Expert Opinion

Biodegradable elastomers in drug delivery

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Background: Biodegradable elastomers have been used in many different manners for controlled drug delivery. The development of new biodegradable elastomers has recently increased, driven mainly by tissue engineering research. *Objective*: This review outlines the different uses of biodegradable elastomers in controlled release. *Methods*: This review was limited to those papers wherein the polymer chosen as the delivery vehicle was demonstrably elastomeric. *Conclusion*: Biodegradable elastomers have an established role in controlled release and an expanding role in combination scaffolds providing controlled release and mechanical stimulation capability for tissue regeneration/engineering.

Keywords: aliphatic polyester, controlled release, elastomer, poly(urethane), tissue engineering

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1. Introduction

Since the first demonstration of sustained drug delivery from a biodegradable polymer device in 1970 [1], there has been a great deal of effort devoted to the investigation of drug delivery from biodegradable thermoplastics such as poly(glycolide-co-lactide), but comparatively little attention devoted to the release of drugs from biodegradable elastomers. Elastomers can allow for different release mechanisms to be considered, in particular osmotic pressure. Additionally, elastomers can be used in applications that require polymer flexibility as well as drug-eluting capability. Moreover, elastomers can also provide structural support as their mechanical properties can be adjusted so as to be similar to those of soft tissues [2]. This latter fact can be used to incorporate drugs, such as growth factors, within porous polymer scaffolds, thus providing both chemical and mechanical stimulation for effective tissue engineering.

Biodegradable elastomers have been prepared as both thermosets [3-16] and thermoplastics [17-38]. Each approach has advantages and disadvantages, and both approaches have been used in preparing drug delivery devices. In the following sections, each approach will be discussed with respect to the rationale for the use of the approach for achieving effective drug delivery.

2. Thermoset elastomers

In thermoset elastomers, the crosslinks consist of covalent bonds. The first published example of a thermoset biodegradable elastomer was that of Schindler and Pitt [4,39], wherein a bis-caprolactone was prepared and co-polymerized with caprolactone and δ-valerolactone. The rationale for the development of this elastomer was to provide a device that maintained its geometry during degradation. Maintenance of device geometry was considered important in order to provide a predictable release rate by diffusion from the device. However, there are no published examples of drug release from these elastomers. This may be due to the fact that the elastomers were prepared by thermal crosslinking at 140°C, and thus could not be used for temperature-sensitive drugs without resorting to drug loading by solvent

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expansion of the pre-formed network, followed by solvent evaporation. This drug loading approach introduces additional manufacturing steps that were likely not compensated by the maintenance of form stability during release.

Cured elastomers have also been formed from aliphatic polyester telechelic prepolymers that have been end-terminated with olefinic groups that can be crosslinked by photo-initiated free radical polymerization (**Figure 1**) [16,40,41]. Photo-initiated crosslinking has the advantage that the reaction proceeds rapidly at low temperatures, and therefore may be suitable for the incorporation of thermally sensitive drugs such as peptides and proteins. The mechanical properties of the resulting elastomers are determined by the molecular weight of each amorphous low glass transition temperature arm in the telechelic prepolymer (**Table 1**). The arms reside between crosslink regions consisting of oligo(acrylate). The length of each arm thus determines the crosslink density and ultimate extension ratio of the elastomer.

These elastomers were developed by the present author's group to provide an osmotically driven drug delivery mechanism. In this type of release, solid particles of the drug, with or without added excipients, are distributed throughout the elastomer bulk. The volume fraction of particles within the device is kept below 30% to ensure that the majority of the particles are encapsulated by the polymer. Upon immersion into an aqueous medium, water vapour partitions into, and begins to diffuse through, the elastomer. Once the water contacts a drug particle, it phase-separates, dissolves a portion of the solid particle at the polymer/solid interface, and forms a saturated solution. The resulting gradient in water activity between the dissolved solution surrounding the solid particle encapsulated by the polymer (hereinafter referred to as a capsule) and the external medium causes water to be imbibed into the capsule, producing a pressure equivalent to that of the osmotic pressure of a saturated solution of the drug or excipient. If this pressure exceeds the resisting pressure of the elastomer, fractures are formed in the elastomer, generating a porous network through which the concentrated drug solution is forced under the pressure difference. This mechanism proceeds in a drug particle layer-by-layer manner throughout the device, and produces a constant drug release period that lasts until ~ 60 – 80% of the total amount of loaded drug is released [42-44]. Initial studies of this release mechanism used non-degradable polymers such as silicone and poly(ethylene-co-vinyl acetate).

This release mechanism has been used, to achieve a constant release of therapeutic proteins such as IFN-γ, vascular endothelial growth factor (VEGF), and IL-2 [45-47]. Protein drug particles were prepared by co-lyophilizing the protein drugs with the excipients bovine serum albumin and trehalose, such that < 1 wt% of the particle was comprised of the protein drug. These protein particles were then suspended in a solution of *star*-poly(ε-caprolactone-co-D,L-lactide) triacrylate, the suspension then poured into a mold and crosslinked by exposure to UV radiation (100 mW/cm^2 for 2 min). The *in vitro* release rate was controlled by the mechanical properties of the elastomer and by the osmotic activity and the amount of the excipient incorporated into the protein particles (**Figure 2**). Increasing the molecular weight of the prepolymer used to form the elastomer from 2700 Da to 7800 Da resulted in a weaker elastomer (**Table 1**) and a slower release rate. This slower release rate was attributed to the need for a greater amount of water to be imbibed into a particle capsule in order to generate cracks within the device. Increasing the amount of the more osmotic excipient in the particles, in this case trehalose, increased the release rate as it generated a greater activity driving force upon dissolution of the particle, and thus an increased rate of water imbibition, which in turn generated cracks within the elastomer bulk within a shorter time frame. A constant release was achieved, despite the fact that the elastomer degraded by hydrolysis, because the mechanical properties of the elastomer remained constant during the release period [16]. Nevertheless, the stability of VEGF was compromised after 7 – 8 days and VEGF was increasingly non-bioactive after that time, dropping from a bioactivity of ~ 80% at day 7 to inactive by day 15 [46]. This decrease in growth factor bioactivity was a result of acidic elastomer degradation product build up within the interior of the device, resulting in an internal pH of < 5 [47]. The bioactivity of IFN-γ and IL-2 was not as affected; their bioactivity remained at > 80% until release was essentially complete. Thus, this release device may only be suitable for the delivery of acid-resistant proteins. Moreover, the potential of this type of release device has not yet been demonstrated *in vivo*.

The present author's group have also used the photocrosslinked elastomer for the release of a local anesthetic, bupivacaine. In this application, the drug was co-dissolved with a 7800 Da acrylated telechelic prepolymer, cast into a mold, and the telechelic prepolymer photocrosslinked using UV radiation to form a film. Release was diffusion controlled, as reflected in the mass fraction released being proportional to the square root of time, and proceeded with minimal initial burst of the anesthetic (**Figure 3**). The rate of release of bupivacaine from these films was similar to that observed for bupivacaine loaded into equimolar poly(lactide-co-glycolide) microspheres, which required ~ 2 weeks for complete release [48,49]. For the intended application, this release rate is likely too long. Possible means of increasing the release rate include adding a hydrophilic porogen into the polymer matrix, such as glycerol, or co-polymerizing poly(ethylene glycol) diacrylate into the elastomer network. Including a porogen would result in a porous elastomer, thus providing a greater surface area in contact with the external aqueous medium, and incorporating poly(ethylene glycol) into the network would enhance the water uptake and degree of swelling of the elastomer, both of which should result in increased drug

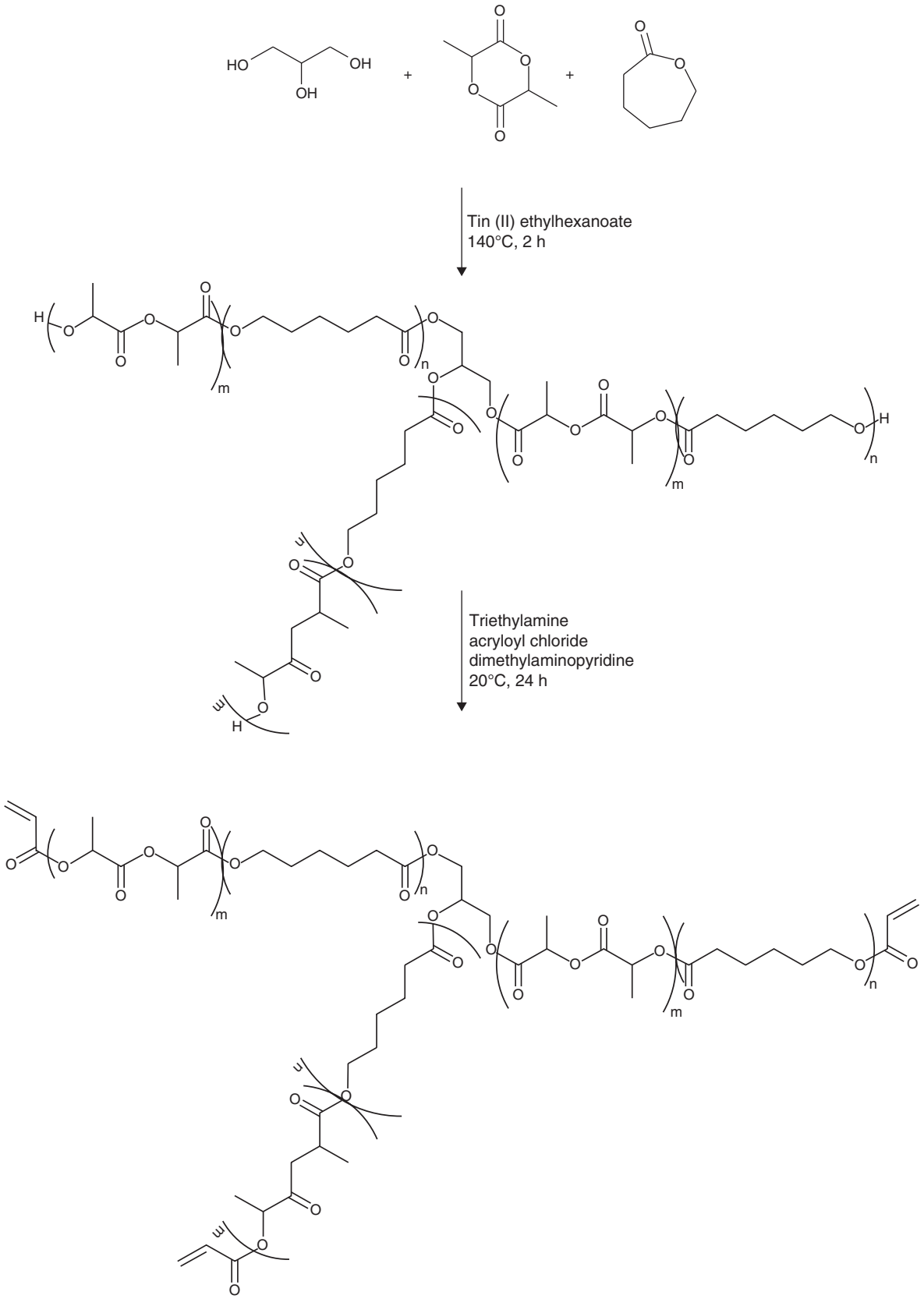

Figure 1. Preparation of *star*-poly(ε-caprolactone-D,L-lactide) triacrylate [16].

Table 1. Mechanical properties of biodegradable elastomers used in drug delivery applications.

Polymer	Elastomer type	E (MPa)	σ (MPa)	ε (%)	Ref.
Star-poly(CL-co-DLLA) triacrylate	Thermoset				[16]
1250 Da		5.30	4.40	79	
2700 Da		1.71	2.99	236	
7800 Da		0.59	1.71	530	
12000 Da		0.38	1.27	710	
Poly(CL-BDA-LDI)	Thermoplastic		6.4 – 30.7	13 – 1600	[38]
Poly(CL-putrescine-BDI)	Thermoplastic	2.4 – 11.9	9.2 – 29	660 – 895	[82]
Poly(CL-co-DLLA)	Thermoplastic				[22]
80:20		1.6	30	> 100	
60:40		0.023	6.4	> 100	
40:60		0.07	3	> 100	
Poly(CL-co-LLA)					
80:20		2	55	79	
60:40		0.12	1.8	84	
40:60		3.3	34	> 100	

BDA: 1,4-butanediamine; BDI: butyldiisocyanate; CL: ε-caprolactone; DLLA: D,L-lactide; LDI: 2,6-diisocyanato methyl caproate; LLA: L-lactide.

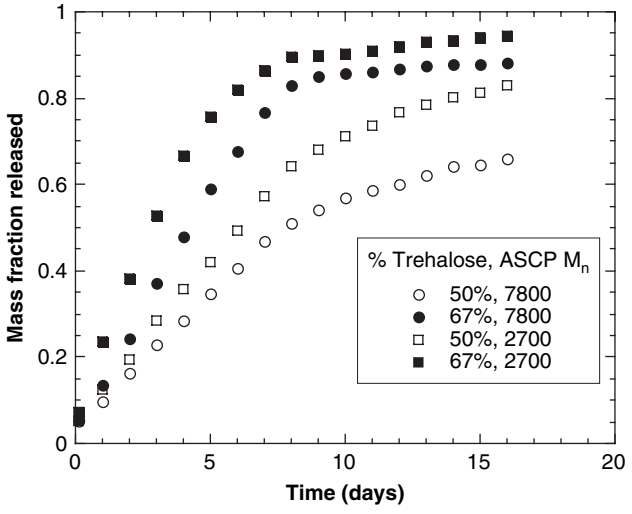

Figure 2. Example of constant release from a biodegradable, photo-crosslinked elastomer and the influence of elastomer mechanical properties on release rate [47]. IFN-γ (< 1 w/w%) was co-lyophilized with varying amounts of bovine serum albumin and trehalose and distributed as particles of < 145 µm in diameter.

release. These films were proposed for the treatment of post-operative pain by being implanted directly into the incision site and sutured in place. Possible advantages of films over microspheres is a more uniform drug distribution in the tissue, easier handling and the ability to hold a suture without tearing.

Diffusional release from cured elastomers will depend on the degree of crosslinking and the monomers used to prepare the elastomer. Crosslinking decreases polymer chain mobility, reflected in an increase in glass transition temperature, and thus decreases solute permeability within the elastomer. The use of telechelic prepolymers allows for a facile means of controlling the degree of crosslinking, through controlling the molecular weight of the prepolymer. Monomer selection will also affect the glass transition temperature of the resulting elastomer. Poly(caprolactone) has a low glass transition temperature of -60°C [50], and poly(lactide) and poly(glycolide) have glass transition temperatures of 57 – 65°C and 37°C, respectively [51]. Thus, incorporating monomers such as caprolactone into the telechelic prepolymers will assist in producing low glass transition temperature crosslinked networks.

The cured elastomers described above are composed of poly(α-hydroxy acids) and, thus, the primary mechanism of degradation *in vivo* and *in vitro* is expected to be hydrolysis [51], although other mechanisms play a role, such as mechanical stress, plasticization of the polymer due to the absorption of lipids or other biological compounds leading to greater water uptake, the release of oxidative species by the foreign body response, the action of enzymes, and a greater solubility of the degradation products *in vivo* [3,39,52-54]. The photo-cured elastomers prepared from *star*-poly(ε-caprolactone-co-D,L-lactide) triacrylate degraded at essentially the same rate *in vivo* as observed *in vitro* [55]. By contrast, Pitt *et al.* found that elastomers prepared from copolymerization of ε-caprolactone,

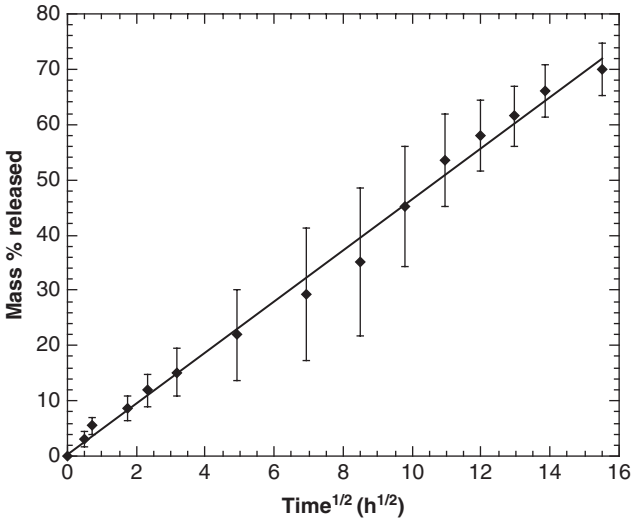

Figure 3. Bupivacaine release from photo-cured *star*-poly(ε-caprolactone-co-D,L-lactide) triacrylate.

δ-valerolactone and a *bis*-caprolactone degraded more quickly *in vivo* than *in vitro* [3] – a result that was attributed to the contribution of enzymatic degradation at the elastomer surface. The difference in the *in vitro* versus *in vivo* degradation behavior of the *star*-poly(ε-caprolactone-co-D,L-lactide) triacrylate-based elastomers of Amsden *et al.* and those of Pitt *et al.* could be due to differences in enzyme susceptibility, or differences in water uptake of the two elastomers. The time to complete degradation of the elastomers have yet to be reported.

Pitt *et al.* showed that increasing the crosslink density of the elastomer resulted in an increase in the degradation time. This result was explained as a decrease in the permeation rate of water into the network and a reduction in chain mobility at the surface retarding enzymatic action. The degree of crosslinking also alters the degradation mechanism. Highly crosslinked elastomers of *star*-poly(ε-caprolactone-co-D,L-lactide) triacrylate were found to degrade in a manner consistent with a surface erosion mechanism, that is, an almost constant mass loss with time, whereas less crosslinked elastomers degraded in a bulk degradation fashion [55]. This difference in degradation mechanism is a result of the slower rate of water penetration into the bulk of the highly crosslinked elastomers compared with the rate of hydrolysis of the ester bonds. This surface erosion phenomenon may be useful in producing an approximately constant release of drug from these elastomers, provided the drug is not prone to acid catalyzed degradation.

3. Thermoplastic elastomers

There has been more research devoted to the use of thermoplastic biodegradable elastomers as drug delivery vehicles. Thermoplastic elastomers contain physical, rather than covalent, crosslinks. Thermoplastic elastomers are typically ABA linear block copolymers wherein the A blocks are immiscible with the B block. The A blocks thus cluster in phase-separated domains, as do the B blocks. One phase-separated domain forms crosslinks, and the other phase-separated region is amorphous and possesses a glass transition temperature much lower than the operating temperature. The crosslink regions can be either crystalline or below their glass transition temperature under operating conditions. The amorphous, rubbery region forms a continuous phase and provides the elasticity. The mechanical properties of the thermoplastic elastomers discussed below are listed in **Table 1**.

A number of biodegradable polyester thermoplastics have been prepared, including: random copolymers of ε-caprolactone and D,L-lactide [17,19,22,33], random copolymers of trimethylene carbonate and D,L-lactide [29], copolymers of ε-caprolactone or trimethylene carbonate with glycolide [27], copolymers of *p*-dioxanone and lactide [26], lactide-trimethylene carbonate block copolymers [30], lactide-butylene succinate block copolymers [31], and poly(lactide)-block-poly(trimethylene carbonate-co-dioxepan-2-one)-block-poly(lactide) [35]. However, reports of drug release from these thermoplastic elastomers in a form where their flexible properties would be used (i.e., as flexible films for placement/suturing into place *in vivo*, where the release mechanism relies on their elasticity, or where they are being used in tissue engineering under dynamic load) are few.

Pitt *et al.* [56] and Buntner *et al.* [57] investigated the release of steroids, and Wada *et al.* [58] examined the release of cisplatin and MD-805 (a thrombin inhibitor) from poly(ε-caprolactone-co-D,L-lactide) films. *In vitro* drug release from these films was diffusion controlled during the early periods, as reflected in the mass fraction released being proportional to the square root of time, followed by a second release phase where polymer degradation accelerated release. In a recent study, Hirose *et al.* [59] prepared films containing the antibiotic vancomycin by dissolving the vancomycin in water, emulsifying this solution in poly(ε-caprolactone-co-D,L--lactide) dissolved in 1,4-dioxane, followed by casting into a mold and solvent evaporation. In this fashion, porous films were formed, with the vancomycin distributed mainly within the pores. Vancomycin was released by dissolution and diffusion through the pores, with a monotonically decreasing release rate, complete by 2 weeks. These films are proposed as an adjuvant for preventing prosthetic graft reinfection in an *in situ* reconstruction, or for the prevention of various local methicillin-resistant *Staphylococcus aureus* reinfections, such as catheter-related infections, surgical-site infections and permanent pacemaker insertion site infections.

Polymer degradation rates were not examined in these release studies; however, the degradation of

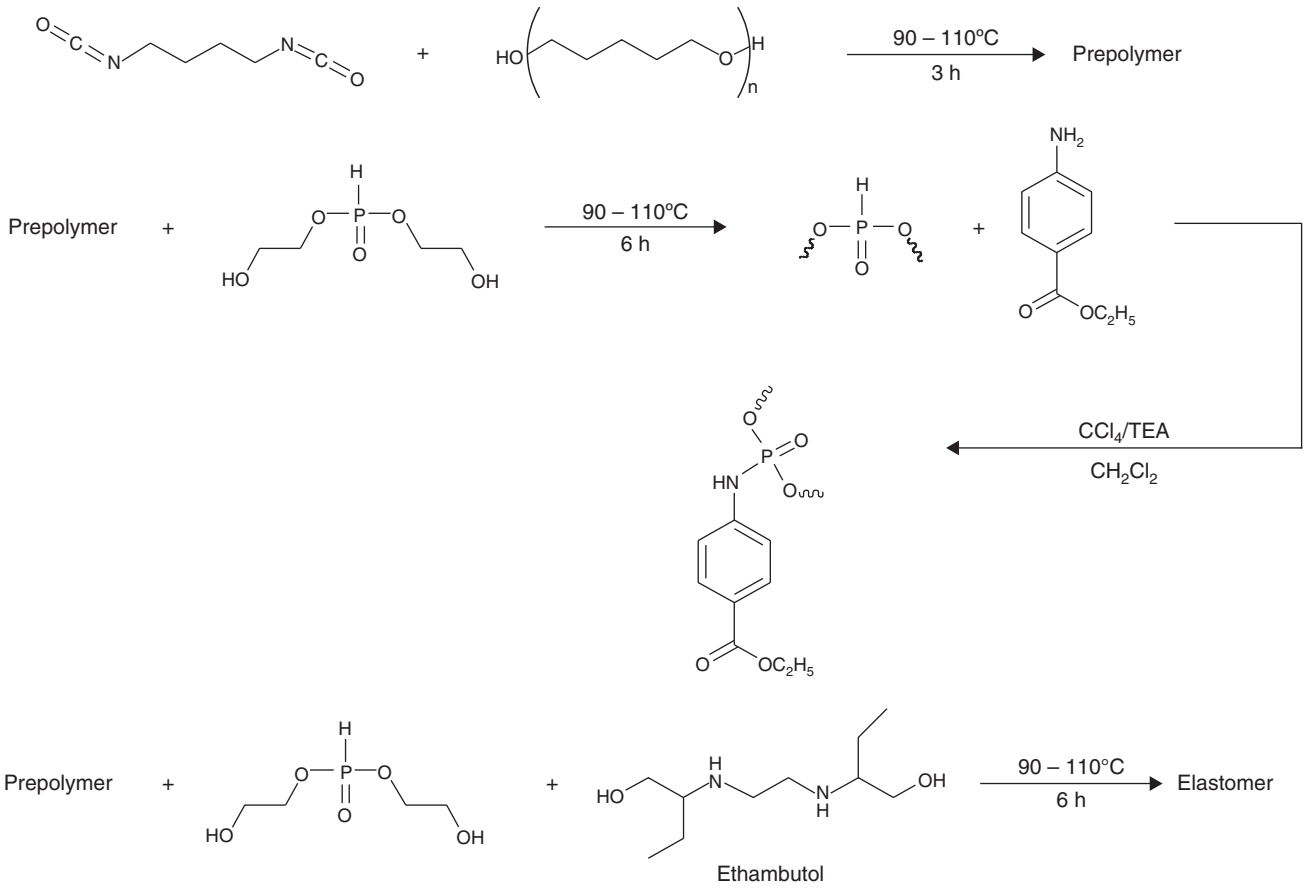

Figure 4. Preparation scheme of Dahiyat *et al.* for benzocaine attached via a hydrolyzable linkage to a poly(phosphoester-urethane) backbone (middle) or containing ethambutol as a comonomer [63].

poly(ε-caprolactone-co-D,L-lactide) polymers of varying monomer composition have been studied by others [60,61] and reviews are available [62]. In general, these polymers degrade at similar rates and in a similar fashion *in vivo* as *in vitro*, with *in vitro* degradation rates increasing as the lactide content of the polymers increases, as a result of the greater hydrophilicity of lactide. For example, polymer rods prepared with 20% lactide required > 2 years to degrade, whereas, those prepared with 37% lactide degraded within ~ 11 weeks [61].

Degradable polyurethanes have also been prepared, often by including a polyester diol [5,23,24,36-38]; however, few controlled release studies have been performed with these elastomers where the drug is loaded into the elastomer. Reddy *et al.* recently prepared theophylline loaded poly(urethane urea) films. The polymer was prepared from a poly(ε-caprolactone) diol reacted with lysine diisocyanate and chain extended with 1,4-butanediamine. The theophylline was loaded into the polymer by solvent casting into films. *In vitro* release demonstrated a diffusion-controlled release profile, with theophylline release from 0.3 mm films complete within 30 h [38]. Although the poly(urethane urea) would be degradable via hydrolysis, it is unclear why this elastomer would be chosen. This elastomer does not provide any advantage over the use of the poly(ε-caprolactone-lactide)-based thermoplastics, as similar mechanical properties can be achieved (**Table 1**), the drug loading conditions would be similar, and similar release profiles could be obtained.

More research effort has been devoted to the preparation of thermoplastic elastomers that contain drug molecules as part of the backbone of the polymer, or that are pendant to the backbone of the polymer. The bulk of this work has been done with polyurethanes, likely due to the low temperatures required for polymerization and the ability to easily incorporate polyfunctional drug molecules into the backbone through chain extension reactions. Dahiyat *et al.* were the first to prepare thermoplastic elastomers that contained drugs either pendantly attached along the backbone via cleavable linkages or incorporated into the backbone as comonomers [63]. These researchers introduced a hydrolyzable phosphoester bond into the backbone by first reacting 1,4 butane diisocyanate (hard segment) with either 400 Da poly(oxyethylene) or 1000 Da poly(tetramethylene oxide), then chain

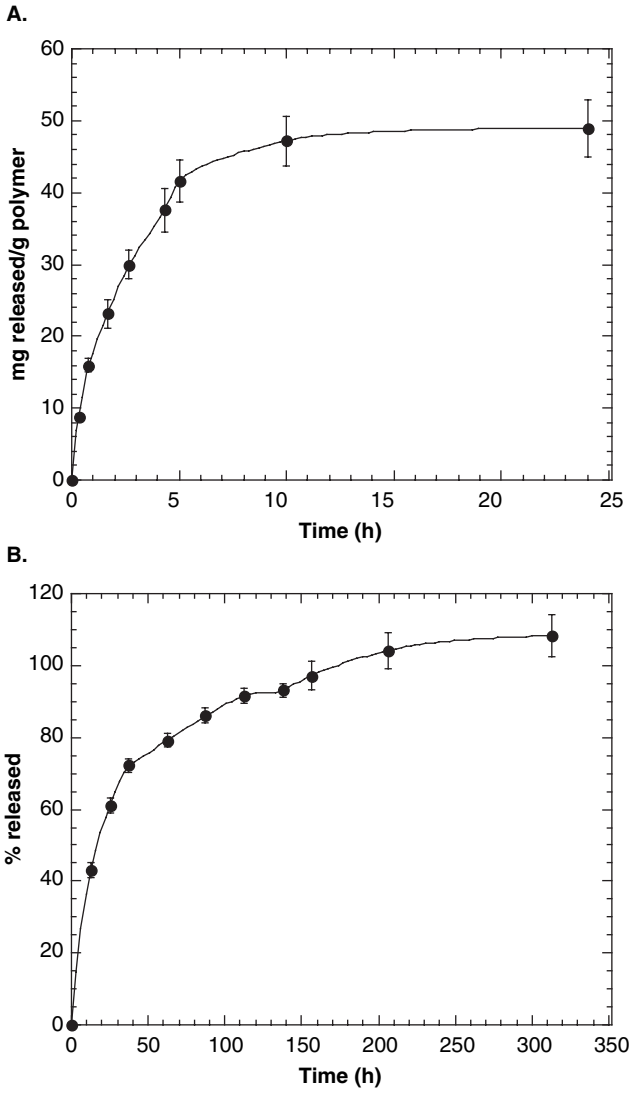

Figure 5. Reproduced *in vitro* release data of benzocaine pendantly coupled to poly(phosphoester-urethane) (A) and ethambutol copolymerized into the poly(phosphoester-urethane) backbone (B) [63].

extending these prepolymers with either *bis*(2-hydroxyethyl) phosphite or *bis*(2-hydroxyhexyl)phosphite in the presence or absence of a diol drug monomer, ethambutol (**Figure 4**). Benzocaine was coupled directly to the backbone through a hydrolyzable phosphoramidate bond, while *p*-amino salicylic acid was coupled via a hydroxybenzaldehyde spacer. Combining a drug as a pendant group produced faster release rates than incorporating a drug into the polymer backbone (**Figure 5**). For example, benzocaine release was essentially complete after 10 h, and ethambutol was released for over 300 h. The difference in the release rates are not due to the location of the drug within the polymer (i.e., pendant versus backbone), but rather due to the greater susceptibility of the phosphoramidate bond linking the benzocaine to the backbone to hydrolysis. The chemical integrity of the benzocaine was retained upon release, and the ethambutol was likely conjugated with oligomers. The release rate followed first-order kinetics, consistent with the rate-limiting step of release being hydrolysis. This approach provided different possibilities for controlling the release of the drugs examined, and potentially other drugs provided they possess suitable functional groups for linking. However, similar release profiles could likely have been achieved by diffusion of these drugs from suitable biodegradable elastomers, such as poly(ε-caprolactone-co-lactide), which would not require the involved chemistry of the pendant drug approach, and avoid potential degradation of the drug possible in the drug–polymer approach. Conjugation of the drug with oligomers, as found with the ethambutol incorporated into the backbone, also poses the additional issues of whether the conjugated drug retains its activity or whether it now possesses some toxicity. These are additional issues that must be resolved through extensive *in vivo* studies before products of this type will reach clinical use.

Similarly, Woo *et al.* have prepared urethane-based antimicrobial polymers in which ciprofloxacin has been incorporated into the backbone (**Figure 6**) [64]. The degradability of these polymers is provided by incorporating poly(ε-caprolactone) as the diol. These polymers are designed to liberate the antibiotic at greater rates in the presence of hydrolases, such as cholesterol esterase, secreted by macrophages as part of the inflammatory response. *In vitro*, ciprofloxacin is liberated at greater rates when incubated with cholesterol esterase, which catalyzes the hydrolysis of long-chain fatty acids, than when in buffer only (**Figure 7**). Despite the aim of having ciprofloxacin released in response to inflammation, the drug will be continually released from the polymer, regardless of the presence of macrophages, because the caprolactone will undergo hydrolysis, albeit slowly. However, it appears that more free antibiotic is released in the presence of enzyme, as the release medium from these *in vitro* degradation studies exhibited greater bacterial growth inhibition. The chain length of the diisocyanate influences antibiotic release, as elastomers prepared with diisocyanatododecane exhibited enhanced release in the presence of the enzyme, but elastomers prepared with diisocyanotohexane did not. The potential of this delivery approach was demonstrated in neutrophil cultures, and the polymer has been shown to be non-cytotoxic to fibroblasts. Nevertheless, there has not yet been any reported demonstration of efficacy *in vivo* and possible toxicity associated with oligomer conjugated ciprofloxacin has not been assessed. Moreover, the total degradation time of the elastomers has not been reported.

Combining the drug–polymer approach with tissue engineering scaffold preparation, Zhang *et al.* copolymerized lysine diisocyanate and glycerol with ascorbic acid [65]. The polycondensation reaction was allowed to proceed until 50% of the diisocyanate was consumed, at which time water

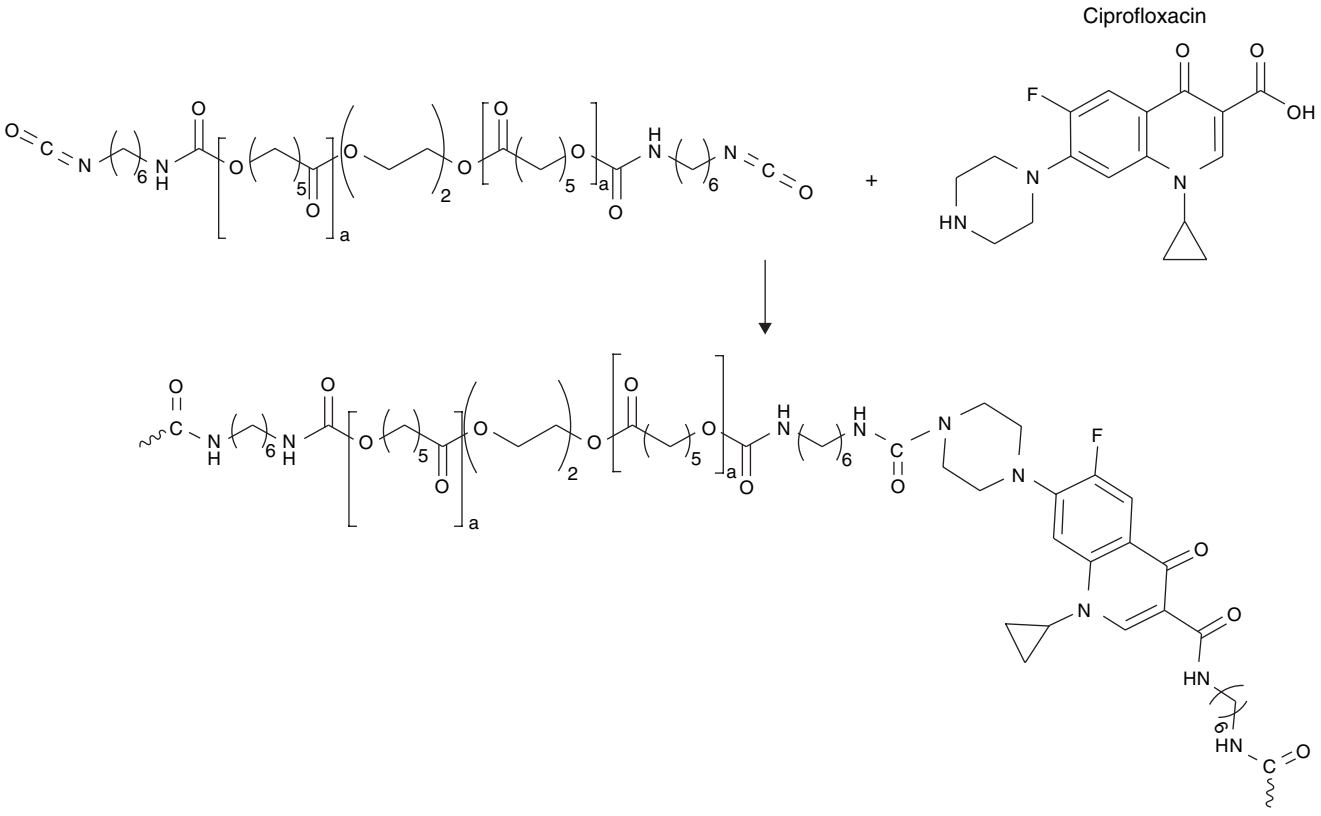

Figure 6. Poly(ester-urethane-ciprofloxacin) of Woo *et al.* [64].

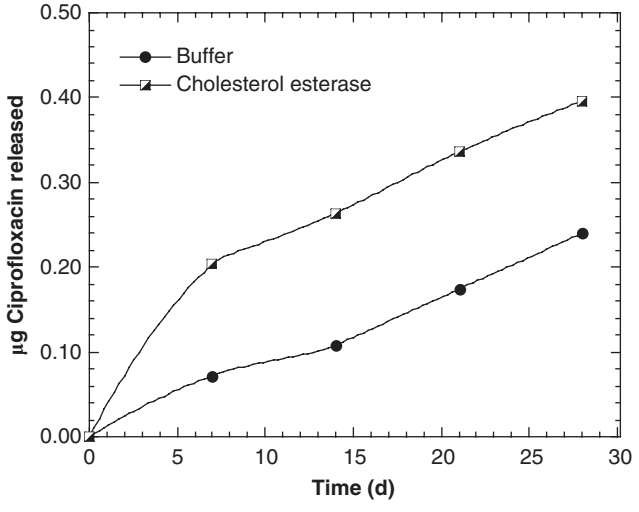

Figure 7. Ciprofloxacin release from poly(ester-urethane-ciprofloxacin) drug polymer of Woo *et al.* [64].

was added to generate a foam. This porous scaffold was designed for the regneration of bone tissue, and was tested with osteoprogenitor cells *in vitro*. Ascorbic acid stimulates the proliferation and production of collagen and alkaline phophatase in osteoprogenitors, leading to their differentiation into osteoblasts. Ascorbic acid was released as the polymer degraded by hydrolysis (**Figure 8**), at a rate that enhanced osteoprogenitor cell proliferation and differentiation into osteoblasts. The rate of ascorbic acid release was similar to that of both lysine and glycerol, and did not produce an appreciable decrease in buffer pH. The rate of ascorbic acid release is consistent with a bulk degradation process. This work is an example of the potential of using elastomeric scaffolds to provide not only mechanical support, but also controlled release to provide chemical stimulation leading to enhanced tissue production.

More recently, Guan *et al.* used the combination of elastomer scaffold plus controlled release of cell stimulating agent to engineer smooth muscle [66]. A poly(ester-urethane) urea was prepared by reacting poly(ε-caprolactone) with butyldiisocyanate, which was then chain extended with 1,4-diaminobutane. This polymer was dissolved in DMSO at 80°C and composite particles of basic fibroblast growth factor (bFGF) plus bovine serum albumin with or without heparin were distributed throughout. The suspension was poured into a mold, and the mold frozen at -80°C. The DMSO was extracted with alcohol at 4°C over 7 days. The mechanical properties of the porous elastomer scaffolds approached those of the human coronary artery; the tubular scaffold had a tensile strength of 2.7 MPa, and the human coronary artery has a tensile strength of 1.4 MPa [67].

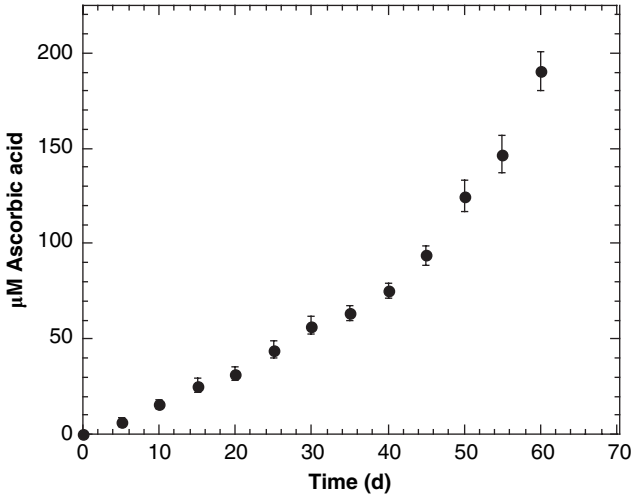

Figure 8. Ascorbic acid release from poly(lysine diisocyanate-glycerol-ascorbic acid) porous scaffold of Zhang *et al*. [65].

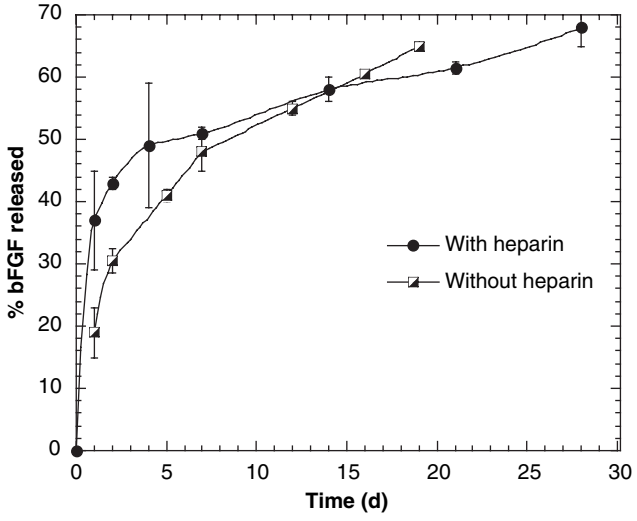

Figure 9. Basic fibroblast growth factor release from poly(ester-urethane)urea porous scaffolds [66].

However, the breaking strain of the scaffolds was much higher than that of arteries (272% versus 90% for human fermoal and politeal arteries) and the stiffness or modulus was not reported. As one discussed application of the elastomer was *in situ* regeneration of blood vessels, elastomer extensibility and stiffness is important as mismatch between the native tissue and the elastomer scaffold will lead to thrombosis and myointimal hyperplasia [68]. The elastomer may be more suitable for other soft tissues, such as cardiac muscle, where stiffness matching is not of such a concern. The objective of incorporating bFGF is to promote angiogenesis into the scaffold *in vivo*, to ensure the survival of the newly grown tissue. bFGF release began with a high initial burst, wherein roughly 39% of the initially loaded bFGF was released within the first day (**Figure 9**). This high burst is probably due to bFGF particles directly at the polymer surface within the scaffold pores. In general, such a high burst release of drug is highly undesirable, as it may lead to undesirable side effects and down regulation of cell receptors for the drug. Subsequent release was much slower, reaching ~ 70% cumulative mass released after 28 days. This secondary phase of release was attributed to a combination of polymer degradation enhancing the porosity of the scaffold and diffusive transport of bFGF dissolved in the pores to the polymer/medium interface. bFGF bioactivity was retained for up to 21 days, after which no bioactivity remained. Unfortunately, the fraction of the released bFGF that was active was not measured at any time point, and this fraction is necessary in order to evaluate the potential success of this delivery approach.

4. Thermosets versus thermoplastics

There have been more drug delivery studies done with thermoplastic elastomers than with thermosets, because of the ease of incorporating different drugs into thermoplastics. A drug can be incorporated into a thermoplastic by co-dissolving in a solvent that also dissolves the polymer, or by distributing the drug as particles within a polymer solution, followed by casting into a mold and solvent evaporation. If the drug is present as particles, then settling of the particles during solvent evaporation may be an issue. A simple approach to overcome that problem is to use a viscous solution or pouring into a mold cooled to a temperature at or below the glass transition temperature of the polymer. The ability to dissolve the polymer also makes possible the production of constructs such as electrospun fibres, which are being intensely examined as tissue engineering scaffolds. Loading drugs into thermosets requires the drug to be unaffected by the crosslinking procedure, and this is unlikely to be the case if the drug is dissolved in a mutual solvent. This problem can be overcome if the drug is present in solid particle form and the polymer is photocrosslinked; however, this approach reduces the number of drugs that can be delivered from these elastomers. Thermosets do have an advantage over thermoplastic elastomers in that they degrade more homogeneously, as they possess no crystalline or high glass transition temperature domains that would degrade more slowly than the amorphous regions. This more homogeneous degradation may result in more predictable changes in mechanical properties with time as the elastomer degrades. Moreover, the release of crystals from the degradation of thermoplastics has been linked to an inflammatory response late in the degradation period [69].

5. Conclusions

Although biodegradable elastomers have been established as biomaterials for a number of decades, relatively few drug

delivery applications using these materials have been investigated. The early work focused on diffusionally controlled delivery, and more recent research has examined the possibility of using the mechanical properties to control release, as in osmotic pressure driven delivery, or the ability to prepare thermoplastic elastomers that contain drug as a comonomer that is released upon hydrolysis. The realization that mechanical stimulation is important in engineering replacement soft tissue for implantation has lead to the use of biodegradable elastomers as both releasing vehicles for cell signalling molecules as well as mechanical scaffolds for dynamic cell growth.

6. Expert opinion

Biodegradable elastomers have been prepared primarily from polyesters and poly(urethanes) containing polyester macrodiols along their backbones. For conventional implantable drug delivery applications, where drug release is controlled primarily by diffusion or diffusion with polymer degradation, the acceptable biocompatibility and release properties of the more widely investigated poly(lactide-co-glycolide) devices make the latter more competitive over devices prepared from biodegradable elastomers. The niche for biodegradable elastomers is for applications where their mechanical properties are beneficial or required. One area where this is possible is in combination with flexible devices, such as biodegradable stents for the treatment of restenosis or as drug-eluting catheters. Flexible polymer sheets may also be suitable for the delivery of compounds effective at preventing post-operative adhesion formation [70,71], providing the degradation of the polymer does not interfere with the wound-healing process. However, there has yet to be a report on drug delivery from such biodegradable elastomers for this purpose in an *in vivo* setting.

Of the possible drug delivery applications for biodegradable elastomers, tissue engineering applications will be the most investigated in the near future. The mechanical properties of the biodegradable elastomers that have been prepared so far can be adjusted so to be similar to that of many soft tissues. For example, the modulus of the cerebral artery and vein are 15.7 and 6.85 MPa, respectively, and their ultimate strains are 50 and 83%, respectively [72]. Moreover, the elastomers may also provide a means of releasing cell signalling compounds, such as growth factors and smaller molecules, which can be used to direct cell growth and induce angiogenesis into the growing tissue *in vivo*. These elastomers must be prepared into porous scaffolds in order to be effective in this regard. As most of these signalling compounds are proteins, the greatest challenge in the development of these scaffolds will be developing fabrication procedures that not only provide porosity, but also produce effective protein release kinetics. Appropriate release would avoid a large initial burst release and maintain the protein at low local concentrations for prolonged periods. For example, preliminary experiments and preclinical trials have shown that a continuous and local administration of growth factors at an ischemic site is necessary to induce effective generation of new blood vessels [73-76]. This is because most angiogenic factors also act as survival factors for endothelial cells and exposure to a single growth factor needs to be sustained to prevent early apoptosis of the migrating endothelial cells. The presence of the growth factors at the ischemic site is required for periods of 3 – 4 weeks [73,77]. It is also important that the released protein maintain its bioactivity. As discussed above, the bFGF released from the porous scaffolds of Guan *et al.* was no longer active after 21 days of release. The non-active protein is likely denatured, and denaturation may also result in the protein becoming immunogenic when released *in vivo*.

Recently, biodegradable and elastic shape-memory polymers have been developed [78,79]. These elastomers have a temporary shape and are designed to have a pre-programmed shape that the elastomer can revert to under thermal stimulus. The polymers revert to the programmed shape through entropic relaxation of a loaded stress, and this relaxation can occur within minutes. Potential uses for these materials include biodegradable sutures and stents [80,81]. These biodegradable elastomers have not yet been used for drug delivery and represent an exciting new possibility for combining mechanical functionality with localized drug delivery.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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