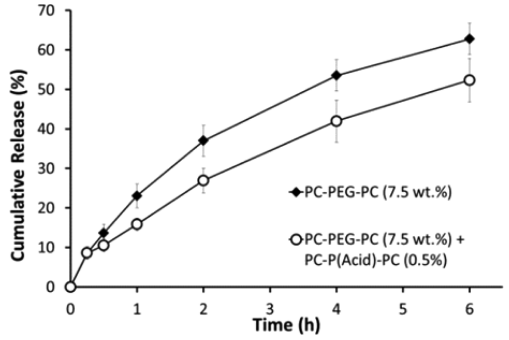

Figure 4. Vancomycin release from hydrogels as a function of time.

Da) and the presence of a number of hydroxyl groups that can form hydrogen-bonding interactions with PEG. Nonetheless, the release of vancomycin from the hydrogel containing the anionic PC-P(acid)-PC was significantly slower compared to that without. For instance, at the 6 h time point, 52% of the antibiotic was released from the anionic composite hydrogel as compared to 62% being released from the charge-neutral PC-PEG-PC hydrogel. This shows that the release of positively charged drugs can be adjusted depending on its designated application.

Compared to vancomycin, the effect of electrostatic interactions on diclofenac release was greater. For example, about 50% of vancomycin was released over 6 h, while the amount of diclofenac released was less than 20%. Except for the electrostatic interactions between diclofenac and P(TMA) in the cationic composite hydrogel matrix, there might exist hydrophobic interactions between the benzene groups in diclofenac and P(TMA), which further slowed down drug release.

Interestingly, contrary to what we observed for hydrogels containing PC-P(thiouronium)-PC (Table 1), we found that the rheological properties of the hydrogels were strongly

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Table 2. Average Values of G' (Storage Modulus) and G'' (Elastic Modulus) of Drug-Loaded, Charged ABA Triblock Copolymer PC-PEG-PC Composite Hydrogels Measured at 25 °C, 10−25 rad/s

#	polymer[a]	amt of polymer (wt %)	drug[b]	amt of drug (wt %)	solvent	G' (Pa)	G'' (Pa)
1					PBS	932 ± 40	205 ± 14
2			DCF	0.75	PBS	1613 ± 26	501 ± 32
3	PC-P(TMA)-PC	3.75			PBS	1514 ± 90	418 ± 46
4	PC-P(TMA)-PC	3.75	DCF	0.75	PBS	3720 ± 246	1177 ± 95
5					10 mM phosphate buffer	791 ± 29	146 ± 16
6			VAN	0.5	10 mM phosphate buffer	934 ± 22	200 ± 7
7	PC-P(acid)-PC	0.5			10 mM phosphate buffer	1266 ± 47	442 ± 26
8	PC-P(acid)-PC	0.5	VAN	0.5	10 mM phosphate buffer	1217 ± 61	385 ± 39

[a]Every entry contains 7.5 wt % PC-PEG-PC. [b]DCF = diclofenac; VAN = vancomycin.

influenced by the incorporation of both PC-P(TMA)-PC and PC-P(acid)-PC as well as the drug into the composite hydrogels. For example, the incorporation of block copolyelectrolytes PC-P(TMA)-PC or PC-P(acid)-PC into the polymer matrix (Table 2, entries 3 and 7, respectively) increased the total polymer concentration in the hydrogels and resulted in higher storage moduli as compared to hydrogels comprising PC-PEG-PC alone (Table 2, entries 1 and 5). The addition of diclofenac and vancomycin also led to higher gel strength, possibly due the equilibrium shift of PC-PEG-PC toward micelle formation[22] in the presence of the charged small molecules, thereby resulting in greater intermicellar interactions. Furthermore, the mixing of PC-P(TMA)-PC and diclofenac with PC-PEG-PC resulted in a combinatory effect of the above and gave rise to a much stiffer hydrogel with higher storage modulus value (G' 3720 Pa, Table 2, entry 4) as compared to hydrogel compositions lacking either PC-P(TMA)-PC, diclofenac, or both (Table 2, entries 1−3). Similar triblock copolymer- and vancomycin-dependent rheological properties were observed for the anionic hydrogel formulations, although to a lesser extent due to the low loading levels of both PC-P(acid)-PC and vancomycin, owing to their poor solubility at higher concentrations. Flow sweep measurements showed that the hydrogel containing both PC-P(TMA)-PC and diclofenac was more viscous at low shear rate compared to other compositions; nevertheless, all of the hydrogels examined demonstrated thixotrophic behavior (Figure S7) and injectability.

Finally, the effects of the hydrogels on mammalian cells were evaluated by treating human dermal fibroblasts with the hydrogels in different compositions, as listed in Table S1. Cell viabilities remained high at above 98% for all hydrogel formulations, thereby demonstrating the absence of undesired toxicity to mammalian cells (Figure S8). The concentrations of drugs used in the cytotoxicity test were in the range of those used in formulations for clinical evaluations,[23] thereby suggesting that the composite hydrogels can serve as a matrix for the drug dosage required for clinical use.

In conclusion, we have synthesized polycarbonate-based triblock copolyelectrolytes and demonstrated that both cationically and anionically charged hydrogels can be formed by simply incorporating these charged copolyelectrolytes into the gel network formed from PC-PEG-PC. Importantly, thiouronium-functionalized gels exhibited marked antimicrobial activity against both Gram-negative and Gram-positive bacteria. Furthermore, the release of charged therapeutic cargo was also shown to be regulated in a facile manner via the formation of charged composite hydrogels loaded with either trimethylammonium- or carboxylic acid-functionalized block copolyelectrolytes. The biocompatibility and thixotropic property exhibited by these gels lend themselves toward use as topical agents for skin treatment or as injectable matrices for subcutaneous delivery of therapeutic agents. The modular mix-and-match approach shown here will enable fine-tuning of parameters such as drug release profiles and rheological properties for enhancing therapeutic delivery, ultimately leading to a functionally versatile class of biodegradable hydrogel materials.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and additional characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.5b00527.

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Notes

The authors declare no competing financial interest.

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