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Synthetic biodegradable elastomers for drug delivery and tissue engineering*

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Abstract: Synthetic biodegradable elastomers are an emerging class of materials with many potential clinical applications including drug delivery and tissue engineering. Biodegradable elastomers offer advantages of structure diversity, tunable properties, and a wide range of processing capabilities. This review highlights some recent developments in various aspects of biodegradable materials synthesis, characterization, and processing with a specific focus on structure-processing–property relationships. Biodegradation mechanisms and issues regarding tissue biocompatibility of these materials are discussed. Applications of synthetic biodegradable elastomers, including use as a materials platform for controlled release systems, tissue engineering scaffolds, and engineered substrates for in vitro cell–biomaterials interactions will also be presented.

Keywords: biodegradability; biomaterials; drug delivery; elastomers; tissue engineering.

INTRODUCTION

The development of biomaterials represents a critical aspect of improving human health by serving in part as a bridge between advancements in biological sciences and effective implementation in translational medicine. There also exists a synergistic interaction between biomaterials development and biology in which unique material platforms can be used to investigate more complex phenomena. Natural biomaterials such as extracellular matrix (ECM) proteins and glycosaminoglycans (GAGs) have proven to be worthy subjects of scientific study themselves. They have also been implemented as useful material platforms in (1) the study of fundamental biological functions and (2) the advancement of medicine through drug delivery and regenerative medicine, for example. A comprehensive understanding of the chemical, mechanical, and physical aspects of natural biopolymers presents a significant intellectual and scientific challenge worthy of pursuit. There are numerous advantages in utilizing this class of materials for clinical applications. However, the widespread implementation of natural biopolymers as clinically relevant biomaterials is subject to numerous limitations. The relatively narrow structural, chemical, and physical diversity of natural biopolymers exhibits a narrow range of properties. Natural biopolymers are subject to tedious purification techniques, processing variability [1], potential regulatory issues [2], and the potential to induce potentially dangerous immune responses when used as xenografts or allografts [3]. Synthetic peptide biomaterials produced through recombinant DNA and protein engineering strategies have been introduced as a possible means to overcome these limitations [4]. Although protein-based biomaterials have shown promise in achieving native-like prop-

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erties through synthetic polypeptide sequences [5], materials synthesis and production is very costly due to the dependence upon recombinant microbial hosts for synthesis as well as subsequent purification steps.

The rapidly increasing functionality of biodegradable synthetic polymers allows this class of materials to be used more broadly in clinical applications. Initial developments in this emerging field were restricted primarily to polyesters with simple α-hydroxy acids including glycolic acid and lactic acid. These thermoplastic polymers were relegated to simple medical functions such as bioresorbable sutures. However, the potential impact for biodegradable devices and temporary implants is growing rapidly. One prominent example is the development of biodegradable cardiovascular interventional therapies [6]. The first biodegradable stents were fabricated using poly(L-lactide) (PLA) and initially tested in the late 1980s. Although this technology has been sufficiently advanced to incorporate drug-eluting capabilities [7], significant materials challenges remain. The concept of biodegradable devices has also been extended to the development of drug delivery microchips. Initial efforts in this area employed traditional materials used in silicon machining and microfabrication techniques [8]. Next-generation microchips utilized PLA and poly(L-lactic-*co*-glycolic acid) (PLGA) as the bulk materials in these devices to achieve multiphasic release profiles. More recently, biodegradable electronic implants are emerging as another class of devices, which use PLGA as a bulk material component [9]. Biodegradable electronic components may even be extended into consumer products to realize environmentally friendly compostable devices [10,11]. The demonstration of complex drug release profiles and the addition of electronically active components illustrate the increasing functionality of biodegradable medical implants. The level of sophistication of synthetic biodegradable materials has also increased in parallel. The mutual advancement of biodegradable polymers and device capabilities is important in developing temporary diagnostic and therapeutic medical implants. One particular thrust in advancing bioresorbable polymers lies in the desire to greatly improve the mechanical properties. Soft tissues exhibit a Young's modulus on the order of 10 kPa to over 20 MPa with strains varying from approximately 30 to 300 % [12,13]. This range of mechanical properties stimulates at least two prominent notions: first, the materials that are designed to interface with these tissues must span a wide range of mechanical properties in order to minimize the possibility of modulus mismatch; second, ubiquitous aliphatic polyesters, such as poly(ε-caprolactone) (PCL) or α-hydroxy polyesters such as PLGA, may not be suitable for many soft tissue applications despite approval from the U.S. Food and Drug Administration (FDA) for use in some applications. PCL [14] and PLGA [15] both exhibit intrinsic Young's moduli on the order of 100 MPa. The potential mechanical mismatch between high-modulus implants and soft surrounding tissue can produce injurious inflammatory reactions, which can be exacerbated in dynamic mechanical microenvironments. Modulus matching of medical implants has motivated further expansion of the available mechanical parameter space [16]. This in turn has led to the development of synthetic biodegradable elastomers, an emerging class of biomaterials with unique mechanical properties including large, reversible deformations [17]. In addition to the potential for improved biocompatibility, advanced biodegradable elastomers may improve the deployment of temporary medical implants through non-invasive surgical procedures. This perspective explores structure–processing–property relationships associated with these materials and their potential use in biomedical applications. Various examples will also be discussed including applications drawn for applications in drug delivery, tissue engineering, and in vitro cell–biomaterials interactions.

SYNTHESIS STRATEGIES

General strategies

The synthetic strategies typically employed to produce these classes of materials are analogous to the general considerations observed for other biodegradable systems: (1) biodegradable linkages; (2) monomer composition consisting of metabolizable or bioexcretable moieties; and (3) capacity for

chemical or physical crosslinking. The additional requirement for crosslinking can be accommodated by several methodologies, which are in turn contingent upon the processing and property requirements. Step-addition polymerization reactions require, at the minimum, a chemical system where at least one of the components exhibits a bonding functionality of three or greater. This functionality can be incorporated by simply selecting the appropriate monomer. Other types of polyfunctional starting materials may also be employed including oligomers with functional side groups. Star polymers also present a similar option for this methodology by creating a system that exhibits a relatively wide range of properties and facile processing and preparation. One class of elastomers incorporating star-polymer monomers based on 3-arm-star-poly(lactones) crosslinked with tolylene diisocyanate can achieve a range of Young's modulus range between 1.36 and 766.7 MPa with a sol content of less than 2 % [18]. Although the intrinsic biocompatibility of the crosslinker may be questionable, this example illustrates the potential range of properties that is achievable with star polymers.

Crosslinked networks via polycondensation

Polycondensation reactions via step addition are a versatile class of reactions that can be used to realize a wide range of chemistries that are in turn suitable for biodegradable elastomers. Crosslinked biodegradable elastomers are primarily composed of esters [19] and amides [20] (Fig. 1). The asymmetry of these bonds also allows for flexibility in the choice of monomer pairing as well. For example, elastomers may be composed of polyols condensed with diacids [19], polyacids condensed with diols [21] (Fig. 2), and various other combinations including anhydrides, amines, ethers, and vinyl-containing components [20,22]. The preparation of biodegradable elastomers using step-wise addition polycondensation exhibits numerous disadvantages, however. Step-addition polymerizations using two bifunctional monomers typically result in sensitive reaction kinetics with small processing windows and high polydispersity indices (PDIs). These issues are exacerbated when the aforementioned concerns of step-addition condensation reactions are coupled with multifunctional monomers that are necessary to produce crosslinked networks. For example, polycondensation reactions of polyfunctional maltitol with sebacic acid can lead to PDIs as high as 4 or more [23]. There are more complex synthetic routes to

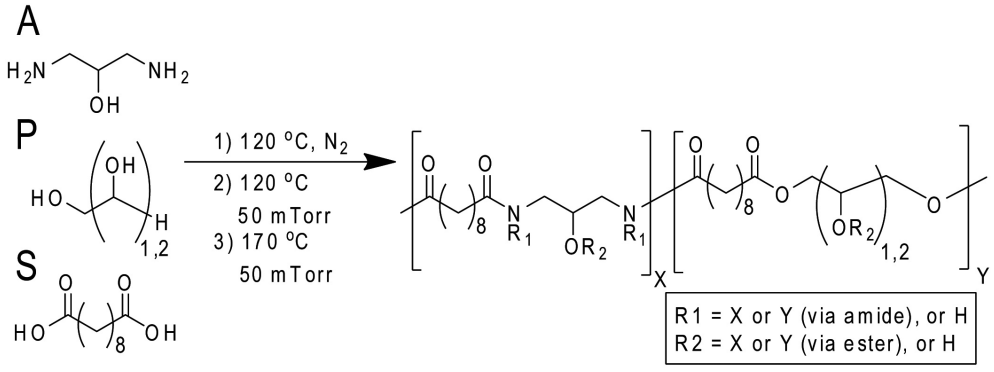

Fig. 1 Synthesis scheme of APS polymers. The general synthetic scheme of poly(1,3-diamino-2-propanol-*co*-polyol sebacate)s (APSs) incorporated the following monomers; (1) a multifunctional amine group (A), which was chosen to be 1,3-diamino-2-hydroxypropane in this example, (2) a polyol (P), and (3) a diacid (S). Glycerol and D,L-threitol were chosen as representative polymers while sebacic acid was chosen as the diacid because of its ubiquitous presence in polyesters for biomedical applications. These monomers were melted at 120 °C under a nitrogen blanket followed by a reduction in pressure to induce polymerization. Further polymerization to produce solid slabs was continued at 170 °C at 50 mTorr. In this scheme, R_1 represents either a single hydrogen, or bond to either the X-segment or Y-segment via amide bond. R_2 represents either a single hydrogen, or bond to X-segment or Y-segment via ester bond. Reprinted with permission from ref. [20], copyright © 2009, Elsevier.

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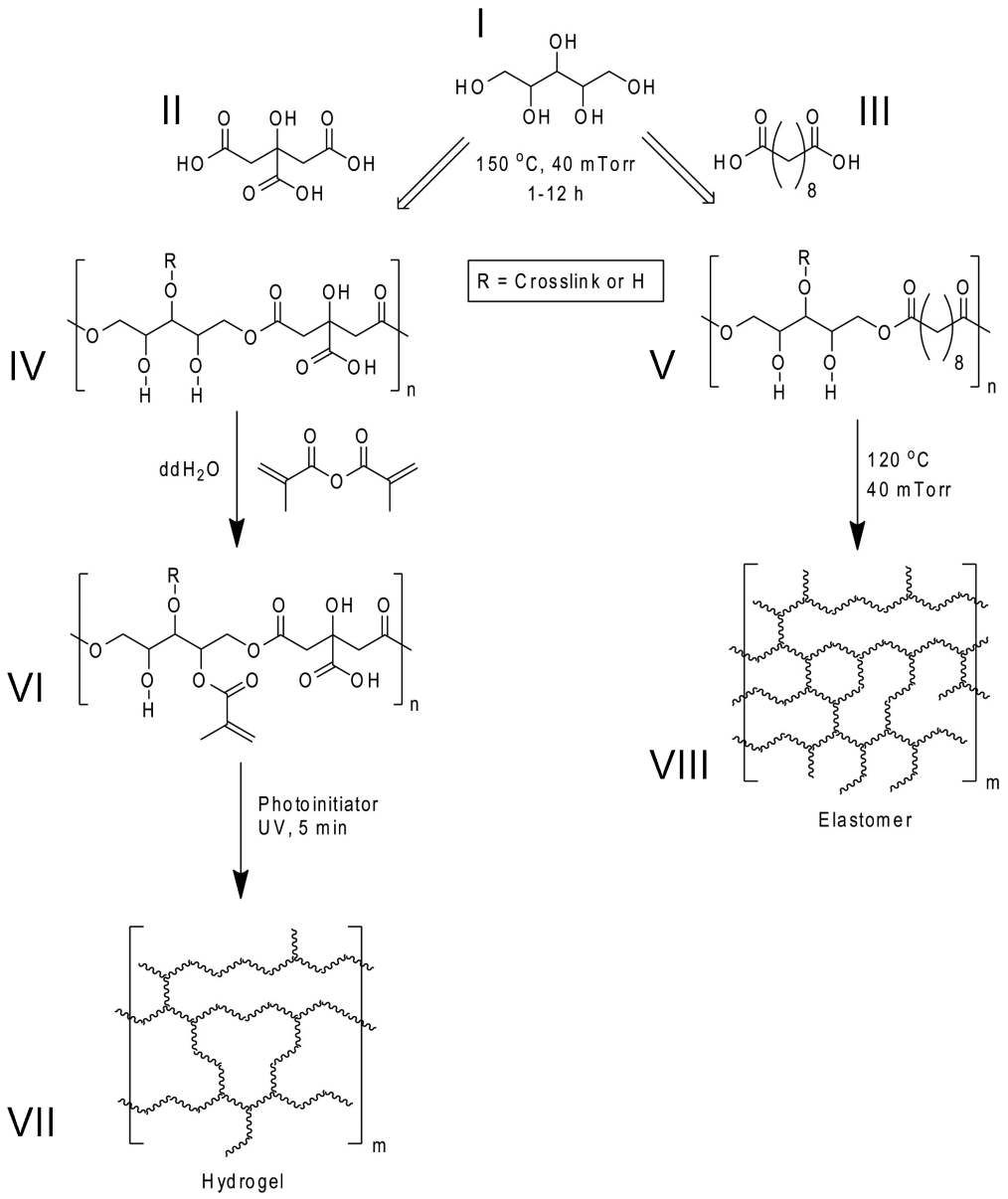

Fig. 2 General synthetic scheme of xylitol-based polymers. Xylitol (I) is polymerized with citric acid (II) or sebacic acid (III) into poly(xylitol citrate) (PXC) (IV) or poly(xylitol sebacate) (PXS), respectively (V). Photocrosslinkable hydrogels were obtained by acrylation of PXC in ddH_2O using methacrylic anhydride to yield PXC-methacrylate (PXCma) (VI). PXCma is polymerized into a hydrogel network (VII) by free radical polymerization. Further polycondensation of PXS yields a tough elastomeric network (VIII). A simplified representation of the polymers is shown. R can be H, $–OCH_2[CH(OR)]_3CH_2OR$ (xylitol), $–CO(CH_2)_6COOR$ (sebacic acid), $–CO(CH_2)ROC(COOR)(CH_2)COOR$ (citric acid), or $–C(CH_3)=CH_2$ (methacrylate group).

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overcome some of these issues. For example, glycidyl chemistries can be used to create polymers with lower PDIs to serve as prepolymer starting materials [24]. Subsequent polymerization steps can then be used to realize the final crosslinked network. Atom-transfer radical polymerization (ATRP) may also serve as an alternative synthesis strategy in order to lower the PDI of network precursors [25]. The synthesis of precursors to elastomeric networks enables another aspect of control. This flexibility lies in the decoupling of the prepolymer and crosslinking (curing) reactions.

Photocrosslinked elastomers

Step-addition polymerizations typically employ curing conditions at elevated temperatures, which reduce the range of applications for biodegradable elastomers processed in this matter. For example, the incorporation of bioactive molecules or viable cell populations is virtually impossible, which obtrusively limits the application of these polymers as material platforms for drug delivery and tissue engineering. High-temperature curing processes also subject polymers to rapid oxidative degradation. Free radical polymerization techniques, in general, have the ability to overcome some of these limitations. This topic will be discussed in more detail in the section entitled "Processing". Free radical polymerization reactions can be initiated thermally. However, the free radical polymerization of biodegradable elastomers is typically associated with photopolymerization. This processing capability relies on the presence of photocrosslinkable moieties. Photocrosslinkable polymer chemistries typically employ photoactive diene-based modifications (Fig. 3). These species may be added through terminal addition or backbone modification. Two common routes for this modification are based upon the esterification of free hydroxyl groups using acid chlorides with labile dienes such as acryloyl chloride or methacryloyl chloride [26]. These modifications exhibit a straightforward procedure and can be utilized to

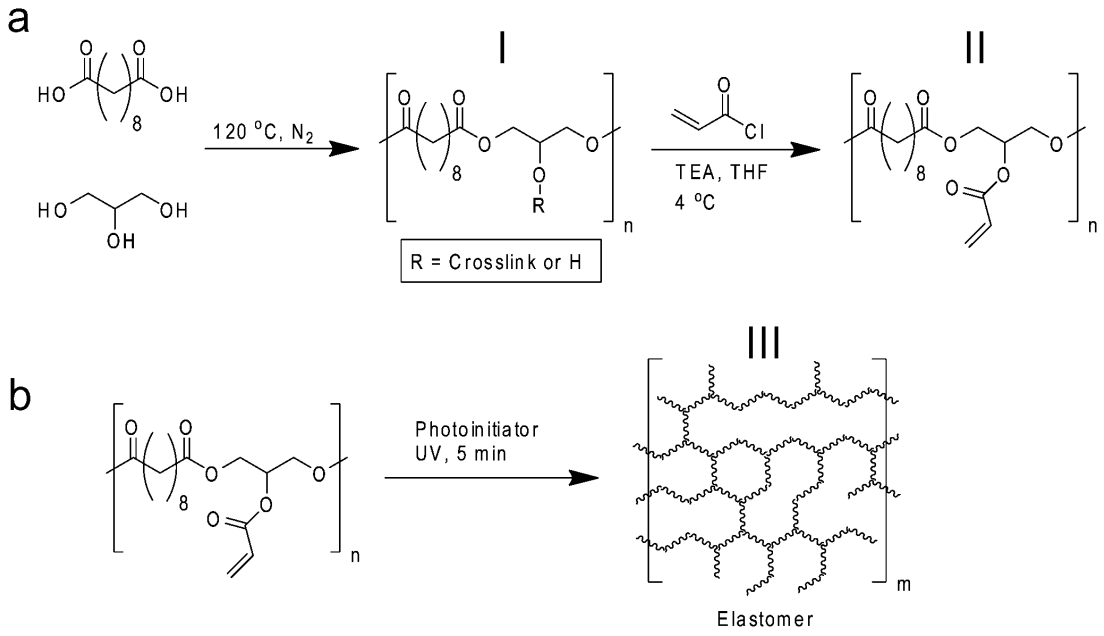

Fig. 3 Preparation of photocrosslinkable biodegradable elastomers. (a) Schematic representation of the polycondensation reaction between glycerol and sebacic acid, which yields the PGS prepolymer (I). These macromolecules are modified with pendant photoactive diene groups to yield the acrylate-modified prepolymer termed poly(glycerol-*co*-sebacate)-acrylate (PGSA) where R is H or polymer chain. (b) This prepolymer can be photocrosslinked into the final elastomeric network.

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extend the processing capabilities of a wide range of polymeric systems. Other techniques include the use of star-based polymers that are extended and end-modified with photofunctional groups. For example, four-arm star-shaped polymers based on extension of PLA can be modified with methacrylic anhydride or a vinyl-containing diisocyanate group [27]. The result is a polymer that can be photopolymerized to produce the crosslinked elastomer. Acrylation of PCL-PLA star polymers is another convenient method for producing photocrosslinkable biodegradable elastomers [28]. The macroscopic mechanical and thermal properties of this class of materials were found to depend upon the molecular weight of the acrylated prepolymer. However, the glass-transition temperature (T_g) was almost completely independent of the molecular weight of the prepolymer. Photocrosslinkable systems based on PCL macromolecules have also been explored extensively [29,30].

Alternative network formation

Elastomeric networks can also be prepared using macromolecular precursors with labile pendant groups that can bound through the use of multifunctional crosslinking additives. This strategy is widely employed for the preservation of natural biological materials, including proteins, through crosslinking with dialdehydes such as formaldehyde or glutaraldehyde. While this chemistry is adequate and appropriate for synthetic systems, other crosslinking chemistries may be able to expand the functionality of crosslinked systems. Diisocyanates represent another crosslinking reagent that is able to produce biodegradable crosslinks [31]. Specifically, diisocyanates have been used in this manner to prepare crosslinked elastomers using star-based precursors such as 6-arm-star poly(L-lactide-*co*-ε-caprolactone) and star poly(glycolide-*co*-ε-caprolactone). The addition of ethyl 2,6-diisocyanatohexanoate to these reactants in toluene at elevated temperatures produces elastomers with carbamate linkages. This synthetic approach is somewhat general and could be applied to form a wide variety of monomers including polyester macromolecular network precursors [32].

Oligomers can be crosslinked through free radical polymerization by incorporating photoactive diene bonds in the backbone of these precursors. Unsaturated polyester oligomers have been prepared using numerous synthetic steps. 2-butene-1,4-diol can be used in combination with a ring-opening polymerization of D,L-lactide to yield a product with integrated dienes [33]. This product is then chain-extended with fumaric acid to produce a polyunsaturated polyester. This unique prepolymer can then be crosslinked using thermal activated free radical polymerization via benzoyl peroxide as the initiator. Polycondensation reactions can be used to prepare other types of poly(ester ether)s as demonstrated in the synthesis of poly(hydromuconic acid-*co*-diethylene glycol-*co*-adipic acid) [34]. The incorporation of unsaturated bonds within the backbone enables crosslinking of this precursor through free radical polymerization. This synthetic route allows for the resulting biodegradable networks to be processed into various geometries including films and particles. A family of poly(ester-urethane) ureas (PEUUs) can be synthesized from polycaprolactone and 1,4-diisocyanatobutane. Lysine ethyl ester or putrescine are used as chain extenders to enhance crosslinking. The surface of PEUUs can be post-modified with radio-frequency glow discharge followed by coupling of arginine–glycine–aspartic acid (RGD)-containing species.

Thermoplastic elastomers represent a unique capability when set in the context of biomaterials for drug delivery and tissue engineering. The superior mechanical properties of thermoplastic elastomers can be attributed to the unique block co-polymer structure in which “hard” blocks, typically comprised of hydrophobic moieties, are linked together with “soft” blocks that are composed of hydrophilic species. The hard blocks aggregate to form crystalline domains, which serve as noncovalent crosslinks for the resulting polymer network. Soft segments enable elastomeric properties such as reversible deformation and large strains. Biodegradable thermoplastic elastomers have been prepared by using triblock co-polymers arranged in the following arrangement: PLA-PCL-PLA [35]. Networks formed from these triblocks exhibit two glass-transition temperatures; one at –27 °C and one +41 °C. These two tempera-

tures correspond to the PCL and PLA segments, respectively, in which PCL serves as the soft segment and the PLA serves as the hard segment. The molecular weight of the blocks of these co-polymers was varied between 89 000 and 124 000 Da with a narrow polydispersity index between 1.15 and 1.20. A similar approach has also been previously applied to synthesis thermoplastic polyesters consisting of a tri-block structure of PLA-PEO-PLA [36]. Given the potential for diversity in composition with tightly controlled polydispersity and high molecular weights, extending the concept of thermoplastic elastomers to synthetic biodegradable polymers is an effective method to expand the potential suite of processing capabilities.

PROCESSING

Thin films

The choice of processing considerations of biodegradable elastomers is governed primarily by the intended function of the material as well as the final intended application. Perhaps the simplest strategy for processing biodegradable elastomers lies in the potential formation of thin films using solely prepolymer starting material. Thermoset elastomers can be cured into thin films with ease by exposing the macromolecular precursors to high temperature under vacuum, which simultaneously melts the polymer into the final form and crosslinks the network. This process is typically completed in the absence of solvents or initiators. The primary advantage of thermal crosslinking is the simplicity of the processing and the elimination of additives. Curing thermoset biodegradable elastomers into thin films using this technique also allows for replica-molding techniques (Fig. 4). Replica-molding is suitable for imparting 2D arrays of micron- and sub-micron-scale features in these materials. Variations of this process can be used to fabricate a variety of systems including microfluidic devices [37,38] and textured surfaces for various applications including contact guidance of cell populations [39] and tissue adhesion devices [40]. The curing of thermoset elastomers exhibits several significant limitations, however. As previously mentioned, processes that require temperatures in excess of 100 °C and high vacuum prohibit the incorporation of bioactive components and ultimately limit the spectrum of downstream applications. There are also processing limitations related to geometry. Curing processes in films greater than 1 mm in thickness can result in spatial variation in crosslink density within the network and significant out-gassing of reaction by-products. Each of these artifacts can produce undesirable heterogeneous properties throughout the final form. Out-gassing can also lead to practical issues such as bubble formation within the network.

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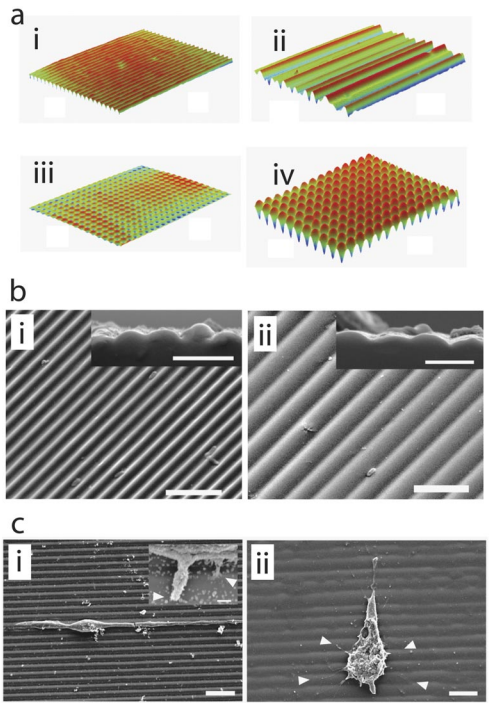

Fig. 4 Replica-molding of thermoset biodegradable elastomers. (a) Noncontact optical profilometry of replica-molded PGS elastomers suggests that many geometries can be investigated including (i) ordered grating, (ii) disordered grating, and ordered (iii) pits and (iv) pillars. (b) SEM images of microfabricated PGS substrates with a (i) 2.5 μm period and (ii) a 4.1 μm period. (c) Bovine aortic endothelial cells cultured on substrates with topographic structures of (i) 2.5 μm period exhibited spindle-like morphologies, higher alignment frequency, and more elongated geometry, when compared to substrates having a (ii) 4.1 μm period. Cells extend filopodia, which appear to make contact with the apex of the microstructures of topographically patterned substrates as indicated by triangles in the figure (a inset, b). Scale bars represent 10 μm in the large figures and 5 μm in the insets of panel (b). Scale bars represent 10 μm in the large figures and 1 μm in the inset of panel (c). Reprinted with permission from ref. [39], copyright © 2006, Elsevier.

Complex structures

Many aliphatic macromolecular precursors to biodegradable elastomeric networks are soluble in common solvents. Notable exceptions are those that possess amide bonds, which are only soluble in exotic solvent systems [41,42]. Solvent processing is suitable for spin coating and curing for the formation of uniform thin films on the order of 1 μm or smaller in thickness. Prepolymer solutions can be molded into complex geometries with features on small length scales. Solvent processing also allows for the formulation of microparticle-based gels, which can then be crosslinked in situ [26,43]. Solvent-processing capability also allows for soft-lithography techniques including microcontact printing, contact force lithography, and related processes. Prepolymer solutions can be processed into microstructures using other techniques including electrospinning. For example, poly(glycerol-*co*-sebacate)-acrylate (PGSA) can be dissolved in ethanol and electrospun in conjunction with a poly(ethylene oxide) (PEO) carrier polymer to improve the electrospinning potential [44]. The characteristic length scale of the resulting network structures is on the order of 1 μm, and the morphology of these structures can be controlled by adjusting the concentration of PEO in the system. Free radical polymerization using photocrosslinking in combination with thin film processing provides a photolithographic capability. In this sense, photocrosslinkable biodegradable elastomers function as a "negative resist", which can poten-

tially be used for patterning cell populations or as a material for microelectromechanical systems (MEMS) [45]. The soft nature of these materials also allows for subtractive processes including laser ablation [46] and porogen leeching [26]. In general, the range of processing capabilities of biodegradable elastomers is comparable to many other synthetic polymer systems. Processing water-soluble macromers into hydrogels allows for the facile incorporation of bioactive components [47,48]. Furthermore, water-soluble photocrosslinkable hydrogel precursors are able to be rapidly processed into a variety of forms using various techniques including microfluidic patterning, electrospinning, and soft-lithography [49].

CHARACTERIZATION OF BIODEGRADABLE ELASTOMERS

Mechanical properties

The mechanical properties of synthetic biodegradable elastomers are the most unique physical aspect of this class of biomaterials. Traditional mechanical characteristics such as Young's modulus, ultimate tensile strength (UTS), and maximum elongation at break are figures of merit that define, in part, the range of potential applications. The mechanical properties of these elastomers are based on several factors including chemistry, stoichiometry, and processing conditions. These factors directly influence the degree of crosslinking, which governs the mechanical properties such as Young's modulus in an ideal elastomer. For example, biodegradable elastomers based on poly(glycerol-*co*-sebacate) (PGS) systems exhibit a range of Young's moduli from approximately 0.2 to 2 MPa with elongations at break from 30 to 200 % [19,50]. However, the resulting window of mechanical properties is relatively limited. Poly(polyol sebacate)-based (PPS) elastomers exhibit a wider range of mechanical properties, which can be altered by adjusting the functionality of the monomers and the stoichiometry of the reactants [51]. One PPS formulation consisting of a 1:1 ratio of xylitol and sebacic acid was processed into films with a Young's modulus of 0.82, a UTS of 0.61 MPa, and a maximum elongation of break of 200 % [23]. Maltitol, a polyfunctional carbohydrate, was polymerized in a 1:4 ratio with sebacic acid. The resulting elastomers exhibit a Young's modulus up to 380 MPa, a UTS of 18 MPa, and a maximum elongation of break of 11 %. The expanded range of mechanical properties can be attributed to the distribution of chemical functionalities. Other synthetic compositions are able to achieve an even broader range of mechanical properties. For example, PEUUs are highly flexible, with breaking strains of 660–895 % and tensile strengths from 9.2–29 MPa [16]. The overall range of mechanical properties that can be achieved in synthetic elastomers is striking. Although the initial mechanical properties may be well characterized, these characteristics exhibit a temporal dependence and change as the material biodegrades, either in vitro or in vivo. Degradation processes can impact the mechanical properties through several prominent mechanisms. The primary effect of degradation on modulus is through the degradation of crosslinks. Bond cleavage increases the molecular weight between crosslinks, reduces the Young's modulus, and increases the maximum elongation at break. However, these degradation processes also produce a secondary effect. Hydrogen bonding (H-bonding) is an intramolecular force that is responsible in part for high strength properties of natural materials including collagen. H-bonding interactions can also be recapitulated in synthetic systems that feature hydroxyl groups interacting with esters or carboxylic acid groups. This interaction, which can be revealed through Fourier transform-infrared (FT-IR) spectroscopy, also plays an important role in the mechanical properties of elastomers. As elastomers degrade via hydrolysis, for example, the incidence of these H-bonding groups increases, which can in turn dynamically impact the material during degradation processes. The strength of these interactions can be attenuated by electronic screening in aqueous solutions with ionic species. The T_g of some elastomer compositions has been observed to be in excess of 40 °C [20,51]. These formulations may, therefore, be glassy at physiological temperatures and in turn may lose the desirable compliant mechanical properties that would otherwise make the material suitable for biomedical applications. However, physiologic conditions also produce hydration and swelling, which ulti-

mately leads to T_g depression of these networks [52]. Therefore, most polymer networks will retain their rubbery state upon hydration in physiologic conditions.

Biodegradation

Similar to the mechanical properties, the biodegradation behavior of elastomeric biopolymers is directly dependent upon a combination of the synthesis scheme and the processing. The primary aspects of biodegradation properties are bond cleavage rate, the mode of degradation, and the resulting degradation by-products. Many biodegradable elastomer systems exhibit tunable biodegradation kinetics and timelines. Ostensibly, the biodegradation kinetics is a direct consequence of the chemistry and the physical properties of the crosslinked network. A precise, quantitative understanding of biodegradation processes, both in vivo and in vitro, has not yet matured. Similar models have, however, been developed for more common biomedical polymers such as PLGA [53]. A theoretical framework would be immensely useful in predicting the structure-processing–property relationships described herein. A comprehensive understanding of these degradation processes may be complicated by chemical and structural diversity of this class of materials. The motivation for developing models of degradation behavior for linear thermoplastic polymers such as PLGA may arise due to the widespread use of nominally one type of material in the medical field. This situation lies in contrast to the materials space for synthetic biodegradable elastomers, which is populated by chemically and physically diverse compounds with no "gold standard". However, understanding the specifics of elastomer biodegradation is a critical component to motivating synthesis schemes and processing conditions while also defining the potential range and limits of biomedical applications.

The rate of biodegradation can be tuned by simply adjusting the crosslinking density. It is thought that increasing the degree of crosslinking (decreasing the molecular weight between crosslinking) may lead to drastic reduction of biodegradation. A comprehensive study of the degradation of PGS revealed that this parameter is not a particularly sensitive component in the resulting kinetic behavior [50]. PGS prepolymer, prepared in identical manner, was then cured from 42 h up to 114 h. These dramatically different curing conditions resulted in a compressive Young's modulus that was measured between 0.4 and 1.5 MPa, respectively, which is over a 3-fold increase. This increase in crosslink directly corresponds roughly to a 3-fold increase in crosslink density through the simple rubber elasticity relationship. The amount of gel that was liberated from these networks upon in vivo degradation at a predetermined endpoint varied between 10 and 20 % of the network by mass. In vitro enzymatic degradation studies demonstrated an even smaller disparity in network mass loss at any given time point. These results suggest that altering the crosslink density via alternative process considerations is not effective in dramatically altering the biodegradation timeline. As a corollary, it may instead be possible to better control these systems at the molecular level by incorporating bonds that are resistant to hydrolysis and esterase activity.

The desire to incorporate both amide and ester bonds into crosslinked elastomers through polycondensation reactions motivated the synthesis and characterization of elastomeric poly(ester amide)s [20]. This class of synthetic elastomers includes compositions such as such as poly(polyol-*co*-1,3-diamino-2-hydroxy propane sebacate)s (APSs). This general biomaterials system allows for a wider range of degradation kinetics as well as a tractable system with which to study particular aspects of biodegradation phenomena both in vitro and in vivo (Fig. 5). The relative amounts of ester and amide bonding in these crosslinked systems are tuned by altering the stoichiometry. Systematically altering the relative ratios between esters and amides provides a set of materials that may aid in the elucidation of biodegradation mechanisms. Furthermore, the incorporation of esters and amides allows specific enzymatic degradation phenomena to be targeted by virtue of selecting the appropriate enzymatic species in a controlled in vitro degradation environment [42]. Furthermore, the in vitro degradation results, which can be precisely defined, can be used to form a basis of comparison with in vivo degradation results as well. The disparity in hydrolysis kinetics between esters and amides can also be used to elucidate

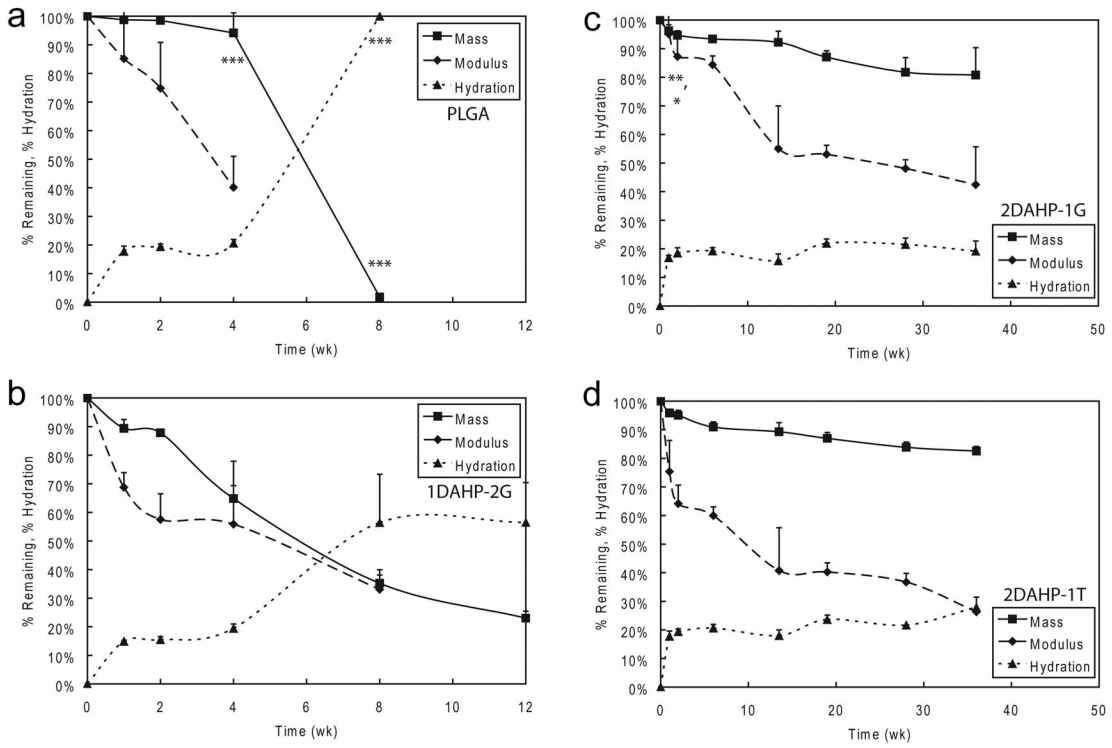

Fig. 5 In vivo degradation kinetics of poly(ester amide)s. Mass, hydration, and compressive Young's modulus are monitored throughout in vivo degradation of select elastomeric poly(ester amide)s in comparison to (a) PLGA. The synthesis of APS elastomers is shown in Fig. 1. The polyols utilized for this specific set of materials are (b,c) glycerol and (d) D,L-threitol. The ratio of the reactants is adjusted to tune the specific properties. 2DAHP-1G corresponds to a 2:1 ratio of 1,3-diamino-2-propanol to glycerol, 1DAHP-2G corresponds to a 1:2 ratio of 1,3-diamino-2-propanol to glycerol, and 2DAHP-1T corresponds to a 2:1 ratio of 1,3-diamino-2-propanol to D,L-threitol. 2DAHP-1G formulations exhibit extended mass lifetimes during in vivo degradation compared to 1DAHP-2G formulations. These elastomers exhibit mostly surface erosion as characterized by mass loss. PLGA control materials degrade primarily by bulk degradation as expected. Reprinted with permission from ref. [42], copyright © 2008, Wiley-VCH.

aspects of hydrolytic degradation processes. Taken together, this class of materials in combination with controlled in vitro degradation provides unique insight. First, the degradation kinetics could be altered significantly with only subtle alterations in stoichiometry. The in vitro degradation half life could vary from 4 weeks to 2 years, which reflects the sensitivity of this parameter on chemical bond composition alone. Second, the hypothesized mode of degradation could also be tuned by virtue of material composition. Elastomeric poly(ester amide)s with a higher incidence of ester bonds were found to degrade more rapidly in vivo compared to elastomers with a higher incidence of amide bonds. This result is consistent with the observed degradation kinetics of other types of biodegradable materials [54]. However, it was also observed that the mode of in vivo biodegradation is also dependent upon the composition of the material. Elastomeric poly(ester amide)s that contain high amounts of esters degrade primarily through surface-erosion mechanisms via enzymatic activity. Conversely, elastomeric poly(ester amide)s that contain high amounts of amides degrade primarily through bulk degradation via hydrolytic processes. The typical manner of controlling the biodegradation mode of a polymeric implant is to control the relative rates of water diffusion and hydrolysis [55]. This example demonstrates that the degradation mode can be governed through subtle alterations in chemistry.

Biocompatibility

The observed improvement in in vivo biocompatibility profiles of biodegradable elastomers is hypothesized to be a result of the mechanically compliant nature of these implants. Improved in vivo biocompatibility is also an indication that the implants are not exuding cytotoxic components at appreciable concentrations into the extracellular space. In vivo biocompatibility is somewhat difficult to characterize uniformly across materials because nearly all studies vary in terms of time points, animal model, implant location, and the arbitrary selection of biological markers that are analyzed. In vitro biocompability is perhaps a more potent measure of the chemical and mechanical properties that are more predictive of the performance of the material because of the more controllable aspect of biological interactions. Many synthetic biodegradable elastomers are generally observed to be biocompatible in vitro. Aliphatic elastomeric films processed from a variety of compositions are shown to support cell growth from a number of phenotypes that might be relevant for tissue engineering applications [32]. The attachment and growth of fibroblasts, smooth muscle cells, endothelial cells, Schwann cells, and neuronal bodies have all been demonstrated on polyester-based elastomeric films of various compositions [23,51]. Poly(ester amide) elastomers promote spreading of various phenotypes in vitro [20,56]. This may be due to either or both of the following: (1) enhanced electrostatic interactions via the presence of cationic primary amines; (2) biomimetic amide moieties, which are present in native proteins. However, it is difficult to directly assess the physicochemical aspects of this attachment process since many of these assays are conducted in the presence of serum proteins which may mask the intrinsic surface properties of the film. One study investigated the in vitro biocompatibility of poly(ester amide) elastomeric films using a cell attachment assay with primary hepatocytes [56]. The presence of amides was found to enhance the attachment of these cells in serum-free conditions. Furthermore, the degree of spreading could be increased by using substrate nanotopography. Although increased spreading is undesirable in maintaining hepatoctye differentiation in vitro, this study demonstrates that the chemical and topographical versatility can be used to influence biocompatibility profiles and cell–biomaterials interactions.

POTENTIAL APPLICATIONS

Controlled release

The great promise of biodegradable elastomeric biomaterials lies in the ability to develop unique medical implants that are medically relevant, bioresorbable, and able to function in mechanically dynamic microenvironments. The tunable mechanical properties and biodegradation kinetics suggest that this material platform is particularly suitable for drug delivery and tissue engineering applications. The application of biodegradable elastomers is particularly suitable for drug delivery systems that are composed of large implants on the order of 1 mm to 10 cm in length. Devices on this length scale would benefit immensely from mechanical compliance and be able to be implanted into tissues that undergo significant mechanical deformation such as the lungs, heart, and joints. The compliant mechanical properties of biodegradable elastomers are also suitable for conformal coatings for medical implants that undergo mechanical activation such as stents. Virtually all tissues and organs in the human body exhibit curvature across at least one dimension. Elastomeric biomaterials are able to conform to these features to create intimate contact with tissue across large areas and to reduce inflammation associated with mechanical perturbation. Drug delivery systems based on photocrosslinkable acrylated star(ε-caprolactone-*co*-D,L-lactide) have been studied for use in delivering protein therapeutics [57]. In vitro drug elution studies using vascular endothelial growth factor (VEGF), interleukin-2 (IL-2), and interferon-gamma (IFN-gamma) were performed using this material system. The protein of interest was co-lyophilized with albumin and trehalose, a stabilizing excipient, to form microparticles. These particles were then loaded into a macromer solution and photocrosslinked to form the final device. Zero-order release kinetics was demonstrated for over 18 days with adequate bioactivity. The elastomeric matrix

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was stable for up to 50 days, at which point the mass decreased dramatically. The release kinetics can be tuned by adjusting the concentration of trehalose in the formulations, which is used as an excipient. In principle, release kinetics can also be altered by tuning a number of material parameters including the crosslinking density and hydrophobicity of the star(ε-caprolactone-*co*-D,L-lactide). Processing parameters such as particle loading and formulation conditions can also be used to tune the release kinetics.

Tissue engineering

Synthetic biodegradable elastomers have enormous potential to advance the fields of tissue engineering and regenerative medicine. The combination of unique mechanical properties, biocompability, biodegradability, and facile processing are enabling technologies for this material platform. Synthetic biodegradable elastomers have been utilized as scaffold materials in many different geometries. Films have been fabricated for potential use in regeneration of planar, 2D tissue structures. Films are convenient for the fabrication and are simultaneously able to provide homogeneous signaling cues to large populations of cells. This may be particularly advantageous for constructing flexible externally applied skin grafts or internal structures such as the bladder. 3D networks have also been fabricated using various fabrication techniques. For example, 3D microfluidic devices have also fabricated using replica-molding and bonding strategies for the in vitro culture of hepatocyte cells for potential applications in liver tissue engineering [38]. Flexible scaffolds for cardiac tissue regeneration have also been fabricated using biodegradable elastomers [46]. In this example, films were imparted with a controlled pore geometry using laser ablation techniques. The intrinsic anisotropy of the pore geometry impacted seeded heart cells and produced a structural anisotropy in the resulting cardiac tissue. This characteristic was reflected in the tissue construct through functional assays such as mechanical properties and electrical stimulation. Photocrosslinkable PGSA has been fabricated into porous scaffold structures. Briefly, concentrated solutions of PGSA were incorporated into molds with a salt porogen. Rapid photopolymerization followed by porogen dissolution produced interconnected porous networks on the order of 100 μm in size. PGSA has also been fabricated into porous structures for cell encapsulation [58]. Porous foam scaffolds consisting of other elastomers have also been fabricated [59]. Drug delivery capabilities are an emerging paradigm in tissue engineering and regenerative medicine. This approach has been expanded to biodegradable elastomeric scaffolds fabricated from PEUU scaffolds [60]. Porous foams were produced using phase-separation/freeze-drying technique. Briefly, PEUU was dissolved in dimethylsulfoxide (DMSO) at a concentration of 8 % and injected into a mold at room temperature. The temperature of the systems was dropped to –80 °C for 3 h and the DMSO was extracted with ethanol. The resulting 3D structure exhibited features on the order of 50 to 150 μm in size. Fibroblast growth factor (bFGF) could be incorporated into this process and released in a controlled manner over the course of 28 days, albeit with a significant burst release component. The subsequent release rate and bioactivity of the remaining FGF after the burst phase was relatively low, but may be easily improved through process optimization. The versatile chemical approaches and processing capabilities of biodegradable elastomers are appropriate for tissue engineering strategies. The examples discussed herein are representative of the unique capabilities of this material platform.

In vitro cell–biomaterials interactions

The utility of applying biodegradable elastomers for studying in vitro cell–biomaterials interactions is based on the versatility of these materials. The properties that govern cell–biomaterials interactions in vitro can be generally classified as either surface chemistry, stiffness [61], or topography [62]. All of these material properties can be systematically altered in biodegradable elastomers by virtue of altering the synthetic route, curing conditions, and post-processing. The additional capability of biodegradability is not directly advantageous, but may be important in the translation of observed in vitro biological

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phenomenon into clinical therapies. Photocrosslinkable biodegradable elastomers based on poly(ethylene glycol) (PEG) have been modified with GRGDS sequences to promote adhesion of bovine aortic smooth muscle cells [63]. Similar approaches were utilized for the adhesion of osteoblasts in RGD-modified PEG hydrogels for bone tissue engineering [64]. The reaction of endothelial cells to microscale grating topography has been studied using replica-molded films consisting of thermoset PGS [39]. The extent of alignment and elongation in endothelial cells cultured on these substrates is proportional to the extent of curvature of the features. Other non-biodegradable material systems have been used to study the impact of substrate stiffness on differentiation [65], spreading [66], and migration [67,68]. One potential application of biodegradable elastomers in these studies is the use of dynamic surfaces, which exhibit changing properties. For example, the kinetics of cell–biomaterials interactions could be studied as the material degrades in vitro, which corresponds to a reduced stiffness. Phenomenological trends in these cell–biomaterials interactions could be directly applied to biodegradable materials systems as well by virtue of the versatility in the processing of these materials. Furthermore, the use of biodegradable materials could be useful in directly translating in vitro constructs that direct cell behavior into therapeutic cell-based biodegradable implants to stimulate tissue regeneration in vivo.

CONCLUSIONS

Biodegradable elastomers are an emerging class of synthetic biomaterials with many advantages for use in medicine and biotechnology. This material platform offers many practical advantages including: (1) diverse synthetic routes, which can be composed of nontoxic monomers; (2) flexible processing capabilities; and (3) an expansive parameter space including biodegradation time lines, mechanical properties, swelling ratios, surface chemistry, and nanotopography. The wide range of properties is advantageous in developing application-specific biodegradable elastomers for use in tissue engineering, regenerative medicine, and in vitro cell–biomaterials interaction studies. Synthetic biodegradable elastomers remain a relatively nascent class of biomaterials, but it is the opinion of the author that the full impact has yet to be realized. Future research directions in this discipline should be focused on several areas of expanding the properties, processing, and applications. Synthetic materials have the unique ability to incorporate naturally occurring monomers with alterative bond connectivity. This notion has been explored in the context of incorporating “passive” monomers that impart no biochemical signal, but are biocompatible and ultimately become integrated into the host metabolism. Synthetic elastomers may also benefit from incorporating bioactive small molecules into the bulk material [69]. This strategy would present a signaling cue throughout the lifetime of the bulk material while also serving as a controlled release mechanism to deliver said cue into the surrounding tissue. Synthetic elastomers will also benefit from expanding polymer-processing capabilities. Expanding processing capabilities is not specific to biodegradable elastomers and may benefit from general advancements in polymer processing. Finally, this material class should be consistently utilized in translational medical research. Demonstrating the value of these materials for use as drug delivery and tissue engineering applications would be beneficial. Advancing this thrust requires cooperation and collaboration between clinicians and materials engineers in order to achieve the proper balance of structure-processing–property relationships. The maturation of synthetic biodegradable elastomers as a materials class is contingent upon the lucid communication of recent, unmet clinical needs and advancements in biodegradable elastomers. This continued interaction will allow biodegradable elastomers to help solve critical issues in human health to alleviate suffering and prolong life.

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