Semibranched polyglycidols as "fillers" in polycarbonate hydrogels to tune hydrophobic drug release

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Complete List of Authors:	Harth, Eva; Vanderbilt University, Department of Chemistry Muthukumar, Murugappan; University of Massachusetts Amherst, Department of Polymer Science and Engineering Stevens, David; Vanderbilt University, Department of Chemistry Rahalkar, Anand; University of Massachusetts Amherst, Department of Polymer Science and Engineering Douglas, Emily; Vanderbilt University, Chemistry Spears, Benjamin; Vanderbilt University, Department of Chemistry Gilmore, Kelly; Vanderbilt University, Chemistry

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David.M. Stevens,[a] Anand Rahalkar,[b] Benjamin Spears, [a] Kelly Gilmore, [a] Emily Douglas, [a] Murugappan Muthukumar [b*] and Eva Harth[a*]

We report on the synthesis of polycarbonate based hydrogels that contain semibranched polyglycidols entrapped into the polycarbonate-diethylene oxide matrix. The primary OH groups of the polyglycidol can also react in a transesterification reaction to form reconfigurable crosslinked materials. We first synthesized allyl and ethylene-oxide functionalized linear polycarbonates with $Sn(OTf)_2$ as catalyst and isoamyl alcohol as initiator. In a reaction with dithiol ethylene oxide and dithiol (poly ethylene oxide) 1.5K, a crosslinked network was formed via thiolene click reactions in the presence or absence of semibranched polyglycidols. The resulting four hydrogels were analyzed for their swelling capabilities, mechanical properties and degradation in phosphate buffered saline. Paclitaxel was chosen as a model drug to study the drug release from these two carriers and was incorporated during the crosslinking reaction. The presence of the polyglycidol as well as the length of the dithiol crosslinker influenced the swelling capabilities, were responsible for a varied drug release behavior and the remarkable stress resistance. The present work introduces and compares polyglycidols as components into polycarbonate crosslinked materials that are either entrapped or covalently attached to the polycarbonate backbone to establish models of structure property relationships for hydrogels used for controlled drug delivery *in vivo*.

Introduction

Polymeric networks continue to be essential in the development of hydrogel materials for advanced biomedical applications.[1, 2,2] These versatile polymer networks are increasingly important materials due to their tunable network composition which can undergo simultaneous network forming and deforming processes.[3] Such materials have helped to make significant improvements in the area of tissue engineering in segmenting biological and synthetic structures or in the area of re-shapeable glass-like polymers called vitrimers.[4] Much effort has been devoted towards acrylate based materials as they are biocompatible and hydrophilic with the ability to swell, protect and release their cargo.[5] The main components in many of these smart, stimuli-responsive materials in which the chemical or mechanical properties[6] of the hydrogel can change depending on temperature,[7] pH,[8] magnetic field[9] and solvent, are functionalized linear acrylates and multiarm-PEG structures[10] to react under mild and fast reaction conditions such as thiolene-click reactions.[11] However, the degradability as well as the limited versatility of the available PEG building blocks have been an obstacle to further diversify the network architecture. Current research in the field is devoted to include degradable components to investigate stimuli free reactions such as amine-oxime reactions in addition to other click reactions.[12] Although hydrogels have been demonstrated to act as useful drug delivery vehicles, one of the major limitation is the rapid release of the therapeutics. Therefore, advanced hydrogel materials are required to overcome the limitation of rapid drug release in order to allow slower, adjustable release rates that can satisfy various medical needs. Although the hydrophobicity of degradable materials such as polyesters and polycarbonates display some challenge if a high swellability of the material is anticipated, hydrophobic small molecules have a higher residence time in hydrophobic materials as opposed to completely hydrophilic materials in which a rapid release of therapeutics is a common problem. To improve the rate of drug release and swellabilities, a balance between crosslinking density, hydrophobicity, and hydrophobic components must be accomplished. One example, to achieve more sophisticated hydrogels, hyper-branched materials such as dendrimers have been incorporated to entrap materials but also to guide drug release due to their branched and multifunctionality. It results in

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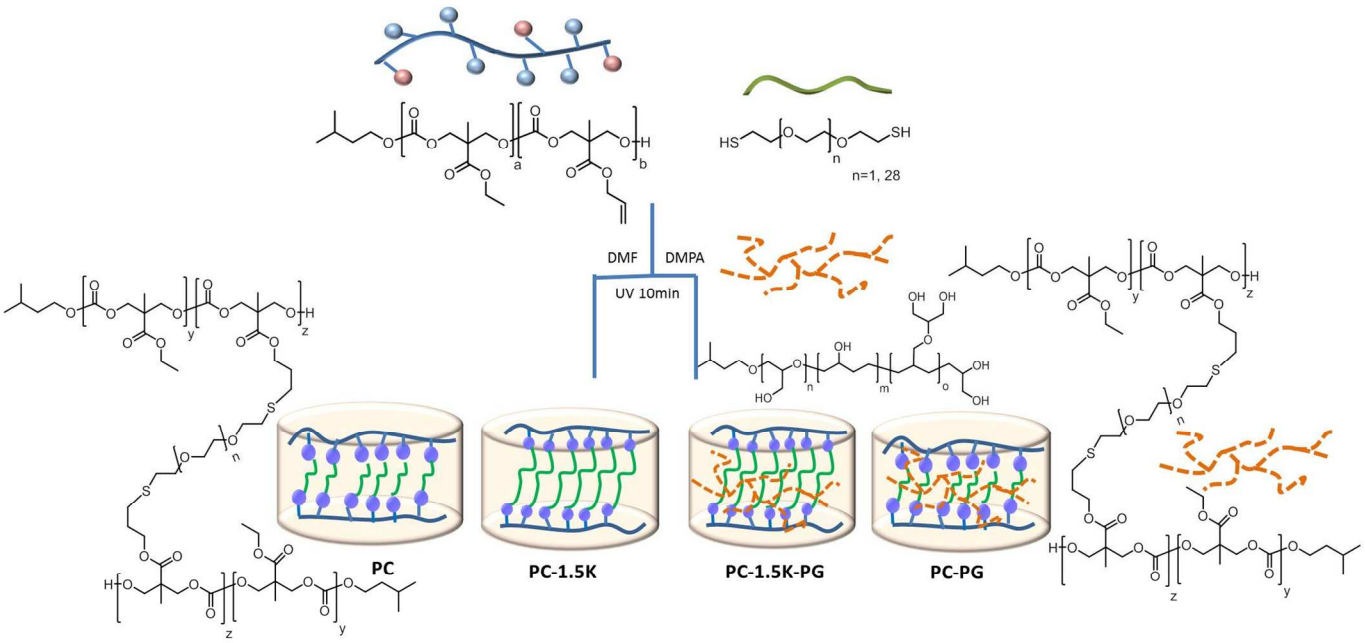

Figure 1. Synthesis of polycarbonate gels with short (PC, PC-PG) or long dithiol crosslinker (PC-1.5K, PC-1.5K-PG) in the presence (PC-PG, PC-1.5K-PG) or absence of polyglycidol (PC, PC-1.5K).

tighter networks and mechanical control in materials that require spatial control of cell adhesion and controlled release of hydrophobic drugs.[13] In this work, we sought to improve and further tune the swellability and hydrophilicity by introducing a three component system consisting of a linear polycarbonate, a linear dithol polyethylene oxide unit and a novel semi-branched polyglycidol with a high number of reactive –OH groups, a branched PEG mimic. Recently discovered semi-branched polyglycidols maintain a lower branching compared to hyper-branched materials but resemble a shorter overall structure in comparison to traditional PEG units used for hydrogel materials.[14] The large numbers of primary hydroxyl groups in semibranched polyglycidols enhances the hydrophilicity of a gel when introduced within the gel network. Polycarbonates[15] are one of the most well-known degradable polymers, and the improvement of synthetic procedures such as organo-catalyzed[16, 17 17, 18]and metal catalyzed [19] reactions enabled the integration of polycarbonates into complex materials. For example, intermolecular crosslinking with difunctionalized short PEG diamines and disulfides facilitated nanoparticles in a variety of selected sizes which consist of nanonetworks from hydrophilic and hydrophobic components.[20] The same concept of polymer crosslinking was translated to the development of three component hydrogels that include the semi-branched polyglycidol component. The polyglycidol[14] does not participate in the crosslinking reaction but rather acts as "filler" in the network to influence the swelling and to control the drug release. However, the OH-functional groups of the polyglycidol can be made part of the hydrogel network through transesterification reactions in the presence of $Zn(OAc)_2$ [4]to reconfigure the network. In this work, we synthesized and studied the influence of the width of the network maintained by the difunctional crosslinker and the introduction of the semibranched polyglycidol on swelling, resistance to mechanical stress and drug release.

Experimental

Materials

Poly(MAC, MEC) and polyglycidols were synthesized as reported previously.[21] Paclitaxel was obtained from LC Laboratories. Spectra/Por® Dialysis membrane was purchased from Spectrum Laboratories Inc. Phosphate Buffered Saline (PBS) was obtained from Gibco by Life Technologies and pH was adjusted to 7.4. Simulated gastric fluid (SGF) was prepared by mixing 2.0 g NaCl with 7.0 mL concentrated HCl, diluting

with water to 1.0 L, and adjusting pH to 1.2. All other chemicals were purchased from Sigma-Aldrich and used as received.

Characterization

^{1}H NMR spectra were obtained from a Bruker AC400 Fourier Transform Spectrometer, with DMSO-d6 as the solvent. High-performance liquid chromatography (HPLC) was carried out using a Waters chromatograph equipped with a Waters 2996 variable wavelength photodiode array detector, a Waters 1525 binary HPLC pump, and a reverse phase column (100 x 4.6 mm i.d., pore size 5 µm, Thermo Scientific). All runs were performed using an isocratic gradient of water and acetonitrile (1:1 v/v) at a flow rate of 1 mL/min. Thermogravimetric analysis (TGA) was carried out using an Universal V4.5A TA instrument and heated from 25 °C to 500 °C at a rate of 10 °C/min.

Thiolene -click model reaction

Allyl-functionalized polycarbonate was synthesized as previously reported.[22] To demonstrate the efficacy of the click reaction, dithiol crosslinker was added to a solution of poly(MAC, MEC) (1 thiol per alkene) and DMPA (0.2 equivalents per alkene) in DMSO-d6 at a concentration of 0.21 M and irradiated with UV light for 5 minutes. The sample was then immediately analyzed by ^{1}H NMR which indicated greater than 95% conversion based on the reduction of the alkene shifts at 5.87 ppm and 5.20 ppm. Therefore, the thiolene click reaction is rapid and successful, even at dilute concentrations. The model reaction was completed using dilute conditions since concentrated conditions result in the formation of hydrogel materials which are insoluble in solvent and cannot be analyzed by NMR.

Synthesis of polycarbonate hydrogel via thiolene click (PC and PC-1.5k)

3,6-dixoa-1,8-octanedithiol (8.6 uL, 5.2 x 10^{-2} mmol) was added to a solution of poly(MAC, MEC) (100 mg, Mn = 4,712 Da, 0.105 mmol alkene) and 2,2-dimethoxy-2-phenylacetophenone (DMPA, 0.2 eq per alkene, 5.4 mg) in DMF (100 uL). The solution was UV-irradiated (365 nm) for 5 minutes. The resulting gel (PC) was soaked and rinsed sequentially with methanol and water to remove unreacted starting material and solvent, and gel was dried via lyophilization. Gels containing longer crosslinker (PC-1.5k) were synthesized in the same manner but using PEG-dithiol (78.6 mg, Mn = 1,500 Da, 5.2 x 10^{-2} mmol) instead of 3,6-dixoa-1,8-octanedithiol.

Synthesis of polycarbonate/polyglycidol hydrogel via thiolene click (PC-PG and PC-1.5k-PG)

3,6-dixoa-1,8-octanedithiol (8.6 uL, 5.2 x 10^{-2} mmol) was added to a solution of poly(MAC, MEC) (100 mg, Mn = 4,712 Da, 0.105 mmol alkene), polyglycidol (100 mg), and 2,2-dimethoxy-2-phenylacetophenone (DMPA, 0.2 eq per alkene, 5.4 mg) in DMF (100 uL). The solution was UV-irradiated (365 nm) for 5 minutes. The resulting gel (PC-PG) was soaked and rinsed sequentially with methanol and water to remove unreacted starting material and solvent, and gel was dried via lyophilization. Gels containing longer crosslinker (PC-1.5k-PG) were synthesized in the same manner but using PEG-dithiol (78.6 mg, Mn = 1,500 Da, 5.2 x 10^{-2} mmol) instead of 3,6-dixoa-1,8-octanedithiol.

Synthesis of PTX-loaded hydrogels and encapsulation efficiency

Hydrogels were synthesized as previously described, but paclitaxel was added (10 mg paclitaxel per 100 mg poly(MAC, MEC)) to the polymer solution prior to UV irradiation. The resulting gels were soaked and rinsed with water multiple times. The washes were collected, lyophilized, and analyzed by HPLC to determine mass of non-encapsulated paclitaxel. Encapsulation efficiency was determined using the equation:

$$((M\_ptx(i) - M\_ptx(w))/M\_ptx(i)) \times 100\%$$

where $M_{ptx(i)}$ is the initial mass of paclitaxel added to the reaction and $M_{ptx(w)}$ is the mass of washed paclitaxel determined by HPLC.

Swelling studies

Prepared gels were soaked in deionized water or simulated gastric fluid (pH = 1.2) and allowed to swell for 24 hours. The swelled gels were then gently blotted dry before recording the swelled mass (M_{sw}), and the sample was then lyophilized to record the dry mass (M_{dry}). The percent water content post-swelling was quantified using the following equation:

$$((M\_sw - M\_dry))/M\_dry \times 100\%$$

Degradation Studies

An initial swelled mass (M_i) was recorded by submerging the gels in PBS (pH 7.4) for 24 hours and gently blotting dry before recording the mass. Gels were then submerged in PBS (pH 7.4) at 37 °C for the duration of the experiment. At each time point, the gels were gently blotted and a mass was recorded (M_t) before being submerged into fresh PBS (pH 7.4) at 37 °C. The percent mass remaining at each time point was quantified using the following equation:

$$M\_t/M\_i \times 100\%$$

Unconfined Compression Testing

The hydrogel samples for mechanical testing were prepared as previously described. The resulting hydrogel products were tested in triplicate at a rate of 1mm/min on an Instron 5944. The compressive modulus was determined using the initial linear region for each sample on the stress strain curve.

***In vitro* drug release**

The release of paclitaxel from the gels was measured in PBS (pH 7.4) or simulated gastric fluid (pH 1.2), both buffers containing Tween-80 (0.1% v/v) and stirred at 37 °C. Initial paclitaxel concentration was 0.15 mM. At each time point, the supernatant was collected and replaced with an equal volume of fresh release medium. For release studies in PBS, the supernatant was directly analyzed by HPLC. For release studies in simulated gastric fluid, the supernatant was neutralized to pH 7 with sodium bicarbonate, extracted three times with dichloromethane, organic fractions were combined, and solvent was evaporated. The resulting sample was dissolved in acetonitrile/water (1:1, v/v) and analyzed by HPLC. Samples were injected (30 uL) to a reverse phase column (100 x 4.6 mm i.d., pore size 5 um, Thermo Scientific) using an isocratic gradient of acetonitrile and water (1:1, v/v) with a variable wavelength detector (227 nm).

Results and Discussion

Hydrogel Synthesis

Hydrogels were formed via thiolene click crosslinking of allyl-functionalized carbonate copolymers and a dithiol crosslinker in the presence or absence of polyglycidol. Without polyglycidol, hydrogels were prepared by reacting the allyl with the short or long (1.5k) dithiol crosslinker in DMF with DMPA (0.2 eq per alkene) under UV light (365 nm) for 5 minutes to yield gels PC and PC-1.5k, respectively. Gels readily formed within minutes and were rinsed with methanol and water to remove unreacted material and residual DMF. Yields were determined by measuring the dried mass of the gel compared to the total mass of the precursor reactants, and typical yields were greater than 90%. In a separate series of gels, water-soluble polyglycidol was added to the precursor mix to investigate the change of gel properties due to introducing a hydrophilic component to the hydrogel matrix. Additionally, the entrapped polyglycidol can be used for post-modification reactions such as transesterification. These gels (PC-PG and PC-1.5k-PG) contained a 1:1 ratio of polycarbonate to polyglycidol by mass and were synthesized by reacting the allyl of the polycarbonate with the short or long (1.5k) dithiol crosslinker as described previously. The polyglycidol did not impede the thiolene reaction and was successfully incorporated into the crosslinking network as indicated by the yields (greater than 75%) after soaking and rinsing with water and methanol sequentially (Figure 1). To ensure free polyglycidol was effectively washed away, these gels were soaked in water before rinsing several times with water and methanol.

Zinc acetate mediated transesterification reaction for gel network configuration

Zinc acetate has been shown to promote transesterification rearrangements at high temperatures that lead to the development of novel materials called vitrimers and were established by Leibler and coworkers.[4] Here, we used zinc acetate to covalently attach the non-covalently entrapped polyglycidol to the polycarbonate backbone. Thus, a catalytic

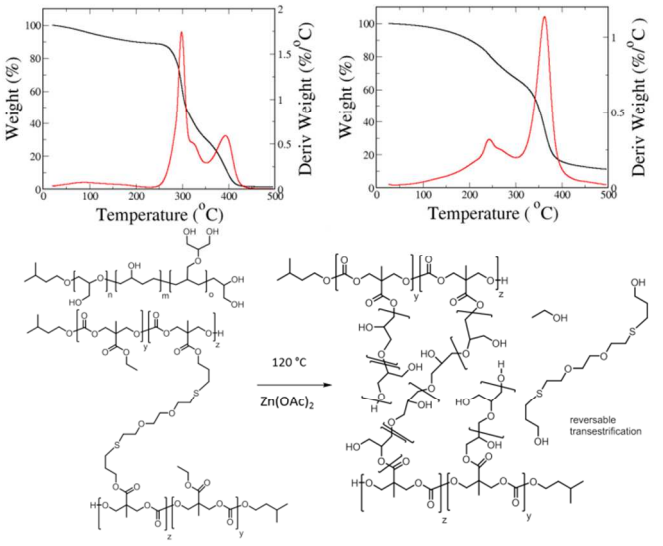

Figure 2. Thermogravimetric analysis of polycarbonate-polyglycidol hydrogel before (left) and after zinc acetate catalyzed transesterification (right).

amount of zinc acetate was mixed into the polymer precursor solution before gel formation to demonstrate reconfiguration capabilities. After gel formation, the gel was added to a 120 °C oil bath overnight, yielding a physically tougher gel due to the polyglycidol becoming covalently attached to the ester side groups of the polycarbonate. Thermogravimetric analysis (TGA) was used to characterize the materials before and after the transesterification step. As seen in the top TGA curve in Figure 2, the polymer materials began to degrade at 270 °C. In the first-derivative curve (%/°C), two inflection points were seen at around 300 °C and 400 °C which indicate the points of greatest rate of weight change. The two inflection points are typical of a mixture which makes sense considering the polycarbonate gel and polyglycidol are non-covalently attached. However, a significant change in the TGA curve was seen after transesterification. As seen in the bottom TGA curve in Figure 2, the change in weight curve is more representative of a single-component material. Although two inflection points were still seen in the first-derivative curve (%/°C), the greatest rate of weight change occurred at 360 °C. These findings suggest the material underwent chemical modification during the transesterification step. Since transesterification is reversible, it is likely that not all polyglycidol became covalently linked within the network which would account for the first inflection point seen at 240 °C or could be attributed to a loss of the original, linear crosslinking unit in the gel due to the transesterification reaction and exchange and replacement with the polyglycidol structure.

Tunable swelling ability of hydrogels

Although gels made from hydrophilic polymers typically exhibit excellent water sorption capabilities[23], the hydrogels prepared in this study had low to moderate water sorption

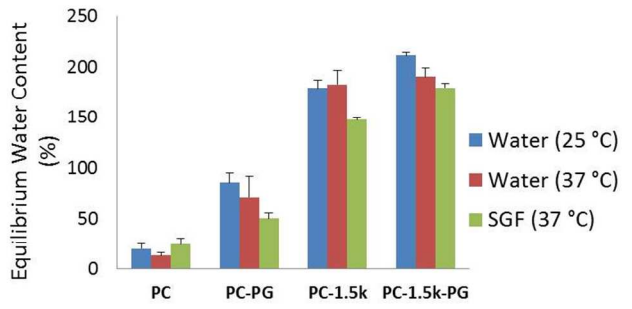

Figure 3. Swelling ability of each type of hydrogel in water (25 °C and 37 °C) and simulated gastric fluid (pH 1.2).

ability. As expected, water swelling increased with increasing hydrophilicity within the gel network. Equilibrium water content at room temperature averaged 20.0% for PC gels, 85.5% for PC-PG gels, 179% for PC-1.5k gels, and 211% for PC-1.5k-PG gels, and the swelling ability was not sensitive to temperature or pH (Figure 3). The low water absorption for PC is expected due to the very hydrophobic nature of the polycarbonate backbone. Although the presence of the ethylene oxide crosslinker allows for a more hydrophilic environment, it is not enough to overcome the hydrophobicity of the polycarbonate unless the PEG crosslinker has a significantly greater molecular weight such as with the PC-1.5k gels, which had 9-fold greater swelling values compared to the PC gels. Also, the presence of polyglycidol in the network improved water swelling significantly, likely due to its hydrophilic nature. By simply adding this hydrophilic "filler" to the short crosslinker gels, swelling values increased over 4-fold. It is important to note that the recorded dried mass of the gels before and after swelling in water were generally consistent with each other, indicating insignificant degradation and loss of material during the duration of these swelling experiments. However, PC-PG and PC-1.5k gels lost mass after swelling in simulated gastric fluid (SGF), likely due to degradation but also because the gels broke into smaller pieces which made it difficult to measure the mass.

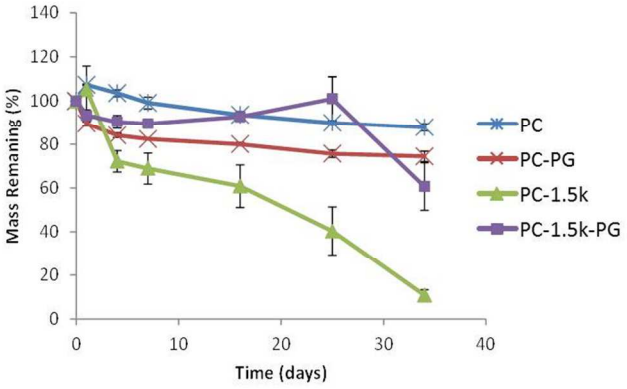

Figure 4. Degradation profiles of hydrogels in PBS at 37 °C

Polycarbonate materials degrade hydrolytically at very slow rates[24], and previous studies indicate the primary method of degradation of these gels is from hydrolysis of the ester side-group.[25] For *in vivo* applications, predictable gel degradation is imperative, and a tunable degradation would be ideal to meet specific needs of individual biomedical applications. Degradation experiments of the prepared gels were conducted under simulated physiological conditions (PBS pH 7.4 at 37 °C) and monitored by measuring the swelled mass over time. In all cases, the gels degraded slowly (Figure 4). Interestingly, gels containing the short crosslinker had significantly slower degradation rates with PC at 88% and PC-PG at 74% remaining mass after 34 days. This is likely due to the overwhelming hydrophobicity of these gels which are less likely to attract water for hydrolysis. PC-1.5k-PG gained mass up to day 25 before a loss of mass was recorded at day 34.

Mechanical Properties

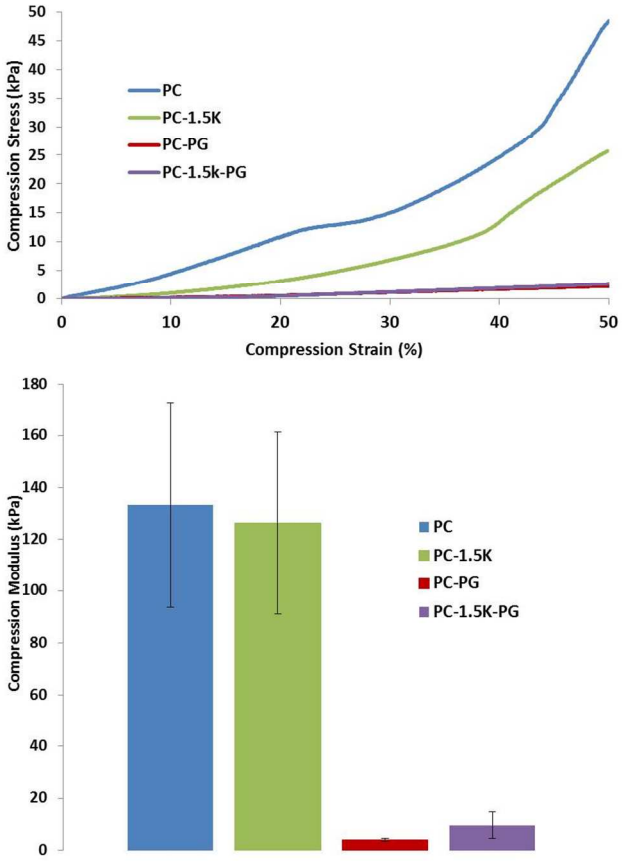

Figure 5. Mechanical properties of the PC hydrogel series using the unconfined compression test.

The mechanical properties gathered from the unconfined compression tests revealed a remarkable effect of the polyglycidol when used as "filler" and additive in the studied hydrogels (Figure 5). The longer PEG linker in the hydrogels (PC-1.5K) showed a higher deformation in contrast to the

hydrogels make with the shorter linker (PC). The addition of the polyglycidol "filler" adds as expected and additional parameter that contributes to significant deformation to the hydrogels PC-PG and PC-1.5k-PG and is relatively independent if the hydrogels contain the longer or the shorter dithiol crosslinker. The polyglycidol fillers decrease the stiffness with high deformability whereas the gels without the "fillers" increase in mechanical strength. The mechanical properties of the gels stemming from transesterification reactions will be discussed in a separate communication.

Paclitaxel encapsulation and drug release

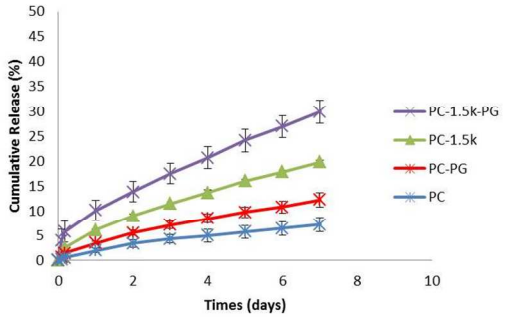

Figure 6. Cumulative release of paclitaxel from the PC hydrogel series in PBS (pH 7.4) at 37 °C.

In order to encapsulate paclitaxel into the gel, the drug was mixed with the polymer precursors prior to gel formation, and these gels were purified as described previously. The solvent rinses were collected and analyzed for non-encapsulated paclitaxel by HPLC. Loading efficiency was determined by comparing the amount of non-encapsulated drug with the amount initially added to the polymer mix, and in all cases, loading efficiency was very high (> 98%). PTX-loaded gels were placed in PBS (pH 7.4) at 37 °C to monitor the *in vitro* release rate of paclitaxel. In all cases, paclitaxel was released at controlled rates with PC achieving as low as 7.2% drug release and PC-1.5k-PG achieving as high as 29.9% drug release after 7 days (Figure 6) The rate of release is relatively proportional to the gel's water swellability as the gels with greater swelling ability released paclitaxel at faster rates. More swelling would potentially allow faster rates of diffusion of paclitaxel from the gel. The differences in release rates can also be attributed to greater pore size within the gel networks although these differences are likely due to the combination of both pore size and network hydrophilicity. For example, PC-1.5k achieved 19.8% drug release after 7 days compared to 7.2% achieved by PC. The use of the significantly longer linker (1.5k) greatly enhances the hydrophilicity within the gel network, but it also potentially increases pore size within the network as crosslinks will not be as closely-knit as seen with the shorter crosslinker in PC. Additionally, polyglycidol played a significant role in drug release as seen in the 12.2% drug release after 7 days with the PC-PG gel which is 1.7-fold faster than PC. Again, this is attributable to polyglycidol's ability to enhance hydrophilicity within the network, but since polyglycidol acts as an additive, it can potentially affect pore size and drug release kinetics as well. [26] PC and PC-PG gels containing paclitaxel were also

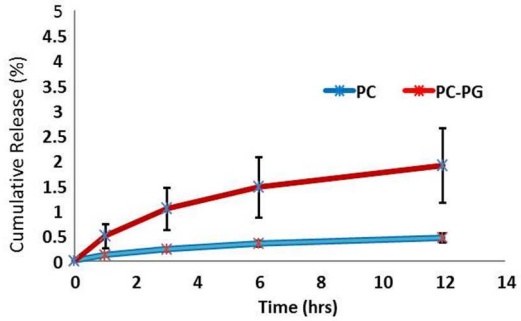

Figure 7. Cumulative release of paclitaxel from the PC hydrogel series in simulated gastric fluid (pH 1.2).

used to measure drug release in simulated gastric fluid (pH 1.2) to determine if these gels could retain their therapeutic cargo in acidic conditions for an oral drug delivery route. In both cases, very little paclitaxel (less than 3%) was released even after 12 hours in the simulated gastric fluid (Figure 7). This suggests that these types of gels could potentially be investigated as an oral drug formulation. Also, the ability to withstand the acidic conditions of the stomach allows these gel materials to potentially act as enteric coating for other drug formulations.

Conclusions

A series of hydrogels were synthesized and characterized by their water swelling ability, degradation profile, mechanical strength and drug release profile. Allyl-functionalized polycarbonates undergo thiolene click reactions with dithiol crosslinkers to form insoluble, gel materials when conditions are concentrated. Hydrogels were formed with different sized crosslinkers in the presence or absence of a hydrophilic component, polyglycidol. The insertion of a hydrophilic component within the gel network caused significant effects on water swelling ability, deformability as well as rate of drug release. Additionally, increasing the size of the dithiol-PEG crosslinker resulted in similar effects. All gels degraded hydrolytically at slow rates and therefore could be used for various drug delivery routes including oral and implants. The ability to form a gel in the presence of a drug allows the possibility to create novel drug delivery formulations of a therapeutic that requires sustained release, with an overall drug release rate that can be adjusted by manipulating the hydrophilicity within the gel network. Therefore, this novel hydrogel material can act as a platform delivery formulation to meet the needs of various sustained release applications.

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Notes and references

[a] *Vanderbilt University, Department of Chemistry,7619 Stevenson Center, Nashville, Tennessee, USA. Fax: 01-615-343-1234; Tel: 01-615-343-3405; E-mail: eva.harth@vanderbilt.edu,*
[b] *Department of Polymer Science and Engineering, Room A212, Conte Research Center, University of Massachusetts Amherst , 120 Governors Drive, Amherst, MA 01003, USA, Fax: 01-413-545-0082; Tel:01-413-577-1212; Email:muthu@polysci.umass.edu*

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