9
Biodegradable Elastic Hydrogels for Tissue Expander Application

Thanh Huyen Tran, John Garner, Yourong Fu, Kinam Park, and Kang Moo Huh

9.1
Introduction

9.1.1
Hydrogels

Hydrogels are three-dimensional polymeric networks capable of absorbing a large amount of water or biological fluids while maintaining their basic structure [1, 2]. In the polymeric network, hydrophilic polymers are hydrated in an aqueous environment. The term "network" implies that crosslinked structures have to be present to avoid the dissolution of the hydrophilic polymer chains into the aqueous phase. Hydrogels can be classified into chemical and physical hydrogels based on the nature of crosslinking. In chemical hydrogels, the polymer chains are crosslinked by covalent bonding. If the polymer chains are crosslinked by non-covalent bonding, such networks are called physical hydrogels.

Since water molecules are the major component of the hydrogels, the mechanical strength of most hydrogels is rather low. That is, the storage moduli (G') of most hydrogels fall between several hundreds or several thousands pascals when the water content is high [3]. The poor mechanical strength and toughness after swelling are major disadvantages of using hydrogels. Therefore, the improvement of the elasticity of hydrogels is of great interest, since high elastic hydrogels are more suitable for application that bear mechanical loading, such as cartilage implant materials.

9.1.2
Elastic Hydrogels

Elastic hydrogels are hydrogels that are resilient and resistant to compression and elongation in their dried or water-swollen states. The elastic hydrogels possess the capability of withstanding cyclic mechanical strain without cracking or suffering significant permanent deformation [4]. The molecular weight of the polymers should be high enough, and the glass transition temperature (T_g) should be low

Handbook of Biodegradable Polymers: Synthesis, Characterization and Applications, First Edition. Edited by Andreas Lendlein, Adam Sisson.

enough, to impart elastomeric behavior of the hydrogels [5]. Shape-memory hydrogels constitute a class of elastic hydrogels that can be elastically deformed and fixed into a temporary shape, and have ability to recover the original, permanent shape on exposure to an external stimulus such as heat or light [6].

For most biomedical applications, biodegradable elastic hydrogels are favored over nondegradable hydrogels. This is because they can be removed or eliminated by natural degradation from the applied sites in the body under relatively mild conditions, thus eliminating the need for any surgical removal processes after the system fulfills its goal. Biodegradable polymeric systems also provide flexibility in the design of delivery systems for large molecular weight drugs, such as peptides and proteins, which are not suitable for diffusion-controlled release through nondegradable polymeric systems [7]. In addition, the degradation can be utilized to control the rate of drug release and the physicochemical properties of the hydrogel systems, and thus to provide flexibility in the design of biomedical devices, such as drug–biomaterials combination products. However, proper techniques for predicting hydrogel degradation rates are critical for successful application of these degradable systems as they facilitate the design of implants with optimal degradation profiles that result in proper rates of drug release or tissue regeneration and hence maximize therapeutic effects.

9.1.3 History of Elastic Hydrogels as Biomaterials

Earlier works in elastic hydrogels were mainly focused on development of shape-memory hydrogels for fabrication of devices and implant stents. The first publication mentioning shape-memory effects in hydrogels was made by Osada *et al.* in 1995, who discovered a new phenomenon of a polymer hydrogel made by radical copolymerization of acrylic acid and *n*-stearyl acrylate having elastic memory that could be stretched to at least 1.5 times of its original length when the swollen gel is heated above 50 °C [8, 9]. Since then, biodegradable shape-memory polymers have been synthesized, including network polymers formed by crosslinking oligo(ε-caprolactone) dimethylacrylate and *N*-butylacrylate [10], a multiblock copolymer of oligo(ε-caprolactone) and oligo(*p*-dioxanone)diol [11], and polyesters of poly(propylene oxide) (PPO) with polylactide or glycolide [12]. Improvement of the stiffness and recovery force of shape-memory polymers can be achieved by the synthesis of shape-memory composites. Zheng *et al.* synthesized polylactide and hydroxyapatite composites which demonstrated better shape-memory effect than pure polylactide polymer [13].

Recently, with the increasing interest in engineering various tissues for the treatment of many types of injuries and diseases, a wide variety of biodegradable elastic hydrogels with desirable mechanical, degradation, and cytophilic properties have been developed. Elastic superporous hydrogel hybrids exhibiting mechanical resilience and a rubbery property in the fully water-swollen state have been reported by Park *et al.* These hydrogel hybrids of acrylamide (AM) and alginate could be stretched to about 2–3 times of their original lengths and could be loaded

and unloaded cyclically at least 20 times. This property can potentially be exploited in the development of fast- and high-swelling elastic hydrogels for a variety of pharmaceutical, biomedical, and industrial applications [14, 15]. However, these systems lack biodegradable properties for various biomedical applications. Wen *et al.* developed biodegradable, biocompatible polyurethane-based elastic hydrogels by changing chain extenders. The hydrogels were highly elastic in its swollen state and comparable degradation and cytocompatible behaviors to polylactide. This may find the applications in both soft- and hard-tissue regeneration [16, 17]. In recent years, block copolymers of biodegradable polyesters such as poly(ε-caprolactone) (PCL), polylactides (PLAs), poly(glycolic acid) (PGA), and polylactide-*co*-glycolide (PLGA), and hydrophilic polyethylene glycol (PEG) have received considerable attention as potential biomaterials because of their combined advantages of the biodegradability of the polyesters and the biocompatibility of PEG [18–20]. The block copolymers also have some unique properties based on their amphiphilic nature. The block composition and structural characteristics can be utilized to modify various physicochemical properties such as biodegradation, permeability, swelling, elasticity, and mechanical properties [21–23]. Typical hydrogels are glassy and brittle in the dried state and it is difficult to change the shape and size of the dried state. Huh *et al.* have developed biodegradable PEG/PCL and PLGA–PEG–PLGA/PEG hydrogels showing flexible and elastic properties even in the dried state that they remain intact after repeated bending or stretching to twice the original length [24].

Further, elastic hydrogels with self-healing capacity were synthesized by hydrophobic association through micellar copolymerization of AM and a small amount of octyl phenol polyethoxy ether acrylate. These hydrogels showed high recovery even after extensive stretching and self-healing after being cut into two parts which can be used as shrinkable or thermal sensitive materials [25].

While covalently crosslinked hydrogels have the ability to control the elastic behaviors, one limiting factor is the difficulty in guaranteeing removal of impurities, such as unreacted monomers, sol fractions, nonaqueous solvents, and initiators. Feldstein *et al.* demonstrated the formation of water-absorbing, elastic, and adhesive hydrogels through hydrogen bonding of three pharmaceutical grade components poly(*N*-vinylpyrrolidone) (PVP), PEG, and poly[(methacrylic acid)-*co*-(ethyl acrylate)] [p(MAA-*co*-EA)] without introduction or formation of toxic by-products. The hydrogels are malleable under various processing conditions such as drawing, molding, and extrusion, suggesting a wide range of applications in the biomedical and cosmetic fields [26].

9.1.4 Elasticity of Hydrogel for Tissue Application

Most natural tissues, such as heart, blood vessels, skeletal muscle, tendon, and so forth, are very elastic and strong. If the biodegradable polymers are either too stiff/brittle with low elongation, or very soft with relatively low strength, the mechanical properties of these polymers are not compatible with natural tissues.

The hydrogels are good candidates for tissue applications when their elastic moduli are close to that of natural tissue components. For instance, articular cartilage contains ~70% water and bears loads up to 100 MPa, but most hydrogels, either synthetic or natural, can be easily broken indicating that they are much weaker than native cartilage tissue. The degradable elastic polyurethane hydrogels have elastic moduli ranging from 16.8 ± 3.3 to 26.6 ± 3.9 MPa, which are very close to the properties of native cartilage showing promise for soft- and hard-tissue regeneration [17].

For engineering of soft tissue, elastic hydrogel scaffolds are desirable since they are amenable to mechanical conditioning regimens that might be desirable during tissue development. Elasticity values of most of the single component hydrogels were lower than 10 kPa, while higher percentage of multicomponent hydrogels exhibited high elastic mechanical property up to 100 kPa [3]. The compressive modulus of hard tissue such as articular cartilage is in the range of 0.53–1.82 MPa [27]. In order to promote cartilage regeneration, a hydrogel scaffold must be able to exhibit mechanical integrity in the face of loading from the body, while at the same time guide appropriate cartilaginous tissue growth. A biodegradable hydrogel scaffold with elastic properties could be useful for application in cartilage treatment.

9.2 Synthesis of Elastic Hydrogels

9.2.1 Chemical Elastic Hydrogels

Chemical hydrogels are those that have covalently crosslinked networks. Thus, chemical hydrogels will not dissolve in water or other organic solvents unless covalent crosslinks are cleaved. There are generally two different methods to prepare chemical elastic hydrogels. Chemical elastic hydrogels can be prepared by polymerization of water-soluble monomers in the presence of bi- or multifunctional crosslinking agents. Chemical hydrogels can also be prepared by crosslinking water-soluble polymers using chemical reactions that involve functional groups of the polymer. Due to the high strength of the covalent linkages, the three-dimensional networks of hydrogels are permanent and the formation of crosslinks is usually irreversible.

9.2.1.1 Polymerization of Water-Soluble Monomers in the Presence of Crosslinking Agents

Polymerization of water-soluble monomers in the presence of crosslinking agents results in the formation of chemical hydrogels. Typical water-soluble monomers for the preparation of chemical elastic hydrogels include acrylic acid, AM, hydroxyethyl methacrylate, and so on. The crosslinking agents for the synthesis of elastic hydrogels are not only low-molecular-weight agents such as *N,N'*-methylenebisacrylamide but also inorganic agents such as hectorite clay.

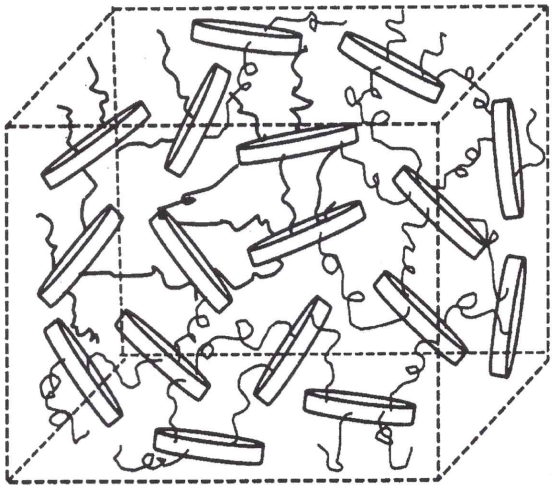


Figure 9.1 Structure of nanocomposite hydrogel using Clay-S by *in situ* polymerization.

For example, a novel highly resilient nanocomposite hydrogel with ultra-high elongation was prepared by polymerization of monomer (AM or *N*-isopropylacrylamide (NIPAAm)) in the presence of the inorganic hectorite clay as a crosslinker (Clay-S), initiator (potassium persulfate), and accelerator (tetramethyldiamine) [28]. As shown in Figure 9.1, Clay-S forms a stable uniform dispersion in a solution that contains monomer and other reagents. Polymerization is initiated on the surfaces of the clay, and polymer chains are attached to the clay surface to form clay-brush particles, and finally, the aqueous dispersion is converted into a nanocomposite hydrogel of the uniform polymer network of Clay-S and AM, which can distribute stress evenly on each chain. The hydrogel could be elongated to 10 times of its original length and recovered to initial state.

In another approach, a hybrid of chemical and physical hydrogels was prepared from polyacrylamide and sodium alginate [14]. The copolymerization of AM monomer and *N*,*N*′-methylenebisacrylamide as a crosslinker and other necessary ingredients formed superporous polyacrylamide hydrogels. The crosslinking density of the hydrogel was increased by the physical crosslinking of sodium alginate with Ca^{2+}. The mechanical properties of the superporous hydrogels can be significantly increased through this interpenetrating network formation.

9.2.1.2 Crosslinking of Water-Soluble Polymers

Crosslinking of water-soluble polymers by the addition of bifunctional or multifunctional reagents results in chemical elastic hydrogels. Macromers are macromolecular monomers or polymers that contain two or more vinyl groups, acrylates and methacrylates being the most common. The crosslinking reactions can be catalyzed chemically, thermally, or photolytically. Photopolymerization is an increasingly common way to drive the crosslinking reaction.

Degradable polyurethane-based light-curable elastic hydrogels were synthesized from polycaprolactone diol, PEG as soft segment, lysine diisocyanate as hard

segment, and 2-hydroxylethyl methacrylate as chain terminator through UV-light-initiated polymerization. The hydrogels were formed through the crosslinking of methacrylate groups in 2-hydroxylethyl methacrylate via UV light. The PCL:PEG ratios in soft segments were responsible in determining elasticity as well as the strength of the hydrogels [17].

The formation of degradable hydrogels by crosslinking macrodimethacrylates was also reported by Choi *et al.* [12]. Triblock copolymers of PLA–PPO–PLA containing polylactic acid (PLA) blocks and acrylate end groups of PPO were used to create photopolymerizable hydrogels showing shape-memory property.

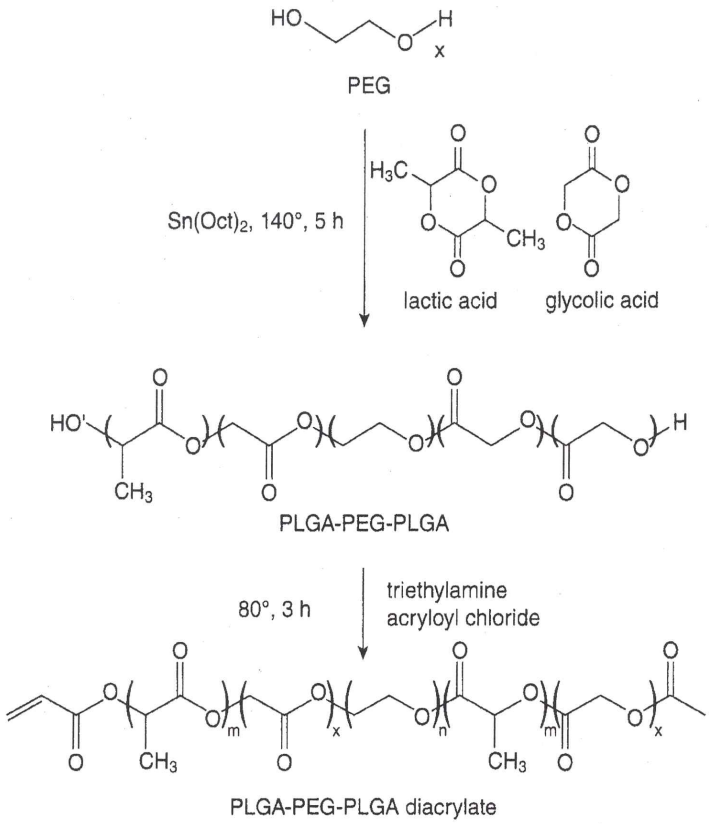
Recently, the formation of elastic hydrogels from block copolymer of PEG and biodegradable polyesters has been extensively investigated. PEG is a hydrophilic polymer and its glass transition temperature is very low due to the flexible chain structure. When PEG was used as a building block for preparing hydrogels with other biodegradable polyesters such as PGA, PLA, and PCL, the hydrogels can show flexible and/or elastic properties [4, 24, 27]. PEG has two hydroxyl groups at both ends of the polymer that can be modified with a vinyl group to form a divinyl macromer. PEG acrylates are the major type of macromers for the preparation of PEG-based elastic hydrogels. For example, chemically crosslinked biodegradable elastic PEG/PCL or PLGA–PEG–PLGA/PEG hydrogels were prepared via radical crosslinking reaction of PEG-diacrylate with PCL-diacrylate or PLGA-PEG-PLGA-diacrylate in the presence of a radical initiator 2,2-azobisisobutyronitrile in a drying oven at 65 °C for 12 h [24]. Scheme 9.1 illustrates the synthetic method of PLGA-PEG-PLGA diacrylate using for crosslinking reaction with PEG-diacrylate under thermal catalyst.

9.2.2 Physical Elastic Hydrogels

Physical gels are the continuous, disordered, three-dimensional networks formed by associative forces capable of forming noncovalent crosslinks [29]. Noncovalently crosslinked hydrogels are formed when primary polymer chains contain chemical moieties capable of electrostatic, hydrogen bonding, ion dipole, or hydrophobic interaction [26]. Physical crosslinking of polymer chains can also be achieved using a variety of environment triggers (pH, temperature, and ionic strength). In physical elastic hydrogels, association of certain linear segments of long polymer molecules forms extended "junction zones." The junction zones are expected to maintain ordered structure. Although noncovalent association are reversible and weaker than chemical crosslinking, they allow solvent casting and thermal processing, and the resulting polymers often show elastic or viscoelastic properties [30].

9.2.2.1 Formation of Physical Elastic Hydrogels via Hydrogen Bonding

Examples of elastic and adhesive hydrogels via the formation of hydrogen bonding are triple blends of PVP, PEG, and p(MAA-*co*-EA). Ternary polymer blends were dissolved in ethanol under vigorous stirring, and then casted into film. The PVP/PEG/p(MAA-*co*-EA) hydrogel was formed via the stable three-dimensional



Scheme 9.1 Synthetic methods of PLGA–PEG–PLGA diacrylate.

hydrogen-bonded network in which p(MAA-*co*-EA) contains H-bond donor groups, PVP contains H-bond acceptors, and PEG contains both. The hydrogel films are malleable and retain their integrity upon hydration – a feature characteristic of covalently crosslinked hydrogels. The polymer blend films remained intact at pH 5.6 but underwent dissolution at pH 7.4 due to loss of hydrogen bonding and development of charge repulsion [26].

Hydrogen-bonding interaction can also be used to produce hydrogels by freeze-thawing. A novel double-network elastic hydrogel fabricated with PVP and PEG was prepared through a simple freezing and thawing method. PVA/PEG hydrogel structure was formed by a PVA-rich first network and a PEG-rich second component, in which hydrogen bonding existed. The two polymers were dissolved in ultrapure water and exposed to repeated cycles of freezing at –20 °C for 8 h and thawing at room temperature for 4 h. Figure 9.2 illustrates the structural formation of elastic PVA/PEG double-network hydrogels. The condensed PVA-rich phase forms microcrystals first, which bridge with one another to form a rigid and inhomogenous net backbone to support the shape of the hydrogels, and the dilute PEG-rich phase partially crystallizes among the cavities of voids of the backbone. PEG clusters in the cavities of PVA networks absorb the crack energy and relax

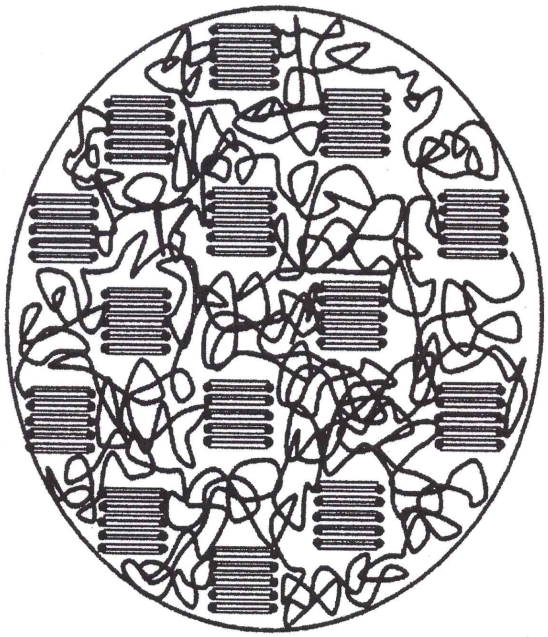


Figure 9.2 Schematic representation of the structural model of PVA/PEG double-network hydrogel.

the local stress either by various dissipations or by large deformation of the PEG chains. The crystalline regions of PVA essentially serve as physical crosslinks to redistribute external stresses [31].

9.2.2.2 Formation of Physical Elastic Hydrogels via Hydrophobic Interaction

Polymers with hydrophobic domains can crosslink in aqueous environment via reverse thermal gelation. Temperature increase promotes hydrophobic interactions resulting in the association of hydrophobic polymer chains. The physical association of hydrophobic domains holds swollen soft domains together and makes the polymers stable in water [32]. The common hydrophobic blocks which can undergo reverse thermal gelation at or near physiological temperature are PPO, PLGA, poly(*N*-isopropylacrylamide), PCL, and poly(urethane) [33].

For example, multiblock copolymers of polyethylene oxide and PCL or PLA were synthesized for the preparation of polymer films by solvent casting method. The multiblock copolymers formed thermoplastic hydrogels via hydrophobic interaction. The block copolymer films were rubbery in both dried and swollen states. The interesting property of these multiblock copolymers was that the swelling increased by increasing temperature and increased further, rather than decreasing, when the temperature was lowered to the initial temperature [30]. Other types of amphiphilic block copolymers of PCL with PLA and PGA were also synthesized to prepare elastic PCL/PLA and PCL/PGA physical hydrogels [4, 27].

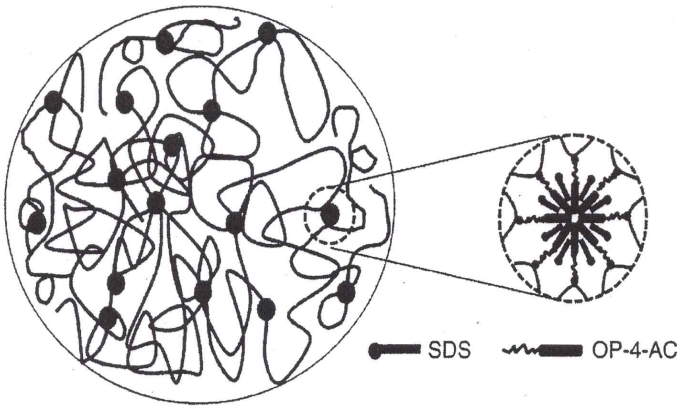


Figure 9.3 Schematic illustration of the hydrophobic association of hydrogels, which consists of associated micelles and flexible polymer chains connected by neighboring associated micelles.

In another example, a new type of physically crosslinked hydrogel via hydrophobic interaction was prepared. An elastic hydrogel with self-healing property was synthesized through micellar copolymerization of AM and a small amount of octylphenol polyethoxyether acrylate in an aqueous solution containing sodium dodecyl sulfate at 50 °C. The hydrophobically modified polyacrylamide was synthesized by the copolymerization of AM and octylphenol polyethoxyether acrylate. After polymerization, hydrophobic association of SDS and hydrophobic microblocks of hydrophobically modified polyacrylamide leads to the formation of associated micelles. These micelles act as crosslinking points, so three-dimensional polymer networks were constructed as shown in Figure 9.3 [25]. Because of the large distance between the associated micelles, all polymer chains between the crosslinking points in the hydrogels were sufficiently long and flexible.

9.3 Physical Properties of Elastic Hydrogels

Some of the most important properties of elastic hydrogels are: the gel mechanical properties, to withstand the physiological strains *in vivo* or mechanical conditioning *in vitro*; gel swelling properties to maintain cell viability; and the degradation profiles to match tissue regeneration.

9.3.1 Mechanical Property

Mechanical properties of elastic hydrogels are evaluated by the measurement of elasticity and stress relaxation. Elasticity is estimated from the tensile strength,

elongation at break, and recovery after stretching. The mechanical tests are performed with hydrogel samples in a fixed cross-sectional area by pulling with a controlled, gradually increasing force until the sample changes shape or breaks. When a constant strain is applied to a rubber material, the force necessary to maintain that strain is not constant but decreases with time, this behavior is called "stress relaxation." Stress relaxation of hydrogels was determined by the following equation:

(maximum stress at a constant strain/stress at the constant strain after holding for a determined time) × 100.

The tensile strength of elastic hydrogels is dependent on the crosslinking density and the flexibility of the water-soluble monomer or macromers in water. The elastic hydrogels exhibit rubberlike profiles in the stress–strain curves with very high elongation at break as shown in Figure 9.4. The recovery after stretching is usually more than 90% when applied up to the tensile strain at break.

Stress relaxation describes how polymers relieve stress under constant strain. In viscoelastic materials, stress relaxation occurs due to polymer chain rearrangement allowing permanent deformation of the materials. By this method, low values for stress relaxation indicate that polymer chain rearrangement is occurring. Example of stress relaxation of elastic hydrogel is given in Figure 9.5. The stress relaxation of all samples was more than 90%, indicating that polymer chain rearrangement is occurring only minimally. Since these hydrogels are highly crosslinked, there is little freedom for rearrangement and, as such, these materials do not deform under stress.

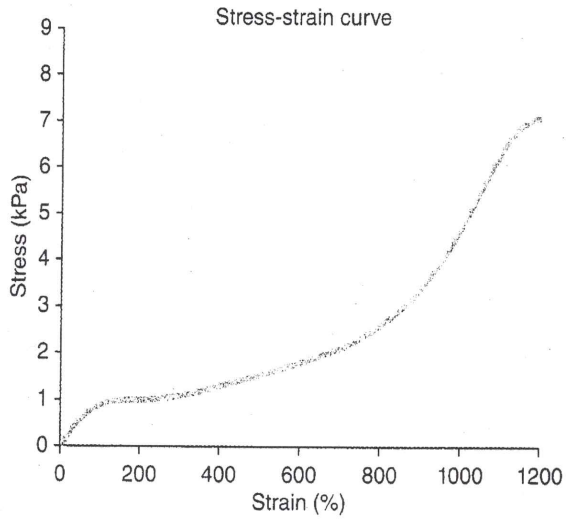


Figure 9.4 Stress–strain curve of elastic film prepared from poly(L-lactide-*co*-ε-caprolactone).

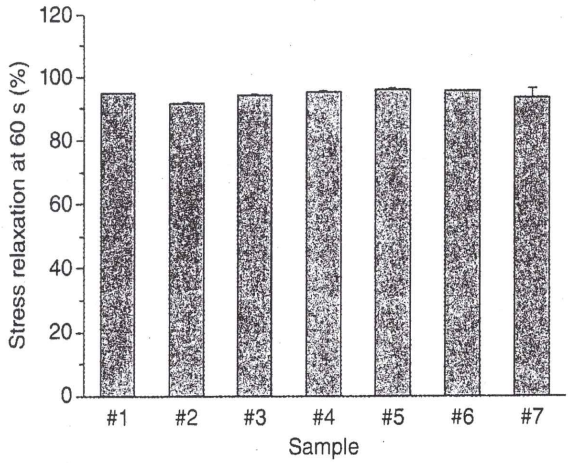


Figure 9.5 Stress relaxation of PLGA–PEG–PLGA/PEG elastic hydrogels.

9.3.2 Swelling Property

The swelling property of hydrogels is usually characterized by measuring their capacity to absorb water or aqueous solutions. The swelling ratio (R_s), which is the most commonly used parameter to express the swelling capacity of hydrogels, is defined as follows:

$$R_s = (W_s - W_d)/W_d \tag{9.1}$$

where W_s and W_d are the weights of swollen and dried hydrogels, respectively.

It is well known that the swelling ratio of hydrogels not only depends on the hydrophilic ability of the functional groups but also on the network space of the hydrogels. Generally, the hydrogel with higher network space presents higher water content. Ionization often provokes swelling due to electrostatic/osmotic repulsion of polyelectrolyte chains.

Swelling pressure is the pressure exerted on the swelling hydrogels due to the osmotic effect or the degradation of the crosslinking structure. The swelling pressure (π_{sw}) of a neutral polymer gel is determined by two opposing effects: the osmotic pressure (π_{osm}) that expands the network and the elastic pressure (π_{el}) that acts against expansion [34]:

$$\pi_{sw} = \pi_{osm} + \pi_{el} \tag{9.2}$$

where $\pi_{el} = -G'$, G' being the elastic (shear) modulus of the hydrogel.

Swelling pressure is usually measured during the degradation of hydrogels at the accelerated condition close to physiological condition, for example, in the

isotonic solution of 0.154 M HCl. Up to present, no relationship between swelling pressure and swelling ratio of neutral hydrogels has been reported. However, it is known that swelling pressure gradually increases in the course of the degradation process and depends on the mechanism of the degradation. For example, the dextran gels are degraded at their backbone, the swelling pressure increases rather continuously; in the case where they are degraded at the crosslinks, it increases more discontinuously and a sudden increase occurs when the gels are completely degraded [35]. Similarly, an increase in swelling ratio of hydrogels occurs in the first period of the hydrogel degradation due to the decrease of the crosslinking density of hydrogels. As the degradation proceeded further, the swelling ratio decreases to zero since the network structure of hydrogels broke down. The swelling ratio and the swelling pressure of a hydrogel depend on internal and external factors. The internal factors are the polymer network of the hydrogel. The swelling ratio and the swelling pressure of a gel are determined by: (i) osmotic pressure, (ii) the rubber elasticity, and (iii) polymer–polymer interaction of the polymer network [36]. The external factors are parameters of the solution like the concentration and electric charge of the solute molecules or ions.

Swelling pressure of hydrogels is also measured under the osmotic condition to determine the ability of the hydrogels as a tissue expander. Osmosis is the main driving force of the volume expansion of an anhydrous gel body in the solutions of living tissue [36]. Mechanical work can be done when hydrogels transform osmosis into real pressure. In this case, the role of a gel to act as a pressure-generating device is based on the balancing of the osmotic pressure and the rubber elasticity. If the swelling pressure can overcome the resistance of the adjacent tissue, it is sufficient to dilate the surrounding tissue at the expected rate [37]. Previous research has established that a pressure close to 100 mmHg is ideal for tissue expansion [38]. As an example, the swelling pressure of PLGA–PEG–PLGA/PEG elastic hydrogels is given in Figure 9.6. All these hydrogels can create swelling pressure more than 400 mmHg which is sufficient for tissue expansion.

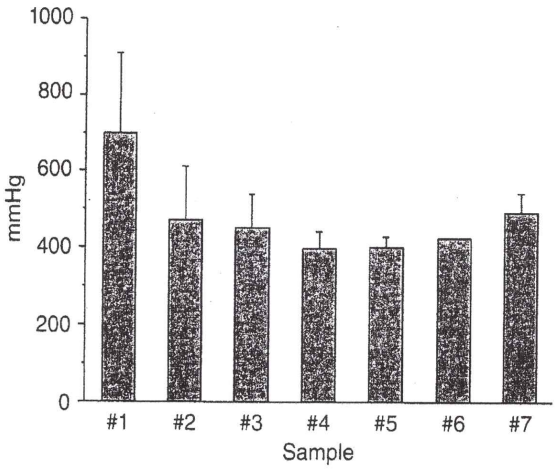


Figure 9.6 Swelling pressure of PLGA–PEG–PLGA/PEG elastic hydrogels.

9.3.3
Degradation of Biodegradable Elastic Hydrogels

Degradation of polymer hydrogel networks can occur by different mechanisms: (i) by hydrolysis of side chains or pendant groups, (ii) by cleavage of the polymeric backbone, and (iii) by cleavage of labile groups in the crosslinks [35]. Biodegradation of hydrogels occurs by either simple hydrolysis or by enzyme-catalyzed hydrolysis. *In vitro* degradation rate of biodegradable elastic hydrogels was generally evaluated by measuring the weight loss and swelling ratio of the samples in phosphate buffered saline solution at multiple time points at 37 °C with gentle shaking to mimic the *in vivo* environment. The degradation of the gel is a function of the crosslink density, as well as the hydrolytic susceptibility of chemical bonds. Hydrogels made from lower molecular weight precursors are more tightly crosslinked and thus degrade more slowly than hydrogels made from higher molecular weight precursors. Degradation of the biodegradable hydrogel network led to decreased crosslinking density, which increased the hydrogel swelling ratio. Figure 9.7 gives an example of *in vitro* degradation properties of PLGA-PEG-PLGA/PEG elastic hydrogels at different ratios of lactic acid/glycolic acid. The hydrogels showed various lag times before swelling depending on the chemical composition of the triblocks and the PLGA-PEG-PLGA/PEG block composition ratio. The hydrogels with higher content of PEG block showed lower degradation rates due to higher crosslinking density of low-molecular-weight PEG. As the degradation proceeded further, the network structure finally broke down so that the hydrogel mass was disintegrated into soluble degradation products.

9.4
Applications of Elastic Hydrogels

9.4.1
Tissue Engineering Application

Due to the high mechanical property, most biodegradable elastic hydrogels are attractive for development or regeneration of both soft- and hard tissues. For example, PEG/PCL and poly(lactide-*co*-caprolactone) (PLCL) elastic hydrogels have been investigated for use as scaffolds for cartilage regeneration [27, 39]. Chondrocyte cells were found to be dispersed evenly through the scaffold material without any further prewetting treatment, and remained viable after 3 weeks of culture. The PEG/PCL scaffold-seeded chondrocytes enhanced the gene expression of chondrogenic differentiation in a time-dependent manner. The formation of neocartilage was increased over 4 weeks after implantation in nude mice [39]. The elastic PLCL scaffolds maintained their mechanical integrity after implantation and guided cartilaginous tissue growth *in vivo* [27].

The application of cyclic mechanical strain during the smooth muscle tissue-engineering process has been found to show increased elastin and collagen

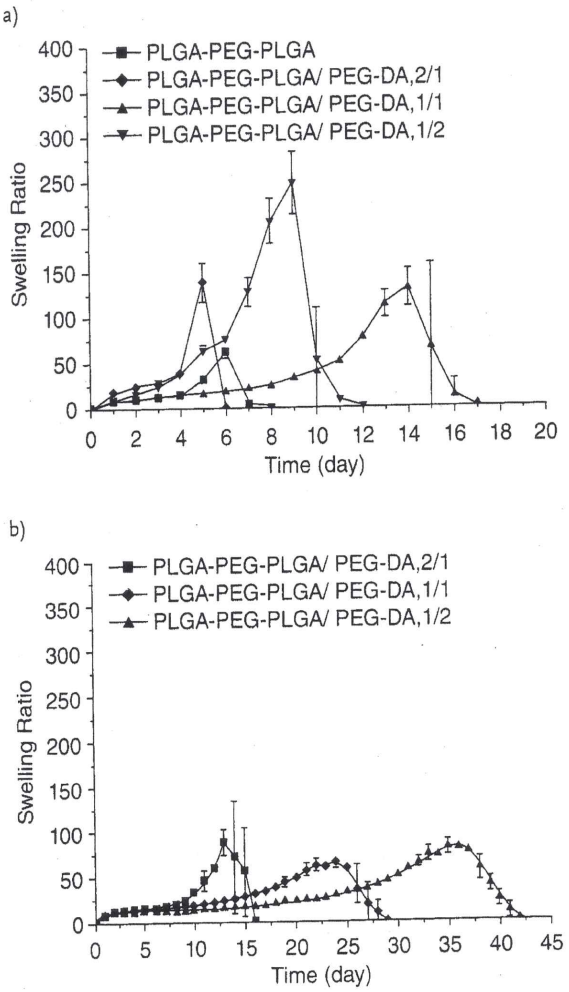


Figure 9.7 *In vitro* degradation test of PLGA–PEG–PLGA/PEG elastic hydrogels (a) LA/GA = 1 and (b) LA/GA = 4 at 37 °C.

production and tissue organization [40]. To achieve this, scaffolds must be elastic and capable of withstanding cyclic mechanical strain without cracking or suffering significant permanent deformation. Elastic biodegradable poly(glycolide-*co*-caprolactone), PLCL, and polyurethane scaffold could be used to engineer smooth-muscle-containing tissue (e.g., blood vessels and bladders) in mechanical dynamic environments [4, 5, 41]. The elastic scaffolds allowed for appropriate smooth muscle cell adhesion and subsequent tissue formation.

9.4.2 Application of Elastic Shape-Memory Hydrogels as Biodegradable Sutures

The medical application of shape-memory polymers is of great interest due to a combination of biocompatibility, tailorable transition temperature, large shape

deformation and complete recovery, and elastic properties of the materials [42]. For example, the mechanical characteristics and degradability of shape-memory, multiblock copolymers can be used for the preparation of smart surgical suture. Lendlein and Langer fabricated a self-tightenable biodegradable suture from a biodegradable, elastic shape-memory polymer. The suture can be loosely connected and then heated above critical temperature to trigger the shape recovery and tighten the suture [11].

9.5
Elastic Hydrogels for Tissue Expander Applications

A material or device designed to induce skin or tissue expansion for the purpose of reconstructive and plastic surgeries has been called a tissue expander. Tissue expanders are temporary inflatable implants that are positioned under the skin to facilitate the increase of tissue dimensions for reconstruction [43]. As an example, Figure 9.8 illustrates a schematic diagram of a skin expander using a flatable balloon.

An ideal expander should have several characteristics: easily placed through a small access site, gradually enlarge over a relatively short time, well tolerated over the long term, avoid uncomfortable inflation spikes, and resistant to infection [44]. In 1982, Austad and Rose introduced a self-inflating expander that consisted of a permeable silicone membrane filled with a hypertonic saline solution [45]. However, the expansion of the silicone balloon takes too long (8–14 weeks) and induces tissue necrosis [46].

The use of hydrogels as tissue expanders in reconstructive surgery was first developed in 1992 by Downes *et al.* who exploited the osmotically driven expansion of a biocompatible poly(hydroxylethyl methacrylate) hydrogel [47]. The hydrogels are placed in their dry, contracted states, and expand gradually to their full size with over 10-fold increase in volume. Wiese verified that hydrogels are efficient materials to induce the tissue expansion using vinyl-2-pyrrolidone (VP)/methyl methacrylate (MMA) copolymeric hydrogel and demonstrating their biocompatibility and swelling pressure [46]. Once implanted, the VP/MMA absorbs body fluids that leads to gradual swelling of the device to a 250–300% in volume as shown in Figure 9.9. Wiese *et al.* also introduced the innovative self-filling device, using a hydrogel matrix consisting of MMA/VP by replacing the CH_3 groups in

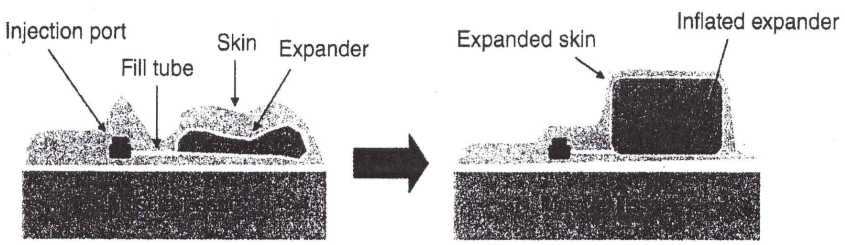


Figure 9.8 Schematic diagram of skin expander using an inflatable balloon.

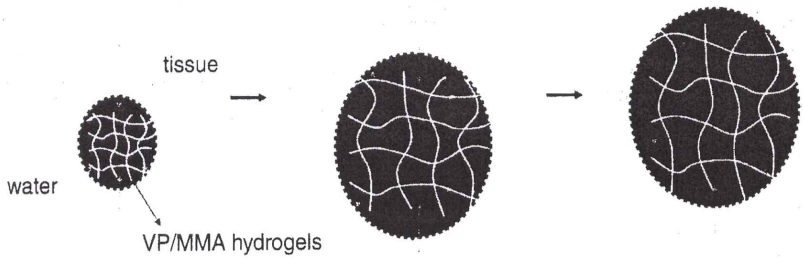


Figure 9.9 Use of VP/MMA copolymeric hydrogels for tissue expansion.

the VP/MMA hydrogel chains with COOH groups, which produced higher swelling than VP/MMA hydrogels [36]. The biocompatibility of VP/MMA hydrogel tissue expander was proved through *in vivo* test using rats; the hydrogels swell and reach their equilibrium swelling rate in 6–8 weeks by absorbing body fluids. This long *in vivo* swelling rates not only avoid tissue necrosis but also allow sufficient time for tissue growth rather than stretching of the skin [48]. Although such attempts use another material for tissue expansion, most clinically used hydrogels are still based on VP and MMA copolymers [43, 48–50].

Recently, Varga *et al.* developed thermosensitive hydrogels consisting of NIPAAm as osmotic tissue expanders. A silicate was added to improve the mechanical behavior of the polymer hydrogel. The rate of hydrogel expansion *in vivo* was highest after 2 weeks without the tissue damage. The hydrogel achieved a 25-fold increase in mass. NIPAAm polymers exhibited the most favorable viscoelastic properties, with the highest tendency to retain their preformed shape [37]. Thus, NPIAAm hydrogels allow the acquisition of more skin for reconstructive interventions. However, the current expanders lack the ability to have their shape and size changed at the time of implantation because these hydrogels are glassy and brittle in the dry state. Therefore, there has been a need to develop flexible and elastic tissue expanders so that they can be easily handled or modified appropriately according to each application. Biodegradable elastic PCL/PEG, PLA–PEG–PLA/PEG, and PLGA–PEG–PLGA/PEG hydrogels were developed for this purpose (Figure 9.10).

All the PLGA–PEG–PLGA/PEG hydrogels were flexible and elastic in dried state, and so they remain intact even after repeated bending or stretching. The hydrogels are able to generate sufficient swelling pressure (more than 400 mmHg) to expand tissue. The actual *in vivo* pressures will be substantially lower than this static condition as the skin and mucosa can stretch reducing the pressure. Furthermore, the PLGA–PEG–PLGA/PEG hydrogels exhibited the lag time before swelling; this will provide sufficient time for the wounded area to heal. The controllable degradation rate makes it possible to apply the hydrogels to various parts of body. The elastic hydrogels with self-inflating behavior, elastic, and delayed swelling properties would be useful as novel hydrogel tissue expanders (Figure 9.11).

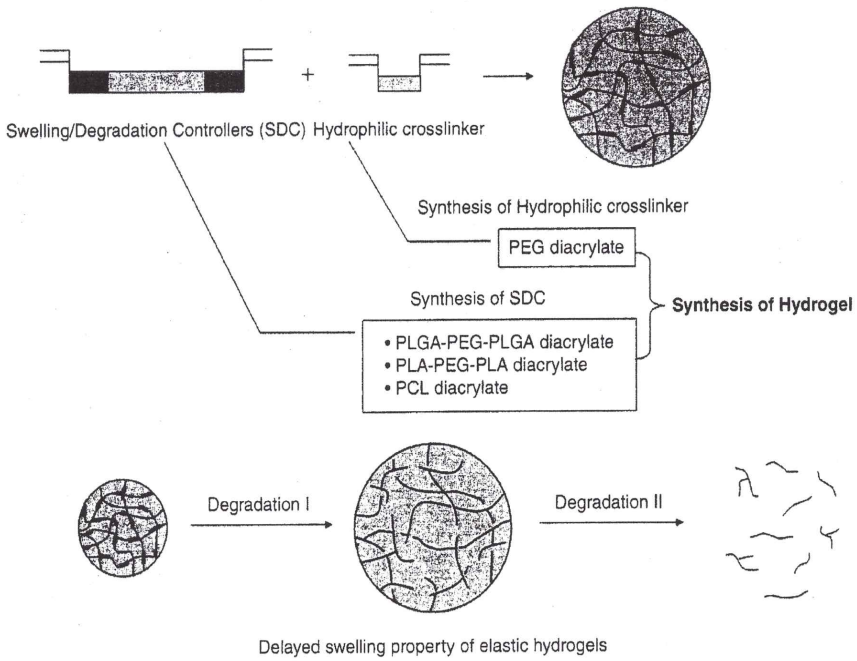


Figure 9.10 Elastic hydrogel tissue expanders with controllable swelling/degradation.

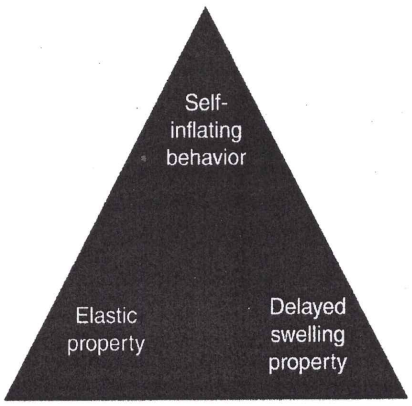


Figure 9.11 A concept of novel hydrogels for tissue expander application.

9.6 Conclusion

Although a number of attractive hydrogel systems are presently available, there are certainly novel systems with improved characteristics. A major concern in the hydrogel development is the mechanical integrity of the systems under modification and processing. Elastic hydrogels can be formed with varying polymer

formulations in three-dimensional patterns. Both chemically and physically crosslinked elastic hydrogels can be rendered biodegradable through the introduction of hydrolytically sensitive groups into the networks. Due to their biocompatibility, biodegradability, and good mechanical properties, biodegradable elastic hydrogels are good candidates as biomaterials for use in medical applications, including tissue engineering. These hydrogels have been used as biodegradable sutures and scaffold materials to engineer various types of tissues in mechanical dynamic environments. Elastic hydrogels with described properties are promising expander candidates which may contribute to more effective harvesting of tissue for reconstructive interventions. However, the synthesis of biodegradable hydrogels with rubberlike elasticity and strength is not easy. Moreover, *in vivo* tests should be done to improve the clinical applicability of elastic hydrogels for tissue expansion as well as other medical applications.

References

1 Hennink, W.E. and Van Nostrum, C.F. (2002) Novel crosslinking methods to design hydrogels. *Adv. Drug Deliv. Rev.*, **54**, 13–36.

2 Kopecek, J. (2007) Hydrogel biomaterials: a smart future. *Biomaterials*, **28**, 5185–5192.

3 Yang, Z., Wang, L., Wang, J., Gao, P., and Xu, B. (2010) Phenyl groups in supramolecular nanofibers confer hydrogels with high elasticity and rapid recovery. *J. Mater. Chem.*, **20**, 2128–2132.

4 Lee, S.H., Kim, B.S., Kim, S.H., Choi, S.W., Jeong, S.I., Kwon, I.K., Kang, S.W., Nikolovski, J., Mooney, D.J., Han, Y.K., and Kim, Y.H. (2003) Elastic biodegradable poly(glycolide-*co*-caprolactone) scaffold for tissue engineering. *J. Biomed. Mater. Res. A*, **66** (1), 29–37.

5 Guan, J., Fujimoto, K.L., Sacks, M.S., and Wagner, W.R. (2005) Preparation and characterization of highly porous, biodegradable polyurethane scaffolds for soft tissue applications. *Biomaterials*, **26**, 3961–3971.

6 Chaterji, S., Kwon, I.K., and Park, K. (2007) Smart polymeric gels: redefining the limits of biomedical devices. *Prog. Polym. Sci.*, **32**, 1083–1122.

7 Kamath, K.R. and Park, K. (1993) Biodegradable hydrogels in drug delivery. *Adv. Drug Deliv. Rev.*, **11**, 59–84.

8 Osada, Y. and Matsuda, A. (1995) Shape memory in hydrogels. *Nature*, **376**, 219.

9 Matsuda, A., Sato, J., Yasunaga, H., and Osada, Y. (1994) Order–disorder transition of a hydrogel containing an *n*-alkyl acrylate. *Macromolecules*, **27**, 7695–7698.

10 Lendlein, A., Schmidt, A.M., and Langer, R. (2001) AB-polymer networks based on oligo(ε-caprolactone) segments showing shape-memory properties. *Proc. Natl. Acad. Sci. USA*, **98** (3), 842–847.

11 Lendlein, A. and Langer, R. (2002) Biodegradable, elastic shape-memory polymers for potential biomedical applications. *Science*, **296**, 1673–1676.

12 Choi, N.Y., Kelch, S., and Lendlein, A. (2006) Synthesis, shape-memory functionality and hydrolytical degradation studies on polymer networks from poly(*rac*-lactide)-*b*-poly(propylene oxide)-*b*-poly(*rac*-lactide) dimethacrylate. *Adv. Eng. Mater.*, **8** (5), 439–445.

13 Zheng, X., Zhou, S., Li, X., and Weng, J. (2006) Shape memory properties of poly(D,L-lactide)/hydroxyapatite composite. *Biomaterials*, **27**, 4288–4295.

14 Omidian, H., Rocca, J.G., and Park, K. (2006) Elastic, superporous hydrogel hybrids of polyacrylamide and sodium alginate. *Macromol. Biosci.*, **6**, 703–710.

15 Qui, Y. and Park, K. (2003) Superporous IPN hydrogels having enhanced

mechanical properties. *AAPS Pharm. Sci. Technol.*, **4** (4), 406–412.

16 Zhang, C., Zhang, N., and Wen, X. (2006) Improving the elasticity and cytophilicity of biodegradable polyurethane by changing chain extender. *J. Biomed. Mater. Res. Part B Appl. Biomater.*, **79** (2), 335–344.

17 Zhang, C., Zhang, N., and Wen, X. (2007) Synthesis and characterization of biocompatible, degradable, light-curable, polyurethane-based elastic hydrogels. *J. Biomed. Mater. Res. A*, **82** (3), 637–650.

18 Zhou, S., Deng, X., and Yang, H. (2003) Biodegradable poly(ε-caprolactone)-poly(ethylene glycol) block copolymers: characterization and their use as drug carriers for a drug carriers for a controlled delivery system. *Biomaterials*, **24**, 3563–3570.

19 Aamer, K.A., Sardinha, H., Bhatia, S.R., and Tew, G.N. (2004) Rheological studies of PLLA. PEO. PLLA triblock copolymer hydrogels. *Biomaterials*, **25**, 1087–1093.

20 Moth, C.G., Drumond, W.S., and Wang, S.H. (2006) Phase behavior of biodegradable amphiphilic poly(*l*,*l*-lactide)-*b*-poly(ethylene glycol)-*b*-poly(*l*,*l*-lactide). *Thermochim. Acta*, **445**, 61–66.

21 Chen, S., Pieper, R., Webster, D.C., and Singh, J. (2005) Triblock copolymers: synthesis, characterization, and delivery of a model protein. *Int. J. Pharm.*, **288**, 207–218.

22 Duvvuri, S., Janoria, K.G., and Mitra, A.K. (2005) Development of a novel formulation containing poly(*d*,*l*-lactide-*co*-glycolide) microspheres dispersed in PLGA. PEG. PLGA gel for sustained delivery of ganciclovir. *J. Control. Release*, **108**, 282–293.

23 Qiao, M., Chen, D., Ma, X., and Liu, Y. (2005) Injectable biodegradable temperature responsive PLGA–PEG–PLGA copolymers: synthesis and effect of copolymer composition on the drug release from the copolymer-based hydrogels. *Int. J. Pharm.*, **294**, 103–112.

24 Im, S.J., Choi, Y.M., Subramanyam, E., and Huh, K.M. (2007) Synthesis and characterization of biodegradable elastic hydrogels based on poly(ethylene glycol) and poly(ε-caprolactone) blocks. *Macromol. Res.*, **15** (4), 363–369.

25 Jiang, G., Liu, C., Liu, X., Zhang, G., Yang, M., Chen, Q., and Liu, F. (2010) Self-healing mechanism behavior of hydrophobic association hydrogels with high mechanical strength. *J. Macromol. Sci. Part A: Pure Appl. Chem.*, **47**, 335–342.

26 Bayramov, D.F., Singh, P., Cleary, G.W., Siegel, R.A., Chalykh, A.E., and Feldstein, M.M. (2008) Non-covalently crosslinked hydrogels displaying a unique combination of water-absorbing, elastic and adhesive properties. *Polym. Int.*, **57**, 785–790.

27 Jung, Y., Kim, S.H., You, H.J., Kim, S.H., Kim, Y.H., and Min, B.G. (2008) Application of an elastic biodegradable poly(L-lactide-*co*-ε-caprolactone) scaffold for cartilage tissue regeneration. *J. Biomater. Sci. Polym. Ed.*, **19** (8), 1073–1085.

28 Zhu, M., Liu, Y., Sun, B., Zhang, W., Liu, X., Yu, H., Zhang, Y., Kuckling, D., and Adler, H.J.P. (2006) A novel highly resilient nanocomposite hydrogel with low hysteresis and ultrahigh elongation. *Macromol. Rapid Commun.*, **27**, 1023–1028.

29 Park, K., Shalaby, W.S.W., and Park, H. (1993) Physical gels, in *Biodegradable Hydrogels for Drug Delivery*. Technomic Publishing Co., Inc., Lancaster, PA, pp. 99–129.

30 Bae, Y.H., Huh, K.M., Kim, Y., and Park, K.H. (2000) Biodegradable amphiphilic multiblock copolymers and their implication for biomedical applications. *J. Control. Release*, **64**, 3–13.

31 Zhang, X., Guo, X., Yang, S., Tan, S., Li, X., Dai, H., Yu, X., Zhang, X., Weng, N., Jian, B., and Xu, J. (2009) Double-network hydrogel with high mechanical strength prepared from two biocompatible polymers. *J. Appl. Polym. Sci.*, **112**, 3063–3070.

32 Huh, K.M. and Bae, Y.H. (1999) Synthesis and characterization of poly(ethylene glycol)/poly(L-lactic acid) alternating multiblock copolymers. *Polymer*, **40**, 6147–6155.

33 Hoare, T.R. and Kohane, D.S. (2008) Hydrogels in drug delivery: progress and challenges. *Polymer*, **49**, 1993–2007.

34 Van Thienen, T.G., Horkay, F., Braeckmans, K., Stubbe, B.G., Demeester, J., and De Smedt, S.C. (2007) Influence of free chains on the swelling pressure of PEG-HEMA and dex-HEMA hydrogels. *Int. J. Pharm.*, **337**, 31–39.

35 Stubbe, B.G., Hennink, W.E., De Smedt, S.C., and Demeester, J. (2004) Swelling pressure of hydrogels that degrade through different mechanisms. *Macromolecules*, **37**, 8739–8744.

36 Wiese, K.G., Heinemann, D.E.H., Ostermeier, D., and Peters, J.H. (2001) Biomaterial properties and biocompatibility in cell culture of a novel self-inflating hydrogel tissue expander. *J. Biomed. Mater. Res.*, **54** (2), 179–188.

37 Varga, J., Janovak, L., Varga, E., Eros, G., Dekany, I., and Kemeny, L. (2009) Acrylamide, acrylic acid and *N*-ispropylacrylamide hydrogels as osmotic tissue expander. *Skin Pharmacol. Physiol.*, **22**, 305–312.

38 Min, Z., Svensson, H., and Svedman, P. (1988) On expander pressure and skin blood flow during tissue expansion in the pig. *Ann. Plast. Surg.*, **21**, 134–139.

39 Park, J.S., Woo, D.G., Sun, B.K., Chung, H.M., Im, S.J., Choi, Y.M., Park, K., Huh, K.M., and Park, K.H. (2007) *In vitro* and *in vivo* test of PEG/PCL-based hydrogel scaffold for cell delivery application. *J. Control. Release*, **124**, 51–59.

40 Kim, B.S., Nikolovski, J., Bonadio, J., and Mooney, D.J. (1999) Cyclic mechanical strain regulates the development of engineered smooth muscle tissue. *Nat. Biotechnol.*, **17**, 979–983.

41 Kim, S.H., Kwon, J.H., Chung, M.S., Chung, E., Jung, Y., Kim, S.H., and Kim, Y.H. (2006) Fabrication of a new tubular fibrous PLCL scaffold for vascular tissue engineering. *J. Biomater. Sci. Polym. Ed.*, **17** (12), 1359–1374.

42 Liu, C., Qin, H., and Mather, P.T. (2007) Review of progress in shape-memory polymers. *J. Mater. Chem.*, **17**, 1543–1558.

43 Kobus, K.F. (2007) Cleft palate repair with the use of osmotic expanders: a preliminary report. *J. Plast. Reconstr. Aesthet. Surg.*, **60**, 414–421.

44 Mazzoli, R.A., Raymond, W.R., Ainbinder, D.J., and Hansen, E.A. (2004) Use of self-expanding, hydrophilic osmotic expanders (hydrogel) in the reconstruction of congenital clinical anophthalmos. *Curr. Opin. Ophthalmol.*, **15**, 426–431.

45 Austad, E.D. and Rose, G.L. (1982) A self-inflating tissue expander. *Plast. Reconstr. Surg.*, **70**, 588–593.

46 Wiese, K.G. (1993) Osmotically induced tissue expansion with hydrogels: a new dimension in tissue expansion: a preliminary report. *J. Craniomaxillofac. Surg.*, **21**, 309–313.

47 Downes, R., Lavin, M., and Collin, R. (1992) Hydrophilic expanders for the congenital anophthalmic socket. *Adv. Ophthalmic Plast. Reconstr. Surg.*, **9**, 57–61.

48 Swan, M.C., Tim, E.E., Goodacre, J., Czernuszka, T., and David, G.B. (2008) Cleft palate repair with the use of osmotic expanders: a response. *J. Plast. Reconstr. Aesthet. Surg.*, **61**, 220–221.

49 Ronert, M.A., Hofheinz, H., Manassa, E., Asgarouladi, H., and Olbrisch, R.R. (2004) The beginning of a new era in tissue expansion: self-filling osmotic tissue expander–four-year clinical experience. *Plast. Reconstr. Surg.*, **114** (5), 1025–1031.

50 Von See, C., Gellrich, N.C., Jachmann, U., Bormann, H., and Rucker, M. (2010) Bone augmentation after soft-tissue expansion using hydrogel expanders: effects on microcirculation and osseointegration. *Clin. Oral Implants Res.*, **21** (8), 842–847.