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Shape-Memory Polymers for Biomedical Applications

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One of the most promising fields for shape-memory polymers is the biomedical field. Shape-memory polymers that can be triggered by various (physiological) conditions such as temperature and moisture have been reported, as well as remotely triggerable shape-memory polymers that make use of electromagnetic fields, ultrasound, etc. These polymers have shown great promise in in vitro studies as well as in early in vivo studies. Their biocompatibility, and in some cases biodegradability, renders them excellent candidates for minimal invasive surgery and for the design of triggerable biomedical devices. The current review provides a nonexhaustive overview of recent developments realized throughout the last decade in the field of shape-memory polymers serving specific biomedical applications while considering relevant triggers and biocompatible chemistries.

1. Introduction

Shape-memory polymers (SMP) are a type of polymers that can virtually indefinitely change between a permanent and a temporary shape. A temporary shape can be obtained through mechanical deformation of the permanent shape, under certain conditions, such as heating above the glass transition or melting temperature, followed by fixation (e.g., by using chemical crosslinking, crystallization, or supramolecular interactions) of the temporary shape while the deformation is maintained. Upon stress release, the polymer will maintain its temporary shape until a suitable (e.g., light, increase in temperature, contact with certain chemicals, etc.) trigger is applied, leading to the recovery of the permanent shape. To date, direct triggers reported in literature mainly include temperature and light. However, indirect triggers such as exposure to a solvent,[1,2] ultrasound,[3] and others have also been reported.[4–7]

Over the past few decades, shape-memory materials have gained increasing attention in biomedical research.[8–20] Due to their ability to memorize complex shapes which are different from their permanent shape, shape-memory polymers are promising candidates to develop tissue engineered constructs.[21] Indeed, they allow for minimally invasive surgery by having a small-sized temporary shape that can expand to its final (patient-specific) shape upon in vivo implantation.[1,22,23] Additionally, they enable the automatic performance of the complex mechanical deformation for which otherwise the manipulation by a surgeon would be needed.[21] To show the promise of this material class, one of the first reports covering shape-memory polymers was a patent which was filed in 1941 referring to an elastic polymer resin with "elastic memory" for dental applications. The resin mentioned in this patent was based on (m)ethyl methacrylate, vinyl chloride, vinyl acetate, and copolymers thereof.[24] Ever since, potential biomedical applications for shape-memory polymers have been explored and gained increasing attention.

While previous reviews covering shape-memory materials have mainly focused on their respective biomedical applications,[25–27] the current review is considering the chemistries applied to date to realize shape-memory according to the needs of the final biomedical application thereby taking into account crosslink density, biocompatibility, material processability, and the applied trigger. In a first part, the requirements for polymers serving a biomedical application will be discussed along with current targeted applications of shape-memory polymers within the biomedical field. Next, attention will be paid to the different chemistries employed to synthesize shape-memory polymers in line with the shape-memory triggers. In addition, notable examples will be applied to illustrate the (potential) biomedical application field. Finally, the recently emerging, reversible shape-memory polymers will be discussed and compared with other reversibly actuating polymers such as hydrogel actuators and liquid crystalline elastomers.

2. Shape-Memory Effect

The shape-memory effect is a property of polymers. It is, however, not an intrinsic property of a polymer but requires specific processing steps. The shape-memory mechanism itself is based on entropic elasticity.[28–30]

The entropically most favorable state of an amorphous polymer chain is its most strongly coiled conformation. Upon elastic deformation, elongation of the random polymer coils will occur and they will align along the direction of the applied stress, thereby reducing the number of possible configurations and thus also reducing the entropy.[30] Since the chain entanglements of polymers with sufficiently high molar mass prevent the movement of the entire polymer chain thereby acting as a kind of physical crosslinks, the release of the stress will cause the polymers to return to their original, more entropically

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favorable, coiled state. This effect has been shown to be present in non-crosslinked, ultrahigh molar mass polyethylene (M_w = 5×10^6 g mol^{-1}).[31] It can be stated that the polymer has a "memory" of its initial, undeformed state. Application of the stress over longer timeframes (hours compared to seconds) will, however, result in slippage of the polymer chains (cfr. creep) resulting in the polymer "forgetting" its original shape.[30,32]

In shape-memory polymers, the slippage of the polymer chains is prevented through means of crosslinking. Material crosslinking, either through chemical or physical crosslinks, will fix the polymer in its most thermodynamically favorable shape, being the permanent shape. When chemical crosslinking is used for the fixation of the permanent shape, an insoluble thermoharder is obtained. Conversely, when physical crosslinking is implemented by making use of intramolecular interactions, a thermoplastic material is obtained which remains soluble in a suitable solvent. Physical crosslinking can be realized for example by making use of crystalline regions in the material. The latter paves the way towards the application of different processing methods to shape a material into a final product.

A solely crosslinked polymer, however, is not to induce shape-memory behavior. In addition to crosslinks, or so-called "hard" regions that fix the permanent shape, shape-fixing, "soft" regions are also required. These regions typically are affected by a certain switch, which can be triggered to "freeze" or "unfreeze" the polymer chains into a temporary, less coiled shape.[28,33] Depending on the shape-memory polymer type, thermal transitions in the polymer chains or reversible chemical crosslinking can be used for the fixation of the temporary shape. These shape-fixing elements will act as additional crosslinks and are able to "freeze" the polymer in a deformed, entropically less favorable state, while storing the energy related to the deformation.[33] When a suitable trigger is applied, the crosslinking of the temporary shape is undone, thereby "unfreezing" the polymer chains, allowing for a recovery of the permanent shape.

However, without programming, no temporary shape can be generated. As a result, it is also important that the polymer is processed in a suitable manner, which will be clarified in the next paragraph. During the first processing step, the permanent shape will be fixed by means of chemical or physical crosslinking. In the second step, the permanent shape can be deformed into the temporary shape and a suitable trigger is applied to "freeze" the temporary shape by means of the shape-fixing regions while maintaining the deformation. When the stress on the polymer is released, it will maintain its temporary shape. The process of shaping and fixing the polymer in its temporary shape is referred to as "programming." Recovery of the permanent shape can be realized by applying a suitable trigger to the polymer to undo the crosslinks introduced during the programming step. Programming and recovery cycles can usually be applied multiple times. However, while literature usually refers to three cycles for the characterization of the shape-memory behavior, no theoretical limit exists prior to material fatigue occurrence. The concept behind shape-memory polymers is demonstrated in **Figure 1**, which shows an energy diagram of the permanent and temporary shape of a thermoresponsive shape-memory polymer. A review reported earlier by Lendlein and Kelch provides a broader view on the thermodynamics behind the shape-memory mechanism.[34]

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Peter Dubruel is currently heading a group of over 30 people. Since the start of 2006, he has been involved in several EU projects. Since end 2006, he has delivered over 20 invited lectures. He has been the spokesperson of the Young Scientist Forum (YSF) from the European Society for Biomaterials (ESB) for more than 5 years.

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3. Quantifying the Shape-Memory Effect

In the present review, the quantification of the shape-memory effect will be limited to the most important parameters that can characterize shape-memory materials as an in-depth review covering the quantification of the shape-memory effect has already been published by Sauter et al.[35]

Using cyclic thermomechanical tests (e.g., dynamic mechanical thermal analysis (DMTA), cyclic tensile testing), it becomes possible to characterize and quantify the shape-memory behavior

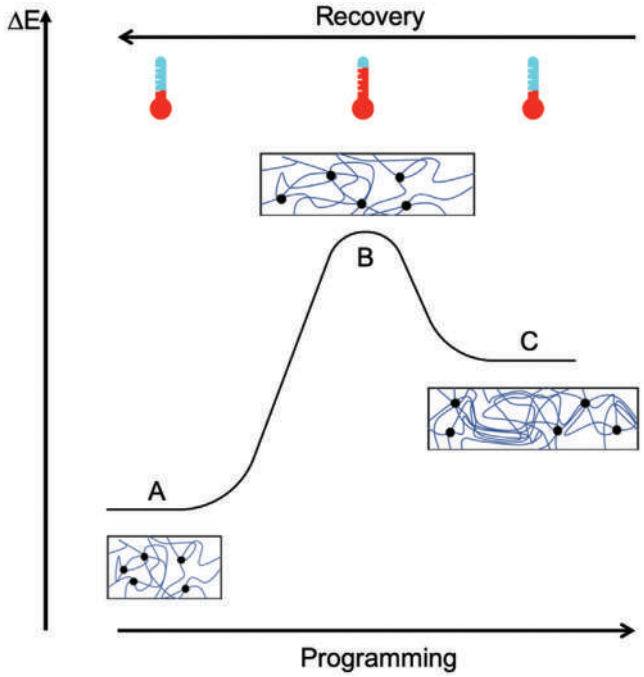

Figure 1. Potential energy diagram of a thermoresponsive shape-memory polymer A) shows the entropically favorable permanent shape, which can be programmed into the less favorable temporary state C) through heating and deformation. The permanent shape A) can be recovered through heating of the temporary shape C). During switching between the temporary and permanent shape, the polymer goes through a transition state B) where the polymer chains have are mobile, allowing for the reorganization of the chains.

of polymer materials. This typically indicates which part of the applied strain can be recovered through the shape-memory effect.

One of the values often used for the characterization of shape-memory materials is the strain recovery (R_r), which indicates to what extent a material can retain its permanent shape. The value can be calculated on a "per cycle" basis compared with the previous cycle or for N cycles compared to the original permanent shape.

$$R_r(N) = \frac{\varepsilon_m - \varepsilon_p(N)}{\varepsilon_m - \varepsilon_p(N-1)} \quad (1)$$

$$R_{r,tot}(N) = \frac{\varepsilon_m - \varepsilon_p(N)}{\varepsilon_m} \quad (2)$$

In these equations, ε_m refers to the maximum strain applied to the sample in % while $\varepsilon_p(N)$ refers to the residual strain in the permanent shape after N cycles.

Another important property for the quantification of the shape-memory effect is the shape fixity (R_f) which indicates to what extent a material can retain its temporary shape in stress-free conditions which reflects the ability of a polymer to fix the deformation.

$$R_f(N) = \frac{\varepsilon_u(N) - \varepsilon_p(N-1)}{\varepsilon_m - \varepsilon_p(N-1)} \quad (3)$$

Here, $\varepsilon_u(N)$ refers to the strain present in the stress-free state after unloading the sample in the N^{th} cycle.[34,36] When reported, the shape fixity and shape recovery values will be provided throughout this review.

Another property of paramount importance for the quantification of shape-memory polymers is the recovery time. This indicates the time it takes for a polymer to recover from its temporary shape toward is permanent shape. When reported, this data will be provided throughout the rest of the review.

4. Biomaterial Requirements

To be useful in a biomedical context, shape-memory polymers have to fulfill a range of general requirements along with application-specific requirements. Since shape-memory polymers are usually derived from conventional polymeric materials, these requirements are generally in line with the requirements for conventional biomaterials with no specific needs being present for shape-memory materials. A first requirement is the nontoxicity of a biomaterial. The latter refers to noncarcinogenic, nonallergic, blood compatible, and noninflammatory materials. In addition, a biomaterial should not leach or release any molecules in case it is not designed to do so.[37] As a second requirement, a biomaterial should be biocompatible and it should perform with an appropriate host response in line with its specific application (i.e., the material should be nonimmunogenic).[37] Here there is an advantage in the use of biopolymers compared to synthetic polymers since the former generally invokes less inflammatory reactions than the latter.[37] An example of these requirements can be found for polymers serving cardiovascular applications during which the polymer will be in contact with blood, as it is important that no thrombus formation occurs at the polymer surface.[38,39] Therefore, no adsorption of proteins should occur on the polymer surface.[40] To evaluate this, a biomaterial should be subjected to hemocompatibility studies.[38,39] Polymers that have been used in the past that comply with this requirement include poly(ε-caprolactone) (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(dioxanone) along with various polyurethanes.[41] A third requirement is that a biomaterial should not provoke a foreign body response.[37] Additionally, another important requirement that biomaterials should fulfill is the match between the mechanical properties of the implant material with those of the surrounding tissue.[37,42] This is generally desired in order to avoid alteration of the in vivo biomechanics in the target region.[42] The mechanical requirements are thus application-specific and depend on the function and the implantation site of the material.[37] For materials that are applied in load-bearing applications, which is the case for hip or knee joint replacements, it is important that the polymer does not fracture or abrades. These materials should also show minimal wear.[38] Furthermore, the polymer should be sufficiently strong to prevent mechanical failure. Therefore, a Young's modulus between 1 and 7 GPa is generally desired for these applications.[42–44] This requirement rules out low-modulus polymers such as hydrogels for load-bearing applications. Additionally many other polymeric materials such as many variations PCL ($E \leq 71$ MPa) are ruled out.[18] **Table 1** shows the moduli of various human tissues and compares them with reported shape-memory polymers and can be indicative for the selection of a shape-memory polymer for use in biomedical applications.

Table 1. Comparison of Young's moduli of several human tissues with reported shape-memory polymers.

Tissue/material	Modulus [MPa]	Refs.
Human tissue		
Femur	2×10^3–19.3×10^3	[45]
Breast tissue	3.25×10^{-3}	[46]
Cornea	24.5×10^{-3} – 20	[47,48]
Lens	1.1×10^{-3} – 10.6×10^{-3}	[49]
Tendon	1.2×10^3	[50]
Skin	0.42–0.85	[51]
Spinal cord & gray matter	2	[52]
Muscle	1.45–20	[53,54]
Shape-memory polymers		
Polyurethanes		
Star-shaped cooligoesters-urethane networks of lactide and glycolide	330–600	[14]
Oligo(ε-caprolactone) diols with oligo (p-dioxanone) diols and diisocyanate	34–90	[21,34,55]
Poly(ε-caprolactone) oligomers polyurethanes with *N,N*-bis (2- hydroxyethyl) cinnamamide	5.01–7.26	[56]
Polyesters		
Oligo-(ε-caprolactone) dimethacrylate and *n*-butyl acrylate	0.5–71	[18,57]
Poly(ε-caprolactone) dimethacrylate	260	[58]
Methacrylated Poly(ε-caprolactone)	0.3–3.5	[59,60]
Polylactic acid–polyglycolic acid dimethacrylate	12–288	[61]
AB-polymer networks with co-oligoester and poly(*n*-butyl acrylate)	12.5	[13]
Electrospun poly(p-dioxane) and poly(ε-caprolactone) networks	3.3–5.0	[62]
Poly(trimethylene carbonate-*co*-D,L-lactide) random copolymers	2.0–4.7	[63]
Poly(ε-caprolactone) networks crosslinked with cinnamoyl moieties	223–511	[64]
Biopolymers		
Chitosan	4246	[2]
Poly[(3-hydroxybutyrate)-*co*-(3-hydroxyvalerate)]	100.1	[65]
Other polymers		
Poly(glycerol dodecanoate)	136.55	[66,67]
Acrylate-methacrylate networks constituting ethylene glycol phenyl ether acrylate and ethylene glycol phenyl ether methacrylate	0.7–31.2	[68,69]
Methylmethacrylate-*co*-polyethyleneglycolmethacrylate	9.3–23	[70]
2-(dimethylamino) ethyl methacrylate, butyl acrylate and tri(ethylene glycol) divinyl ether copolymers	60–625	[71]

Mechanical durability is another important requirement. The latter refers to the minimum period of duration that a biomaterial should be able to fulfill its function.[37]

In some cases, biodegradation also is a prerequisite. Whether or not degradation of an implant material is desired and how fast the degradation should occur is depending on the application and on the duration that an implant should fulfill its function. In this respect, biodegradable sutures are relevant,[72] as these can degrade after wound healing thereby preventing the need for removal of the sutures. The added advantage of shape-memory behavior in this context is the ability to produce sutures that are not only biodegradable but that are also self-tightening. This allows surgeons to loosely suture a wound followed by a trigger to activate the shape-memory effect and close the wound. However, when the polymer material should stay permanent in the body, degradation is not desirable. When (bio)degradation is a desired property of a material, no residue should ideally remain after degradation while the degradation products should be nontoxic.[73] Commonly used biodegradable polymers include polyesters such as PGA, PLA, PCL along with their derivatives, as well as biopolymers such as cellulose or gelatin.[73] Additionally, the degradation speed of the polymer should be tuned to the application, often this coincides with the formation of new tissue and thus polymer degradation should be slower or equal to the formation of new tissue. A final—albeit very important—requirement is the sterilization capability of the polymer, since polymers that cannot be sterilized, are not allowed to serve in vivo applications nor can they be used for in vitro evaluation of cellular response, these materials are thus not suitable for biomedical applications. Ideally, sterilization should not alter the properties of a biomaterial.[39]

5. Biomedical Applications of Shape-Memory Polymers

Shape-memory polymers have already served a plethora of applications. While nonbiomedical applications (e.g., heat shrink tube) also exist, the present review will be limited to biomedical applications of shape-memory polymers. In **Table 2**, an overview of current shape-memory polymers together with their targeted application is given.

5.1. Shape-Memory Polymers for Drug Delivery

As shown in Table 2, a common application of shape-memory polymers is drug delivery. The combination of drug delivery with shape-memory is interesting since the shape-memory effect can easily be used to immobilize the drug delivery device at the target site of drug delivery without the need for external manipulation. The latter allows for a prolonged drug delivery at the target site without the need for multiple injections or operations. Wischke et al. have shown that drug loading in a copolyester urethane shape-memory polymer does not substantially hamper the shape-memory capabilities of the material and that shape-memory materials can effectively be applied for drug release in aqueous environments. Indeed, their study indicates that polymer glass transition and elastic properties are not changed under influence of an incorporated drug while in aqueous environment. They anticipate the use of these polymers in case low drug doses need to be released over several months.[13,17] However, in a recent publication by Jahangiri et al., it was shown that shape fixity values were negatively influenced by drugs loaded through a swelling method in contrast with an in situ drug loading approach, which resulted in a 23% decrease in shape fixity after release of the drug between the two methods.[87] These results show that the performance of shape-memory polymers loaded with drugs highly depends on the method by which the drugs are incorporated and that researchers should opt for incorporating drugs using an in situ drug loading approach when possible to avoid a negative impact on the shape-memory performance.

Li et al. have developed a drug-releasing shape-memory polymer, based on poly(methyl methacrylate-*co*-butyl acrylate), of which the recovery can be triggered using ultrasound which is concomitant with the release of a copper sulfate model compound (5 wt%) (**Figure 2**). Interestingly, this enables the drug release to become stopped at any time together with partially recovered shapes becoming possible.[98] This allows for potential multistep recovery where different intermediate shapes are used together with temporal control over the drug release. Later, Han et al. have reported similar results for a PCL-based, polyurethane shape-memory material.[74] A unique approach for drug delivery using reversible shape-memory polymers was provided by Gong et al. who proposed a reversible shape-memory polymer that could be used as novel shape shifting drug delivery carrier to for example either avoid or promote phagocytosis.[100] To obtain their material, they synthesized six-armed PEG–PCL block-copolymers starting from a six-armed PEG initiator. Next, they modified the polymer with acrylate functionalities to obtain a crosslinkable polymer. The polymer was subsequently processed into microparticles that were able to switch reversibly between a spherical and an ellipsoidal shape with the ellipsoidal particles showing inhibition towards phagocytosis in contrast with their spherical counterparts. This could for example be used to increase the blood circulation time of drug-loaded nanoparticles.

Another advantage of shape-memory polymers as drug delivery vehicles can be found in the field of cardiovascular stents. Conventionally, these are constituted from metals and include a polymeric coating containing drugs when drug delivery is desired. The latter requires additional fabrication steps resulting in an increased cost. However, with shape-memory polymers, the drug can be directly incorporated in the matrix, thereby reducing the fabrication cost.[79,101,102] A comprehensive review summarizing the work done in drug releasing shape-memory polymers and was published by Wischke et al.[103]

5.2. Cardiovascular Applications of Shape-Memory Polymers

Shape-memory polymers have also found their entry in the cardiovascular field. Indeed, several groups have developed intravascular stents[1,79] while the self-expanding, biodegradable REMEDY peripheral stent has even been commercialized.[104,105] Even though the effectiveness of this stent is not yet at the same level as self-expanding nitinol stents, this example shows great potential for shape-memory polymers seeking applications in the cardiovascular field.[104] Great potential for stents based on shape-memory polymers can also be found when targeting intracranial stenosis. Conventional stents composed of stainless steel or shape-memory alloys are too stiff to enable delivery in the neurovascular blood vessels. The latter being mainly due to their small size along with the occurrence of twisting and turning of these vessels.[101] Due to the significantly lower glassy modulus of shape-memory polymers compared to metals, these materials may result in more suitable structures.[79] Additionally, as discussed in Section 4, the mechanical properties of polymeric materials more closely approximate those of the arterial wall, which might lead to reduced restenosis in case of polymeric, shape-memory stents.[79,106] Additional advantages compared with metallic stents include cost-efficient 3D printability and biodegradability.

In addition to intravascular stents, other cardiovascular purposes have also been explored. Montgomery et al. have reported on a functional tissue patch using poly(octamethylene maleate (anhydride) citrate, which can be used for organ repair using a minimally invasive approach through injection. More specifically, their patch can be injected through a 1 mm wide opening followed by expansion in vivo to its original shape without affecting cell viability. They successfully tested their cardiac patches in vivo in a rat model and also realized successful delivery of the patch in pigs at various target locations.[23] This method replaces the open heart surgery that is typically needed for similar injuries. The latter example is illustrative of how shape-memory polymers are able to reduce invasiveness of certain surgical procedures to a great extent.

Maitland et al. on the other hand have developed a laser-activated shape-memory foam. Their method of aneurysm

Table 2. Overview of shape-memory polymers along with their (potential) applications.

Chemical composition	Trigger	Form	Application	Notable characteristics	Refs.
Polyurethanes					
Polyester based					
Copolyester urethane with oligo[(*rac*-lactide)-*co*-glycolide]	Thermal	2D films	Drug delivery	• Tests different drugs • Biodegradable	[17]
PLA/PCL-based poly(urethane) + iron oxide NP + PEG/gelatin	Thermal/ moisture	Scaffold	Bone tissue engineering	• Osteogenic induction • Additive manufacturing	[11]
PCL based polyurethane	Ultrasound	2D shapes	Drug delivery	• Localized recovery • Temporal control over drug release	[74]
PCL-poly(ethylene glycol)-urethanes + vancomycin	Thermal	2D films	Wound dressing	• Promote wound healing • Electroactive • Biocompatible • Free-radical scavenging • Antibacterial	[75]
PCL-based poly(urethane) containing L-lysine	Thermal	Tubes Films	Vascular graft	• Biocompatible • Cellular alignment	[76]
Oligo(ε-caprolactone) diol + oligo(p-dioxanone) diol + diisocyanate	Thermal	Monofilament	Sutures	• Biodegradable • Verified in dead rats	[72]
Other					
Poly(urethane) + CNT	Thermal	Foam	Intravascular treatment of intracranial aneurysms	• Recovery through resistive heating	[77]
Poly(urethane)	Photothermal	Foam	Aneurysm occlusion	• Laser activated • Flow rate depend expansion • In vitro model	[78]
Poly(urethane)	Photothermal	Stent + foam	Vascular stent	• Laser activated • In vitro model	[79]
Poly(urethane) + NiTi	Electro resistive heating	Microactuator coil	Clot removal	• In vitro model	[80]
Poly(urethane)	Photothermal	Microactuator coil	Clot removal	• Laser activated	[81]
Poly(urethane)	Thermal	Spiral fiber	Nerve stimulation	• In vivo studies in mice	[82]
Poly(carbonate urethane) + Fe_3O_4 microsphere	Thermal	2D films	Cerebral embolization	• Decreased platelet adhesion • Promotion of rat vascular smooth muscle cells	[83]
Polyesters					
Poly(ε-caprolactone-*co*-DL-lactide)	Thermal	Tubular stent	Esophageal stenosis	• Biodegradable • In vivo study in a dog	[84]
Methacrylated PCL	Thermal	Tubular stent	Airway stent	• SLA printing	[85]
Poly(ε-caprolactone) acrylate + hydroxyapatite nanoparticles	Thermal	2D films	Bone defect repair	• Presence of hydroxyapatite nanoparticles	[86]
Hydroxypropyl cellulose-g-poly(ε-caprolactone)	Thermal	2D films	Drug delivery	• Compares drug incorporation methods	[87]
Oligo[(ε-caprolactone)-*co*-glycolide] dimethacry- lates and *n*-butylacrylate networks	Thermal	2D films	Drug delivery	• In vivo degradation study in rats	[13]
Poly(D,L-lactide-*co*-trimethylene carbonate)	Thermal	Monofilament Tubular stent	Sutures Stent	• Additive manufacturing	[88]
Oligo (ε-caprolactone-co-glycolide) dimethacrylates	Thermal	Ureter stent	Ureter stent	• In vitro model • Drug releasing	[89]
Poly(ε-caprolactone) + silver nanoparticle grafted cellulose nanocrystals	Photothermal	2D films	Self-tightening sutures	• Antibacterial	[90]
Biopolymers					
Ureidopyrimidinone modified gelatin	Thermal Hydration	2D films	Drug delivery	• ECM mimic • Biocompatible • Biodegradable	[10]

Table 2. Continued.

Chemical composition	Trigger	Form	Application	Notable characteristics	Refs.
Chitosan + carbon nanotubes (CNT)	Hydration	Foam	Noncompressible hemorrhage	• In vivo study in mice and rabbit • Conductive • Antibacterial	[91]
Chitosan, poly(ethylene oxide), glycerol	Hydration	Helical stent	Vascular stent	• In vivo study in rabbits • Biodegradable	[1]
PVA-based					
PVA + glycerol	Hydration	2D films Helix	Drug delivery	• Additive manufacturing	[92]
Gluteraldehyde crosslinked PVA + gelatin	Hydration	Circular staple	Anastomosis of hollow organs Drug delivery	• Cytocompatible	[93]
Other compositions					
Poly(vinylpyrrolidone-*co*-acryloxy acetophenone) Organogels	Thermal	2D films Limb support structures	Limb support	• Proof of concept • Room temperature formation of temporary shape	[94]
Poly(acrylonitrile-*co*-acrylamide) + PEG dimethacrylate + $BaSO_4$	Thermal	Microcoils	Embolization of arteries	• Radiopaque • In vivo study in pigs	[95]
Poly(octamethylene maleate (anhydride) citrate	Thermal	Scaffold	Cardiac tissue patch	• Minimally invasive surgery • In vivo study in pigs	[23]
Poly(*N*-acryloyl glycinamide) + nanoclay	Thermal	Scaffold	Bone tissue engineering	• Additive manufacturing • Promotes osteogenic differentiation • In vivo study in rats	[96]
Poly(ethylene glycol phenyl ether acrylate-*co*-ethylene glycol phenyl ether methacrylate	Thermal	2D films	Ophthalmic devices	• Optical characterization • Biocompatible	[68,69]
Poly(glycerol sebacate) + poly(1,3-propylene sebacate) + kartogenin	Thermal	2D films Foam	Cartilage regeneration	• In vivo study in rats • Cell-free regeneration	[97]
Poly(butyl methacrylate-*co*-methyl methacrylate)	Ultrasound	2D shapes	Drug delivery	• Localized recovery/ release • Temporal control over recovery/release	[98]
Multiple	Thermal	various	Orthodontic devices	• Patent	[99]

occlusion is based on the in vivo expansion of the foam by using a laser to trigger the expansion. They successfully demonstrated the working principle of their shape-memory device

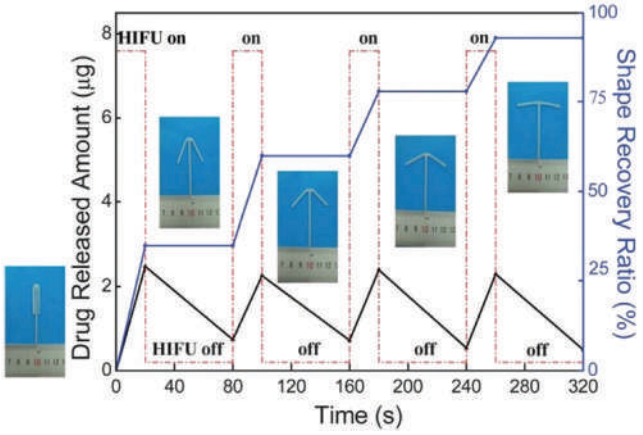

Figure 2. Use of HIFU to simultaneously trigger the recovery of a shape-memory polymer and the release of a copper sulfate drug from the polymer matrix. Reproduced with permission.[98] Copyright 2012, Royal Society of Chemistry.

in vitro.[78] More recently, Wang et al. have developed a shape-memory composite containing carbon nanotubes (CNT) for the treatment of intracranial aneurysms. The presence of the CNT allows for expansion of the shape-memory foam through resistive heating.[77]

Shape-memory polymers also hold potential for the treatment of endovascular thromboses. For example, Small et al. have reported on a shape-memory device that combines nitinol with a shape-memory polymer to create a device that is able to remove blood cloths in an in vitro context.[80] A similar approach was reported by the group of Maitland. However, they used a laser-activated device made solely from a shape-memory polymer.[81] While the examples listed herein are nonexhaustive and many more shape-memory polymers hold potential to serve cardiovascular applications, these examples showcase the potential of shape-memory applications in the cardiovascular field.

5.3. Bone Tissue Engineering Using Shape-Memory Polymers

Shape-memory polymers can also be used to repair bone defects. For example, Zhai et al. produced composite scaffolds

composed of poly(*N*-acryloyl glycinamide) and a nanoclay, which promoted osteogenic differentiation and stimulated the regeneration of bone tissue.[96]

In addition, Tian et al. recently used poly(ε-caprolactone)-based networks containing hydroxyapatite. To incorporate the hydroxyapatite into the network,[107] they modified it with thiol moieties to subsequently react with acrylate-modified PCL through a click reaction to obtain a crosslinked network.[86] Wang et al. 3D printed shape-memory scaffolds incorporating superparamagnetic iron nanoparticles to trigger osteogenic induction. They included both gelatin and PEG in their ink to improve printing thereby leading to scaffolds with improved fixity and recovery ratios. Additionally, the scaffolds containing PEG showed enhanced osteogenesis.[11] The main advantage of shape-memory polymers over other materials applied for the repair of bone defects is that they can be heated to reside in a plastic state, resulting in the possibility to fit into irregular bone defects. Upon cooling, the polymer will become locked in the defect.[86]

Alternatively, the repair of cartilage defects can also be realized. Recently, Xuan et al. published an article about employing shape-memory polymers for the regeneration of cartilage. Their polymer included bioactive kartogenin, which allows the stimulation of cartilage regeneration. The main advantage of shape-memory can again be found in its minimally invasive approach since it can be implanted in a temporary shape which is smaller in size than the final shape thereby complying better with the limited space available as well as the ability to fit irregular defects.[97]

5.4. Shape-Memory Polymers with Antibacterial Functionality

Antibacterial functionality of shape-memory polymers is a trait that can be considered as beneficial for all shape-memory materials that are intended for in vivo usage. This property will reduce the probability of an infection, making the material a better candidate for biomedical applications. In general, shape-memory polymers do not have antibacterial working by itself but require additives that give it its antibacterial effect. These additives can also improve other aspects of the shape-memory polymer, as will be seen further in this section.

In an attempt to obtain light-responsive shape-memory polymers, which will be discussed in Section 8, Toncheva et al. incorporated silver nanoparticles grafted onto cellulose nanocrystals in a PCL-based shape-memory network which resulted in an IR-active shape-memory polymer (780–1400 nm, 150 W). The presence of the silver nanoparticles resulted in antibacterial working of their polymer (minimal inhibitory concentration (MIC) = 16 μg mL^{-1} against Gram-positive bacteria), rendering it potentially useful for biomedical applications such as self-tightening sutures. Additionally, modest shape recovery values of 90% were obtained.[90] Another antimicrobial shape-memory polymer was reported by Zhang et al. who used a diketopyrrolopyrrole-based conjugated polymer as photothermal filler in a polycaprolactone-*co*-polyurethane matrix. Interestingly, the antibacterial effect of the polymer is only active upon irradiation with the near-infrared light (808 nm) used for the recovery of the permanent shape, showing that their antibacterial effect is photothermally induced. Depending on the concentration of the photothermal filler, increasing bactericidal rates were obtained (36.2, 88.4, and 100% for respectively 0.1, 0.2, and 0.5 wt% photothermal filler).[108] A similar photothermal antibacterial effect was observed by Zhao et al. who incorporated carbon-nanotubes in their polymer.[91] These examples illustrate the possible multifunctionality of additives. On one hand, the additives enable the shape-memory polymer to trigger under the influence of light, something not possible in the virgin polymer. On the other hand, these additives introduce an antibacterial working on the polymer. This possibility introduces an interesting opportunity and researchers looking to obtain a photoresponsive shape-memory polymer should consider the added benefit of antibacterial working when selecting an additive to obtain photoresponsivity.

5.5. Other Applications

Besides the applications mentioned in the previous sections, the use of shape-memory polymers has also been explored for many other applications. For example, Li et al. have developed an electroactive poly(urethane) shape-memory polymer as wound dressing material. In addition to the shape-memory properties of the material, which can aid the closure of cracked or open wounds without the need for additional suturing,[109] it also showed free radical scavenging properties. The polymer constituted aniline trimer segments, which seemed to promote the adhesion and proliferation of L929 mouse fibroblasts. In in vitro studies, their polymer shows accelerated wound healing compared to a commercial wound dressing and a nonelectroactive wound dressing.[75]

Zhao et al. have developed an injectable, antibacterial, conductive shape-memory polymer as a hemostatic. Herein, the shape-memory effect can be exploited to fit irregularly shaped wounds combined with the application of pressure after polymer expansion. They mainly envisioned the application of their material to treat hemorrhages and irregular and noncompressible wounds caused by for example explosions.[91]

Another potential application of shape-memory polymers includes a suturing material. More specifically, the suture could be loosely applied in its temporary shape, followed by heating (T = 41 °C) to recover to its permanent shape thereby tightening itself. The applicability of this concept has been shown by Lendlein and Langer.[72] On the other hand, Wan et al. developed an "ink" which can be 3D printed to obtain a shape-memory construct. They demonstrated the applicability of their material as a suture and a stenting material.[88] The main advantage of sutures constituting shape-memory polymers is that they can be self-tightening. More specifically, they can be loosely sutured after which the shape-memory effect can be employed to tighten the sutures. This can overcome difficulties with tightening knots in minimally invasive surgery, where space is limited.[110]

Neffe et al. have developed a ureteral stent based on a biodegradable shape-memory poly(urethane), which can be placed in its temporary shape followed by anchoring in vivo through recovery to its permanent shape. By including drugs in the polymer matrix, such a stent could be used to treat various diseases such

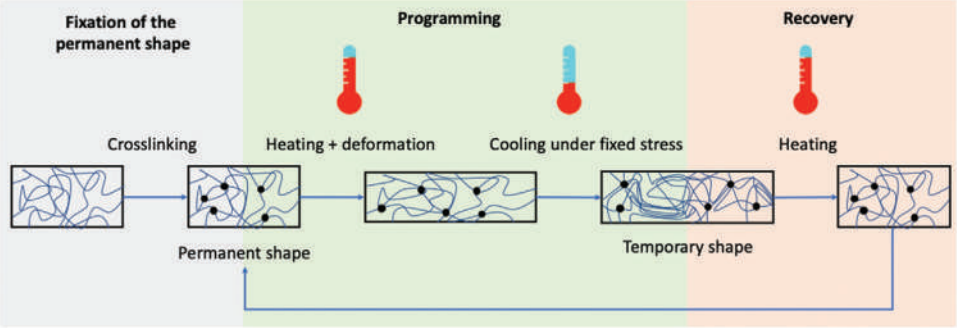

Figure 3. Illustration of the thermally induced shape-memory effect.

as cancer, or assist in the treatment of kidney stones and during pregnancy.[89] Yu et al. have developed an esophageal stent that can be used to treat esophageal stenosis. The advantage of their stent over conventional nitinol stents is the biodegradability, their ability to expand the stent in vivo at body temperature as well as mechanical properties in line with those of the surrounding tissue, thereby potentially reducing complications. Their stent was shown to successfully work in vivo in a dog model.[84]

Shape-memory polymers can also be used to trigger the differentiation of embryotic stem cells, as shown by Song et al. Using a poly(dimethyl siloxane-*co*-ε-caprolactone) shape-memory copolymer, they have shown that these copolymers are able to promote vascular differentiation based on the elastic modulus of the material. Additionally, they incorporated microspheres of their material in embryoid bodies and found differential expression of certain proteins based on the size of the microspheres.[111] A review from Ebara provides an excellent overview of the use of shape-memory polymers to study mechanobiology.[112]

In addition to these examples, Table 2 lists numerous other examples of shape-memory polymers that have already been employed to serve (potential) biomedical applications.

6. Thermoresponsive Shape-Memory Polymers

The class of shape-memory polymers mostly reported to date includes thermo-responsive shape-memory polymers. The switch characteristic for these polymers is usually a direct change in temperature which is either based on the glass transition temperature (T_g),[67] for amorphous polymers, or on the glass transition temperature and crystallization temperature (T_{cryst}), for semicrystalline polymers.[64] The concept of thermoresponsive shape-memory polymer behavior is demonstrated in **Figure 3**. When a polymer is exposed to a temperature below its T_g, the molecular motion of the polymer chains and polymer segments is frozen. Above the T_g, on the other hand, parts of the polymer chain exhibit mobility to some extent. This effect can be exploited as a fixing mechanism for the temporary shape. By deforming the crosslinked polymer at a temperature above its T_g, it becomes possible to stretch the polymer chains into their entropically less favorable state. Cooling a polymer below its T_g will freeze the polymer chains in this unfavorable state through vitrification, thus fixing the temporary shape. The permanent shape can be recovered by heating the polymer above its T_g, thereby restoring chain mobility and allowing the polymer chains to return to their more favorable, coiled state. A similar mechanism is applicable to semicrystalline, shape-memory polymers. More specifically, the permanent shape is fixed by either physical or chemical crosslinks while the shape-fixing elements are the crystalline regions in the material. These crystalline regions are formed during cooling of a crosslinked polymer below its melting temperature while the polymer is being deformed or while a stress is induced. In this respect, the degree of crystallinity is important. More specifically, Lendlein et al. showed that for an AB-polymer network containing oligo(ε-caprolactone) dimethacrylate and *n*-butyl acrylate, the shape fixity decreased with increasing *n*-butyl acrylate content, which was associated with a reduction in crystallinity.[18] As a result, the cooling rate will thus also exert an influence on the shape fixity since fast cooling is generally associated with a lower crystallinity degree.[113] The resulting crystalline regions of the polymer will act as additional net points thereby preventing the polymer chains from slipping and effectively fixing the deformation. Recovery of the permanent shape can be achieved by heating the polymer above the melting temperature of the shape-fixing regions, thereby melting the shape-fixing crystalline regions and allowing the polymer to relax into its more favorable and coiled state (see Figure 3).

Thermoresponsive shape-memory polymers are also very promising for tissue engineering applications since they allow the use of the body temperature as trigger. This renders minimally invasive surgery possible as the scaffolds can be compressed and can self-expand in vivo through their shape-recovery without a need for external manipulation or interaction. For example, a self-expandable shape-memory stent based on poly(L-lactic acid) (PLLA) was already reported by Tamai et al. who successfully tested their stent in in vivo studies in humans. This study shows that shape-memory materials show potential to be employed in a safe and effective manner in humans.[114] The stent became the first biodegradable stent implanted in humans and in the meantime has given rise to a commercially available peripheral stent (REMEDY).[105]

6.1. Chemically Crosslinked, Thermoresponsive Shape-Memory Polymers

A first type of thermoresponsive shape-memory polymer exploits chemical reactions to obtain a chemically crosslinked,

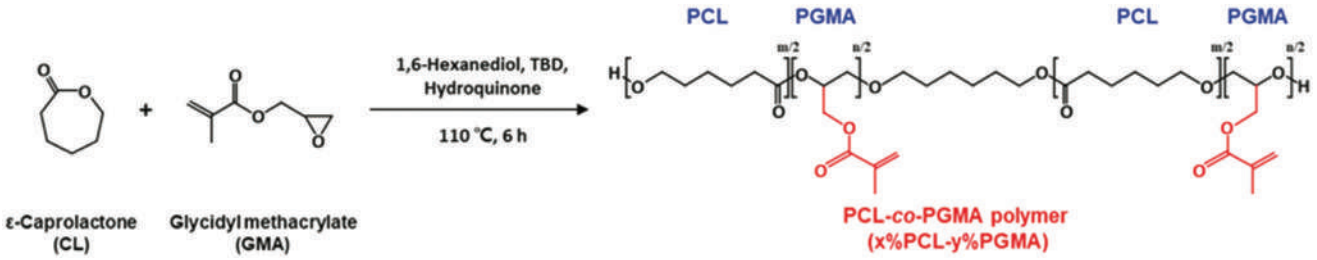

Figure 4. Copolymerization of ε-caprolactone and glycidyl methacrylate to obtain a chemically crosslinkable, shape-memory polymer. Adapted with permission.[116] Copyright 2019, Wiley-VCH.

covalent network that defines the permanent shape of the shape-memory material. Due to the irreversible nature of the network, it is not possible to redefine the permanent shape at a later stage in the process, which is a clear disadvantage of this crosslinking approach. On the other hand, this type of crosslinking results in a more resistant material, both thermally and chemically. Additionally, shape-memory properties of chemically crosslinked polymers tend to have superior shape fixation and recovery.[85] One of the most frequently employed chemical reactions for the creation of a covalent network is the use of polymers containing acrylate or methacrylate moieties, which can be crosslinked through a radical mechanism.[115] It is often used for polymers that are synthesized through a radical polymerization as well as for polymers that are easily modified with (meth)acrylate groups such as poly(ε-caprolactone).[85,116]

An example of the latter is given by Shin et al., who synthesized a copolymer starting from ε-caprolactone and glycidyl methacrylate to obtain a polymer with pendant methacrylate groups (**Figure 4**) and exploiting a melt transition (T_m = 35–40 °C) as trigger for the shape-memory effect. They used the polymer to design a vascular graft for the prevention of vascular stenosis.[116] On the other hand, Yang et al. employed the former method, making use of acrylate and methacrylate monomers in combination with a diacrylate crosslinker to obtain a crosslinked network through a radical polymerization. The shape-memory polymer developed formed micelles in aqueous solutions rendering it a potential candidate for the delivery of hydrophobic drugs.[71]

One of the problems associated with chemically crosslinked shape-memory polymers is their limited processability compared to thermoplastic shape-memory polymers. Melt-based processing such as extrusion is generally not available for this type of polymer due to the presence of chemical crosslinks which prevent the material from flowing. A solution in this respect has already been presented by Kuang et al., who showed that 3D printing of a shape-memory material using the above-mentioned crosslinking approach is feasible. Indeed, they 3D-printed *n*-butyl acrylate and isobornyl acrylate in the presence of a crosslinking agent and semicrystalline poly(ε-caprolactone) (PCL) followed by UV-irradiation to induce crosslinking while the polymer was still in a plastic state, thereby forming a semi-interpenetrating network. Herein, the chemically crosslinked network, responsible for the permanent shape, is based on acrylate crosslinking while the crystallinities in the PCL are responsive for the fixation of the temporary shape. The latter approach resulted in a shape-memory material with excellent shape fixity values (R_f = 99%). The shape recovery on the other hand reduced from 90% to 83% over four cycles, which might be attributed to slippage of the PCL chains which are not chemically linked into the network.[117] This might indicate a flaw in the design of the polymer since it is unlikely that this material would be able to hold its temporary shape for longer time frames due to slippage of PCL chains, leading to a gradual loss of the temporary shape over time. A superior approach has been reported by Zarek et al., who modified PCL-diol chains with methacrylates to obtain a crosslinkable polymer. When this material is crosslinked, the PCL chains are covalently attached within the network, preventing them from slipping. They used this approach to pursue the production of personalized, 3D-printed airway stents. Unlike the previously mentioned approach, this approach resulted in high fixity and recovery values (99% and 98% respectively after three cycles).[85]

One of the factors influencing the performance of a shape-memory polymer is the crosslink density. An example of this is given by Capiel et al. who considered a bio-based shape-memory polymer network containing methacrylated fatty acids. To obtain this polymer, styrene, methacrylated fatty acids and the crosslinker divinylbenzene were applied. However, polymers using divinylbenzene as crosslinker were proven to be too brittle due to the high degree of crosslinking while the use of styrene resulted in a polymer network with a sharp glass transition. This indicates that when flexible shape-memory polymers are required, excessive crosslinks cannot be included since the latter might lead to brittle and hard polymers. On the other hand, a higher crosslink density was shown to result in improved shape recovery with R_r values up to 96% after three cycles.[118] This indicates a balance occurring between brittle, heavily crosslinked polymers with improved shape recovery properties and flexible, less crosslinked polymers with slightly less shape recovery. This tradeoff should be considered when selecting a crosslink density and a polymer for a certain application.

Another way to obtain a chemically crosslinked network is to use multifunctional polymers or graft copolymers in combination with a crosslinking agent such as a diisocyanate. For example, Jahangiri et al. synthesized a hydroxypropyl cellulose polymer with pendant poly(ε-caprolactone) groups. The synthesized graft copolymer was subsequently crosslinked using hexamethylene diisocyanate (HDI). Using this approach, they were able to obtain a polymer with a thermal trigger near body temperature (T_m = 38 °C), rendering it a promising candidate for biomedical applications since actuation will not require the application of external heat, which could potentially

be damaging for the surrounding tissue. Shape fixity values ranged from 84% to 96% (third cycle), with higher values being correlated with more crystallinity of the PCL side chains. This shows that when using crystal-melt transition as a trigger for the shape-memory effect, it is important to have a sufficiently high crystallinity for the crystalline domains to be able to fix the temporary shape. The latter is a disadvantage which is less apparent for shape-memory polymers using the glass transition as a trigger. Shape recovery values of 99% were obtained for the third cycle.[87,119] Furthermore, they showed that the length of the PCL chains has a significant influence on the shape-memory properties, with higher molar masses resulting in more narrow recovery temperatures and higher shape fixity.[87] This result can again be interpreted as the influence of crystallinity on the shape fixity since a higher molar mass of the PCL chains will result in larger shape-fixing crystalline regions that are able to fix the temporary shape to a greater extent.

In addition to the advantages associated with chemical crosslinking which were already discussed (vide supra), covalent crosslinks can also be employed to improve the physical properties of shape-memory materials such as hydrogels. Traditionally, for hydrogels, a high strain capacity and excellent shape-memory properties are not inherent to one single material. Zhao et al. attempted to tackle this issue by using an organogel with phase-transition micro-organogels combined with an elastic hydrogel framework. This allowed them to obtain a material that could be stretched up to 2600% and compressed up to 85% while retaining its full recoverability. The hydrogel was synthesized through emulsion polymerization, resulting in a continuous amphiphilic network. The shape-memory effect of the obtained network is demonstrated in **Figure 5**.[120]

A third reported method to induce chemical crosslinking is by employing pericyclic reactions. An example of this is the dimerization of cinnamoyl moieties through a (2 + 2) cycloaddition upon UV-irradiation ($\lambda > 260$ nm). It should be noted that this chemical bond is reversible upon irradiation with UV-light of a lower wavelength ($\lambda < 260$ nm).[121] The aforementioned property renders polymers containing these moieties potential candidates to act as photoresponsive shape-memory polymers, which will be discussed in Section 8. For example, Wang et al. have reported on a PCL-based polyurethane containing pendant cinnamate groups exploited for polymer crosslinking. Their polymer is a triple shape-memory material, which can be given two distinct temporary shapes. R_f values of 94% for the first temporary shape and 85% for the second temporary shape were obtained while R_r values of 90% for a shape change of the second temporary shape to the first temporary shape and 85% for a shape change from the first temporary shape to the permanent shape were reported. The polymer was shown to be biocompatible as reflected by the high cell viability toward osteoblast cells, indicating noncytotoxicity.[56] A similar crosslinking approach based on the dimerization of pendant anthracene groups has also been reported previously.[20]

6.2. Physically Crosslinked, Thermoresponsive Shape-Memory Polymers

One approach to obtain a physically crosslinked, thermoresponsive shape-memory polymer requires the presence of at least two different domains with different thermal transitions, as is the case for example for block copolymers. The regions with the highest thermal transition (generally melting) can then act as crosslinking elements for fixation of the permanent shape while the regions with a lower thermal transition temperature (regions with lower melting temperatures or the glass transition) can act as switching segments.[29] An example of this is given by Song et al. They synthesized poly(ε-caprolactone)—poly(dimethyl siloxane)—poly(ε-caprolactone) (PCL-PDMS-PCL) triblock copolymers with crystalline PCL regions as hard segments and PDMS as a soft segment. The authors studied the influence of microspheres of this material on the differentiation behavior of embryotic stem cells.[111]

This technique (vide supra) does not only apply to block copolymers but also to homopolymers with a distinct glass transition and crystallization temperature, in this case the crystallites will act as crosslinks for the fixation of the permanent shape while the glass transition can be used to activate the switching elements. In the latter respect, the shape-memory properties can be influenced by the degree of crystallinity of the polymer,

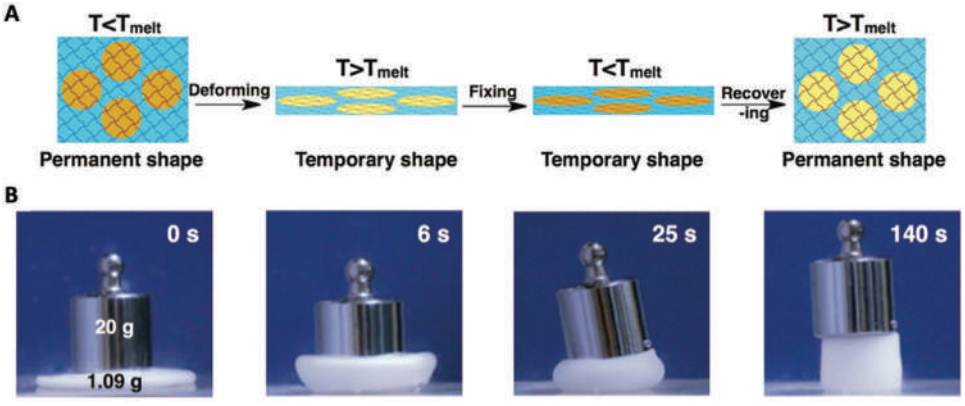

Figure 5. Shape-memory amphiphilic organogel network with high strain capacity. A) The process of programming the temporary shape and the recovery of the permanent shape. B) The recovery of the permanent shape of the shape-memory polymer while under a load several times its own weight. Adapted with permission.[120] Copyright 2017, Wiley-VCH.

as shown earlier by Sobota et al. Indeed, they concluded that higher recovery stresses (going from 4.6 up to 10 MPa) were observed upon increasing the degree of crystallinity in PLLA (5.9%– 42.3% crystallinity). However, recovery rate and shape recovery (92–40%) values decreased upon increasing the degree of crystallinity.[122] This highlights the tradeoff apparent for this type of crosslinking, namely one between recovery stress and shape recovery (rate). Whether or not to choose for higher recovery stress versus faster recovery rate and superior shape recovery is an important tradeoff that can be highly application dependent. Another way to tune the shape-memory properties of PLA-based polymers, which are interesting for biomedical applications due to their biodegradability, is to control the stereocenters present in the polymer backbone. Using this method, Fan et al. were able to obtain glass transition temperatures in the range of 38–46 °C for poly(PLLA-*block*-PDLA urethanes).[123] Reducing the glass transition temperature can be important for biomedical applications since lower temperatures will lead to reduced tissue damage and with transition temperatures near body temperature, shape recovery triggered upon implantation becomes possible. For example, the Igaki-Tamai stent can be expanded through balloon inflation with a heated dye (80 °C, 30 s). However, should the stent be made of a shape-memory material with a lower transition temperature and thus a lower thermal trigger, the need for a heated dye would be eliminated and potential tissue damage could be minimized by exploiting the physiological temperature to expand the stent within a reasonable timeframe.[114] This highlights one of the main disadvantages of thermoresponsive shape-memory polymers. Indeed, obtaining transition temperatures near body temperature is not always straightforward while polymers exhibiting transition temperatures which are too high are not suitable or less suited for biomedical applications.

Another strategy is to make use of supramolecular interactions to fix the permanent shape. For example, Du et al. reported on a PCL-based polymer, terminated with catechol groups. When the polymer is mixed with iron oxide nanoparticles, the catechol groups coordinate with the nanoparticles to form a crosslinked network. Due to the incorporation of the nanoparticles in the network, the obtained material does not only display the conventional thermoresponsive shape-memory behavior but also shows responsiveness to magnetic fields and light. The authors obtained fixity values close to 100% and recovery values beyond 95%.[124] This type of crosslinking thus has the potential to allow for increased responsiveness by enabling a broader range of triggers to be employed compared to the conventional thermoresponsive shape-memory polymers, yet are associated with a reduced chemical stability and inferior mechanical properties compared to chemically crosslinked shape-memory polymers. This could be of interest for the remote triggering of implanted biomedical devices using different possible triggers and selecting triggers more suitable or more likely to reach the implant based on implant location, as well as allowing a broader range of triggers to expand implanted shape-memory devices after minimally invasive surgery. Another example in which coordination with a metal was used for crosslinking of a shape-memory polymer is provided by Yu et al. They reported on chitosan fumigated with ammonia, a process where the chitosan is reacted in an ammonia vapor atmosphere to introduce amine groups in the structure. The modified chitosan can then be crosslinked with Cu^+ ions through coordination. Interestingly, the mechanical properties of the material could be tuned by changing the amount of Cu^+ crosslinker, with more Cu^+ resulting in stronger hydrogels (up to 0.25 MPa).[125,126] The latter renders coordination-based crosslinking an attractive approach that enables straightforward tuning of the physical properties as well as potentially introducing additional triggers within the materials. The disadvantage associated with the latter approach and compared to chemically crosslinked shape-memory polymers is the reduced chemical and thermal stability along with inferior mechanical properties.

Another method to obtain a physically crosslinked network is through hydrogen bonding. Alavijeh et al. made use of ureido pyrimidone hexyl isocyanate to modify gelatin with ureido pyrimidone (UPy) functionalities. The UPy functionalities could then crosslink gelatin through the formation of quadruple hydrogen bonds.[10]

6.3. Hybrid Crosslinking Approaches

An interesting hybrid approach between covalent, chemically crosslinked and physically crosslinked networks was already provided by Zhang et al.[127] More specifically, an acrylonitrile acrylamide copolymer was crosslinked with a PEG methacrylate to obtain a chemically crosslinked network. In water, additional physical interactions arose due to hydrogen bonding occurring between the polyacrylamide parts of the copolymer, with the latter bonds being further stabilized by the dipole–dipole interactions occurring between the acetonitrile polymer segments. Using this approach, the authors were able to obtain hydrogels with a Young's modulus of 16 MPa and a tensile strength of 10 MPa, which is a vast improvement compared to previously reported shape-memory hydrogels. This approach paves the way toward applications including microcoils for the embolization of arteries, a task for which previously reported shape-memory hydrogels were lacking sufficient strength (<1 MPa). Moreover, shape fixity values up to 97.5% and shape recovery values close to 100% were obtained.[95] Alternatively, Le et al. have reported on a multiresponsive shape-memory polymer using two physical crosslinking types together with one type of chemical crosslinking. The material constituted an interpenetrating network of agar and an acrylate-based copolymer. A first type of crosslinking was based on the coil-to-helix transition of agarose, while the second one was based on the coordination of the carboxylic acids with Fe^{3+} ions in the poly(acrylate) side chains and the third, chemical, crosslinking was based on reversible phenylboronic acid (PBA)-diol ester bond formation. Using these different bond types enabled the authors to introduce multiresponsiveness in their hydrogel with a temperature response through the agarose-associated helix-to-coil transitions, a pH response through the formation of chemical PBA-diol ester bonds and a response toward EDTA through the Fe^{3+}-carboxylic acid interactions.[128] These hybrid approaches combine both the advantage of exhibiting the excellent mechanical properties of the chemically crosslinked shape-memory polymers with the tunability of

the physically crosslinked shape-memory polymers. However, due to the presence of physical crosslinks, chemical resistance remains limited. Additionally, an increase in the complexity of designing such polymers renders it uncertain whether the benefits can overrule the disadvantages.

7. Solvent-Sensitive Shape-Memory Polymers

One of the issues associated with thermo-responsive shape-memory polymers is that they often require high temperatures exceeding body temperature, (e.g., 70 °C for a self-expandable PLLA stent[114]) to recover their original shape which might lead to tissue damage and/or the inability to use body temperature as a trigger for the shape recovery.[7,129] One way to tackle this issue is to make use of a solvent to indirectly trigger the shape-memory effect of thermoresponsive shape-memory polymers.[29] The indirect triggering of the thermally activated shape-memory effect can be realized by modifying or omitting the transition temperature (T_{trans}) through immersion in a suitable solvent such as water for hydrogels. The solvent can act as a plasticizer on the polymer chains, thereby reducing the T_g and thus also T_{trans}.[130] If the T_g drops below ambient temperature upon immersion in a solvent, solvent immersion can be used to trigger the shape recovery. Alternatively, when the fixation of the temporary shape originates from crystalline domains, immersion in a solvent can lead to the solvation of the crystalline regions, thereby removing the T_m and the shape-fixing segments, thus resulting in a recovery of the permanent shape.[12]

While organic solvents, such as acetone, methanol, ethanol, and dimethyl sulfoxide have already been reported as trigger[131,132] for the shape-memory effect, the current review will focus on water as trigger in view of the material prerequisites to serve biomedical and tissue engineering applications. Several researchers have already reported on these hydration-triggered shape-memory polymers, which are an example of solvent-responsive shape-memory polymers. For example, Yang et al. and Chen et al. respectively studied the water-responsiveness of an ether-based poly(urethane) shape-memory polymer and a poly(vinyl alcohol) (PVA) shape-memory polymer, both containing hydrogen bonds, and concluded that the presence of water resulted in a weakening of the hydrogen bonds which resulted in a decreased T_g.[133,134] This explains the mechanism behind solvent-sensitive shape-memory polymers and shows that they are merely thermo-responsive shape-memory polymers affected by solvation and plasticizing effects. Other groups also exploit the plasticizing effect of water as a trigger for the shape recovery of shape-memory polymers.

7.1. Biopolymers

Alavijeh et al.[10] have reported on a physically crosslinkable gelatin derivative (GelUPy), through the reaction of the free amine groups in gelatin and an isocyanate group on the ureido-pyrimidone (UPy) synthon. The gelatin derivative is crosslinked based on the dimerization of UPy functionalities (**Figure 6**). The recovery of the gelatin derivative can be triggered both directly through a thermal pathway or indirectly through hydration. For the programming of the temporary shape, they heated the polymer up to 100 °C while being elongated, followed by fast cooling to room temperature to fix the temporary shape. Recovery of the permanent shape could then be achieved by either heating the polymer up to 100 °C or by submersion in water at 37 °C, causing dissolution of the gelatin helices. Due to the slower diffusion of water compared to heat diffusion, the water-activated recovery was slower (i.e., 38 min) compared to the direct thermal recovery (i.e., 17 s).[10] This shows one of the downsides of using a hydration-based recovery compared to a completely thermal recovery, due to the need of a solvent to first diffuse through the polymer matrix before thermal recovery can start. The shape-recovery of hydration-triggered shape-memory materials is substantially slower than thermally triggered materials, which does not use hydration to drop the transition temperature. This makes hydration-triggered shape-memory polymers less optimal for applications where a fast shape-recovery is desired. Gelatin is particularly promising as shape-memory material for biomedical applications and tissue engineering since it mimics the extracellular matrix (ECM).[10,135] Moreover, the modified gelatin derivative showed an excellent cell viability of 99.4% for L929 mouse fibroblasts. Additionally, it was shown that drug delivery is also possible using this shape-memory gelatin derivative.[10] Other groups have also exploited the UPy crosslinking strategy using different polymer backbones such as poly(vinyl alcohol), for which excellent shape recovery ratios of 99% were obtained,[136] or UPy-functionalized (meth)acrylate monomers, exploited to obtain a triple shape-memory polymer.[137]

In addition to gelatin,[10] other biopolymers have also been reported to exhibit shape-memory effect that can be triggered by means of hydration including chitosan,[1,2,138–140] cellulose,[138,141–143] starch,[19,144] collagen,[145] and keratin.[146,147] The practical applications of bio-based shape-memory polymers that can be triggered by hydration become evident in applications such as self-expanding stents as reported by Chen et al.[1] Their chitosan-based stent is able to expand rapidly (150 s), allowing for a minimally invasive insertion of the stent. Moreover, they successfully performed a preliminary in vivo study in the rabbit abdominal without thrombus formation.[1]

7.2. Synthetic Polymers

In addition to biopolymers, synthetic hydration-responsive shape-memory polymers have also been reported. For example, Wang et al. have developed a water-responsive polyhydroxyalkanoate (PHA)-based polyurethane (PHP),[12] containing polyhydroxyalkanoate and poly(ethylene glycol) (PEG) segments. The PHA segments act as hard segments and are responsible for the fixation of the permanent shape through the formation of crystalline regions. The PEG segments on the other hand are the shape-fixing regions responsible for the fixation of the temporary shape through the formation of crystalline regions. Immersion of the polymer in water while residing in its temporary shape will result in the solvation of the PEG-crystalline regions and the concomitant

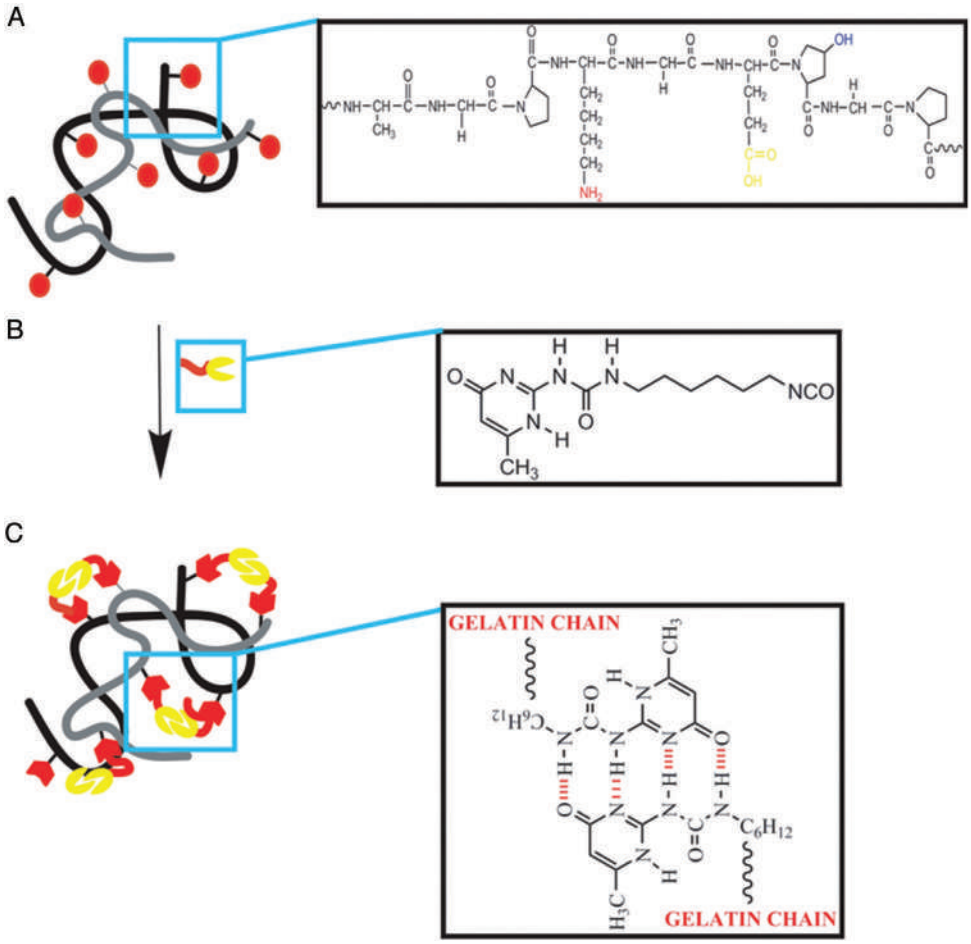

Figure 6. Reaction between A) gelatin and B) the UPy functionality to obtain C) a gelatin derivative crosslinkable through UPy dimerization. Reproduced with permission.[10] Copyright 2017, Royal Society of Chemistry.

release of the stored stress with a recovery of the temporary shape. Similarly, heating the polymer above 80 °C results in the melting of the crystalline PEG regions and thus in recovery of the permanent shape. The authors successfully used their polymer for osteogenic induction by seeding their 3D printed shape-memory scaffolds with hMSC cells. Melocchi et al. have already reported on a shape-memory poly(vinyl alcohol) (PVA)-based drug delivery device that can be retained in the bladder by recovery of the original shape after delivery through a catheter.[92] Their device is 3D printable and showed excellent shape-memory behavior with shape recovery up to 94%. Paonessa et al. also described a drug-loaded, PVA-based shape-memory polymer as a "staple" used for the anastomosis of human hollow organs, a process during which a connection is made between two ends of anatomical structures (e.g., when two ends of the intestines are stapled together after removal of part of the intestine). Their device can also be loaded with anti-inflammatory drugs to reduce inflammation.[93]

Other water-responsive, shape-memory polymers with relevance for biomedical applications including tissue engineering include polyester-based polyurethanes for bone tissue engineering,[11] poly(urethanes) with pyridine functionalities,[134] PEG,[148] PCL,[7,149] poly(2-ethyl-2-oxazoline),[150] and a multitude of other polyurethanes.[151,152]

It should be noted that other applications, such as water-activated, smart, artificial blood vessels and controlled-release devices, are also within reach using water-activated shape-memory polymers.[12] The disadvantage of using synthetic polymers is mainly their lack of cell-interactive properties since these materials are completely foreign to the body, unlike many biopolymers such as gelatin, which is derived from collagen. Advantages associated with these, however, include an increased reproducibility of the materials since less batch-to-batch variations can be anticipated for a completely synthetic material, as well as an increased potential for fine-tuning since there is full control over the whole synthesis process of the polymers.

8. Photoresponsive Shape-Memory Polymers

8.1. Reversible Crosslinking to Obtain Photoresponsive Shape-Memory Polymers

Photoresponsive shape-memory polymers can be subdivided into two classes. The first class can be considered "true"

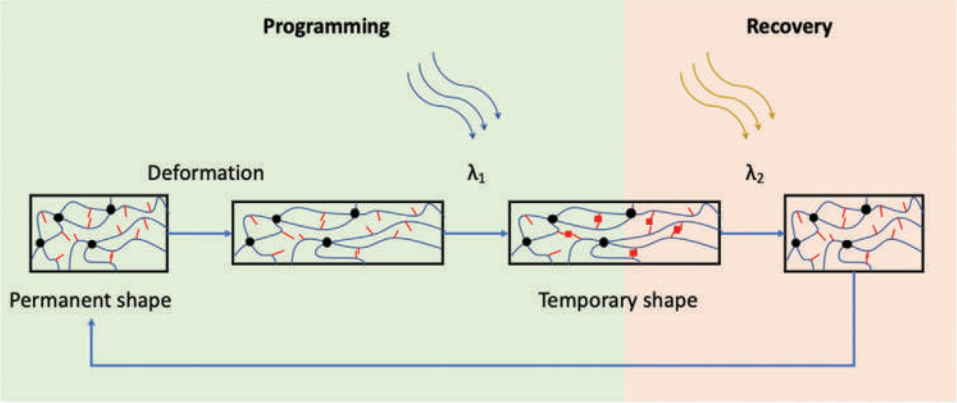

Figure 7. Illustration demonstrating the mode of action of photoresponsive shape-memory polymers.

photoresponsive shape-memory polymers and is based on reversible photochemical crosslinking, while the second class, which will be discussed in Section 8.2., exploits the heat generated by a light source to trigger recovery of a thermo-responsive shape-memory polymer.

The shape-memory effect characteristic for the first class of photoresponsive shape-memory polymers is based on the presence of reversible chemical crosslinks in the polymer material. More specifically, one crosslinker type acts as hard segment while another set of reversible crosslinks is involved in fixing the temporary shape. Irradiating the polymer with the appropriate light wavelengths, which will depend on the type of photosensitive group incorporated in the polymer, can lead to either the formation or breaking of crosslinks. When the crosslinks are formed, the polymer will become fixed in a less coiled, stretched, temporary shape. As a result, the polymer chains are prevented from shifting back to their more coiled, favorable state. However, when crosslinks are broken, the polymer chains are no longer fixed, allowing them to recoil into their thermodynamically more favorable state, resulting in the recovery of the permanent shape. The latter mechanism is demonstrated in **Figure 7**.

In order to develop photoresponsive, shape-memory polymers, the reversible dimerization of cinnamon[153–156] and anthracene[20] functionalities have already been exploited. Cinnamic groups can be reversibly dimerized upon irradiation with UV-light following a [2 + 2] cycloaddition. UV irradiation at $\lambda > 260$ nm results in dimerization while irradiation with UV light characterized by $\lambda < 260$ nm promotes the reverse reaction, as shown in **Figure 8**.

Lendlein et al. have already reported on two shape-memory, acrylate-based polymers using cinnamon functionalities to enable reversible crosslinking. They were able to obtain R_f values up to 52% and R_r values up to 98%.[154] Wu et al. also exploited the dimerization of pendant cinnamamide groups in a biodegradable, photoresponsive shape-memory polymer containing PCL soft segments and PLLA hard segments. They were able to obtain similar R_f and R_r values as observed by Lendlein et al. with R_f values up to 54% and R_r values up to 98%. A reaction scheme for the chemical synthesis of these shape-memory polymers is shown in **Figure 9**.[153] One of the possible explanations for the poor shape-fixity of these shape-memory polymers might be attributed to the *cis–trans* isomerization of cinnamoyl groups. Indeed, it has already been shown that at full conversion, a quarter of the trans isomer is converted into the cis isomer while only three quarters dimerize.[157] Recently, Leng et al. have been able to obtain improved fixity ratios using photoresponsive shape-memory polymers based on cinnamon functionalities. They were able to increase shape fixity in a cinnamic acid hydroxyethyl monoacrylate—acrylamide copolymer up

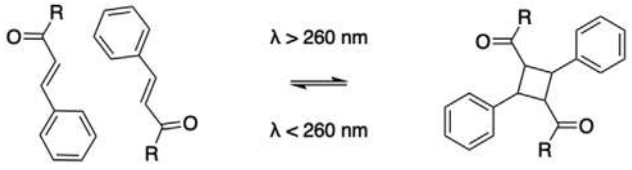

Figure 8. Reversible dimerization of cinnamic groups.

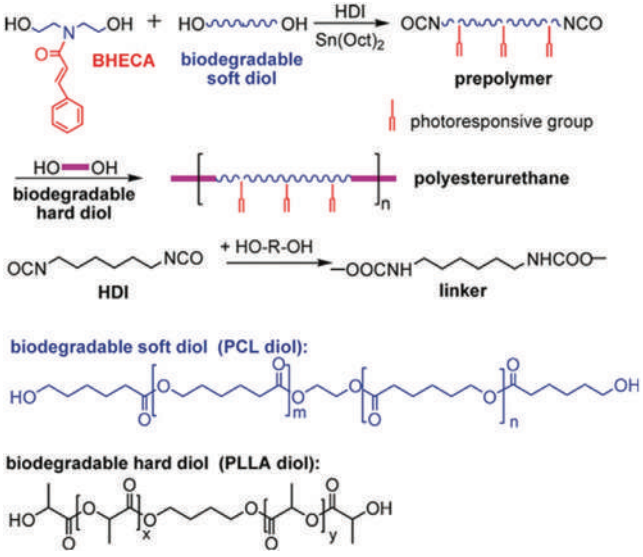

Figure 9. Synthesis of an ester-urethane photoresponsive shape-memory polymer. Reproduced with permission.[153] Copyright 2011, American Chemical Society.

to 98% by increasing the UV irradiation time ($\lambda > 26$ nm) from 5 to 20 min. The shape recovery values were slightly lower compared to previously reported values (i.e., 90%).[155] The improvement in shape fixity most likely was resulting from a higher amount of cinnamic groups present in the polymer synthesized by Leng et al. More cinnamic groups result in the generation of more crosslinks in the temporary shape, thereby preventing chain relaxation to a greater extent which results in a superior retention of the temporary shape. These publications imply that when cinnamoyl functionalities are chosen for the fixation of the temporary shape of photo-responsive shape-memory polymers, one should include high amounts of cinnamoyl groups to ensure sufficient shape fixation.

Anthracene can, similarly to cinnamic groups, become dimerized upon exposure to the appropriate UV wavelengths, following a [4 + 4] cycloaddition mechanism. Irradiation with UV light characterized by $\lambda > 300$ nm induces the dimerization of anthracene, while UV-irradiation exploiting wavelengths <300 nm results in photocleavage of the dimer. This reversible chemical bond was applied by Xie et al. to obtain a photoresponsive PLA–PEG copolymer containing pendant anthracene groups. They were able to obtain a rather poor shape-fixity up to 60% and a shape recovery up to 80%.[20] This might be attributed to suboptimal crosslinking from the cycloaddition approach.

8.2. Additive-Based Photoresponsive Shape-Memory Polymers

The second class of photoresponsive shape-memory polymers exploits the absorption of light to induce heating of thermoresponsive shape-memory polymers and does not suffer from the problem of low shape fixity values. This can be achieved without the need for additional additives as shown by Maitland et al. who have developed a polyurethane-based shape-memory stent that can be photothermally activated by an infrared laser. However, stent extension only reached 60% expansion during exposure to physiological flow rates (180 mL min^{-1}) in an artery model. The latter was due to the occurrence of convective cooling while otherwise (at $T = T_g + 25$ °C), full shape recovery could be achieved in 1 s.[79,158] Additionally, this approach is less efficient while in order to improve the conversion of light into heat, nanoparticles can be incorporated as additives. For example, Leng et al. implemented carbon nanoparticles in a styrene-based shape-memory polymer to improve the photothermal activation of the shape-memory effect using an NIR light source. This method resulted in a polymer with a shape-recovery of 100%.[159,160] By introducing gold nanorods in a poly(vinyl alcohol) shape-memory polymer, Zhang et al. were able to produce a composite that can be photothermally activated depending on the polarization of the irradiating light source ($\lambda = 532$ nm, 7 W cm^{-2}).[161] Unfortunately, the authors did not include quantitative data on the shape-memory properties, which makes it hard to estimate the impact of including gold nanoparticles in shape-memory polymers on the shape-memory performance. Shou et al. also made use of gold nanorods and modified them with PCL, resulting in a more sensitive shape-memory polymer, requiring lower light intensities for recovery (0.4–1 W cm^{-2}). These functionalized nanorods were subsequently incorporated in a PCL-based shape-memory polymer. Irradiation of the temporary shape with NIR light resulted in the recovery of the permanent shape. They concluded that depending on the intensity of the laser light source (0.4–1 W cm^{-2}), the shape recovery effect was local at the point of irradiation or global resulting in the recovery of the entire polymer film.[162] This is particularly interesting since it allows local recovery of the shape-memory polymer. This might broaden the potential applications by making devices with multiple recovery steps of which parts of the shape-memory structure are successively recovered. Leonardi et al. also exploited gold nanoparticles and developed a shape-memory epoxy that can be triggered through irradiation with green light with a wavelength of 532 nm (2 W cm^{-2}). Despite obtaining high fixity and recovery values of 98% and 96% respectively, they did not compare the fixity and recovery of polymers loaded with gold nanoparticles to polymers without nanoparticles, rendering it hard to estimate the impact of the nanoparticles on the shape-memory effect. However, since they obtained relatively high fixity and recovery values for the loaded polymer, the impact of the gold nanoparticles on the shape-memory effect is likely to be minimal.[163] Another chromophore used to convert light into heat for the photothermal activation of a thermoresponsive shape-memory polymer is polydopamine. Li et al. applied a polydopamine coating to obtain a photoresponsive shape-memory polymer. Additionally, application of the polydopamine coating resulted in an improved cell viability with A549 cells adhering to the surface and proliferating while this did not occur for the untreated polymer. Additionally, the reduced platelet adhesion making this a promising technique to obtain photo-responsive shape-memory materials that can be used in biomedical applications.[164] Afterwards, Obiweluozor et al. also applied polydopamine nanospheres to create a shape-memory polymer activated by NIR light (808 nm, 500 mW). They also concluded that the incorporation of the polydopamine nanospheres resulted in a significant increase in cell viability (72–97% increase in metabolic activity) compared to the virgin shape-memory polymer using NIH3T3 fibroblast cells. Additionally, they showed that the inclusion of polydopamine does not impact the shape-memory properties and that increasing the amount of nanospheres decreases the recovery time from 83 to 21 s when increasing the nanosphere concentration from 0.1% to 0.5%.[165] These examples show that the inclusion of polydopamine in shape-memory polymers might be an interesting approach to simultaneously develop a photoresponsive shape-memory polymer and to improve the cell viability of the material while only minimally impacting the performance of the shape-memory polymer. Ishii et al. have incorporated titanium nitride in a poly(ε-caprolactone)-based shape-memory polymer. Incorporation of the titanium nitride nanoparticles resulted in an increased absorption of light, resulting in improved conversion of light to heat compared with earlier composites. Using this method, they were able to obtain full shape recovery of their polymers upon irradiation with solar light at lower thresholds than previously reported with intensities between 130 and 160 mW cm^{-2} while no recovery was observed for the same polymer without the nanoparticles

added.[166] Leng et al. made use of carbon nanoparticles in combination with a shape-memory polymer to show the possibility of a precisely localized trigger allowing for precise control over the location of the shape recovery.[167]

9. Other Shape-Memory Triggers

In addition to temperature, solvent and light, a large range of other triggers have also been investigated for shape-memory polymers in view of potential biomedical applications. Numerous researchers have for example reported on shape-memory polymers that can be activated through means of electromagnetic fields, allowing for the remote activation of shape-memory constructs such as implants.[6,124,168–174] This activation method is based on thermoresponsive shape-memory polymer composites containing magnetic nanoparticles through an inductive effect.[169]

9.1. Electromagnetically Triggered Shape-Memory Polymers

Wilson et al. developed two prototype therapeutic devices using a commercially available ester-based thermoset polyurethane shape-memory polymer. These devices had complex shapes, making them more difficult to remotely activate using lasers or resistive heating.[170] This shows that the use of electromagnetic fields can be beneficial for the remote activation of implants with complex geometries that would otherwise be difficult to activate correctly.

In addition to triggering of shape-memory polymers with oscillating magnetic fields, electric current can also act as a trigger for the shape recovery of shape-memory polymers. Using this method, thermoresponsive polymers can be activated using resistive heating. To date, this has already been achieved by incorporating carbon nanotubes[175,176] or carbon nanoparticles and short carbon fibers.[7] A recent example has been provided by Wang et al. who envisioned a polyurethane–carbon nanotube composite shape-memory polymer as potential treatment for intracranial aneurysms. Due to the incorporation of the carbon nanotubes in the polymer matrix, their shape-memory foam could be expanded through a resistive heating mechanism.[77]

9.2. Ultrasound Triggered Shape-Memory Polymers

Ultrasound-responsive shape-memory polymers have also been reported for their potential to serve biomedical applications.[3,177] In principle, this can also be considered a thermoresponsive shape-memory polymer, yet instead of the direct application of heat, ultrasound is used as a method for heat transfer and to trigger the shape-memory effect. The latter is particularly promising as a way to remotely trigger the shape-memory effect.

In 2015, Li et al. reported on the ability of poly(vinyl alcohol) to be recovered using a commercially available ultrasound device, originally designed for pain relief to patients.[177] They employed an interesting physical crosslinking approach based on hydrogen bonding between the biocompatible PVA and melamine to establish a physically crosslinked hydrogel (**Figure 10**). Fixation of the temporary shape was possible through a freeze/thaw treatment which resulted in the formation of crystalline regions in the PVA. This demonstrates yet another way through which shape-memory polymers can be

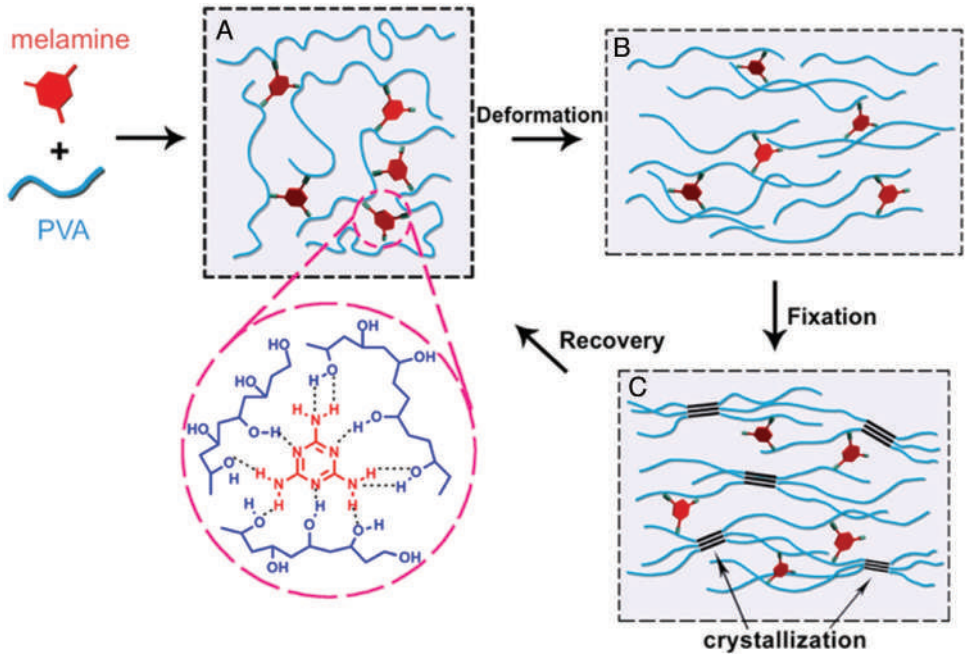

Figure 10. PVA-based hydrogel able to recover with a commercial ultrasound device. A) Physical crosslinking approach using melamine to obtain a hydrogel. B) Deformation of the hydrogel followed by C) freezing or thawing results in fixation of the temporary shape. Application of ultrasound results in the recovery of the permanent shape (A). Reproduced with permission.[177] Copyright 2015, American Chemical Society.

activated inside the body, without the need for direct heat application. More recently, Bhargava et al. designed a mathematical framework for the modeling of ultrasound-induced thermal actuation of shape-memory polymers for controlled drug delivery purposes. They experimentally validated their model using a polymer synthesized from a *tert*-butyl acrylate (TBA) monomer with a di(ethylene glycol)dimethacrylate (DEGMA) crosslinker.[3] Their work will help researchers to further understand ultrasound-activated shape-memory polymers and will aid in the design of specific drug-releasing shape-memory implants or nanocarriers.

9.3. Shape-Memory Polymers Triggered by pH Change

Han et al. have reported on a shape-memory polymer that reacts to a change in pH. The polymer was based on alginate modified with either β-cyclodextrin (CD-Alg) or diethylenetriamine (DETA-Alg). These functionalities allow reversible crosslinking to occur upon variation in pH. The resulting shape-memory material was shown to be biocompatible using an agar diffusion test and trigger no cytotoxic reactions in the presence of a L929 cell line. They obtained a good shape fixity and recovery of 95.7% and 94.8% respectively.[178] Shape-memory materials with such novel triggers are promising with regard to potential medical applications such as drug delivery devices that enable drug release through external stimuli such as ultrasound or by variations present in the body such as lowered pH in the presence of cancer cells.[179]

10. Reversible Shape-Memory Polymers

More recently, advances have been realized to obtain a reversible shape-memory effect, with the shape being repeatedly switched between two morphologies without the need for external manipulation. This material would be potentially useful for biomedical applications such as artificial muscles or for applications for which multiple actuations are desired. While conventional, thermoresponsive shape-memory polymers lose the information retained in their temporary shape upon recovery toward the permanent shape, this limitation does not apply to reversible shape-memory polymers.[180] In 2008, Chung et al. reported on a two-way reversible shape-memory effect based on crosslinked poly(cyclooctene). The polymer exhibited a reversible shape-memory effect under the influence of a constant stress.[16]

Two years later, Lendlein's group developed a polymer with a triple shape-memory effect that showed a similar reversibility to the polymer studied by Chung et al. In other words, their polymer was also reversible upon applying a constant stress. The bock copolymer contained two distinct segments including a poly(pentadecalactone) and a poly(ε-caprolactone) segment (poly(CL-block-PDL)).[181] The reversible shape-memory effect of both these materials was based on crystallization-induced elongation and melt-induced contraction, which allows the polymers to extend and shorten upon applying a constant stress. The latter reversible triple shape effect can however not be considered as a true shape-memory polymer since it does not include the programming of an arbitrary temporary shape, nor is it freestanding.

In 2013, the Lendlein group reported that the earlier described polymer, also exhibited bidirectional shape-memory polymer, and is in fact the first free standing shape-memory polymer that is able to reversibly switch between two of its shapes without the need to exert an external stress or manipulation.[180] The domain with the highest melting temperature ($T_{m,1}$) determines the shape shifting geometry and the domain with the lowest melting temperature ($T_{m,2}$) is responsible for the actuation behavior. Heating above $T_{m,2}$ will lead to a partial recovery of the permanent shape—with this partially recovered shape still containing the information of the original temporary shape—which is stored in the crystalline region corresponding to the higher melting temperature. Cooling the polymer below $T_{m,2}$ leads to the oriented crystallization of the first crystalline region, guided by the other crystalline region and will result in a recovery of the originally programmed temporary shape. Later, the same group also reported on a reversible shape-memory polymer that does not rely on a polymer with two distinct crystallizing domains but it exploits a broad T_m to obtain a reversible, thermo-responsive shape-change through partial melting and recrystallization of a single crystalline region.[183] Wang et al. also reported on a two-way reversible shape-memory polymer using the same principle as first reported by the Lendlein group in 2013. In the latter case, the two crystallizable domains were comprised of poly(ε-caprolactone) and a copolymer of ε-caprolactone and ω-pentadecalactone (p(CL-*co*-PDL)).[180,182] Here, the PCL segment is responsible for partial recovery of the permanent and the original temporary shape while the P(CL-*co*-PDL) segment is responsible for "memorizing" the information contained in the programmed temporary shape. Their reversible shape-memory polymer is nicely demonstrated in **Figure 11** where they showed the reversibility of their polymer upon heating to 60 °C and cooling down to 10 °C for both bending and coiling of the material.[182] Since their material was based on PCL, which is commonly used for biomedical applications, this reversible shape-memory material shows promise for future applications. Indeed, Wu et al. already

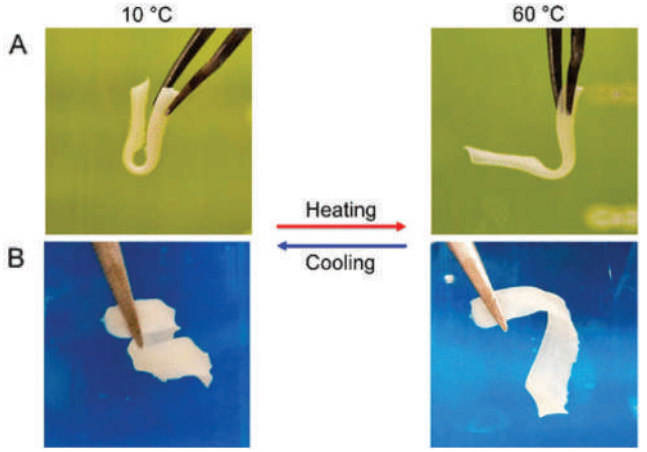

Figure 11. Reversible shape-memory effect in a PCL, poly(CL-block-PDL) crosslinked network. Reproduced with permission.[182] Copyright 2017, American Chemical Society.

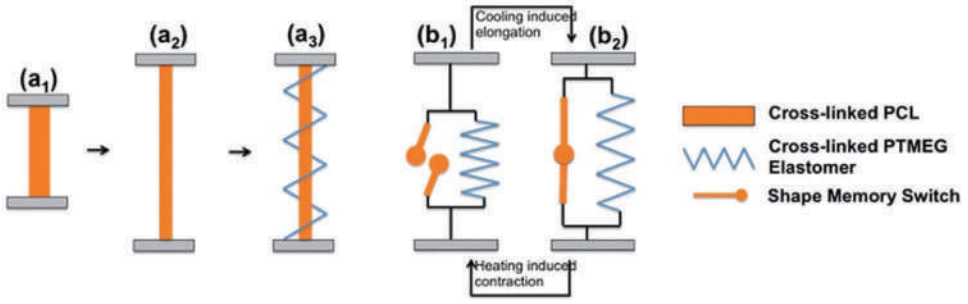

Figure 12. Schematic representation of the switch-spring model of the reversible shape-memory IPN. Reprinted with permission.[184] Copyright 2014, Royal Society of Chemistry.

proposed a reversible shape-memory polymer based on an interpenetrating network (IPN) of PCL and poly(tetramethylene ether) glycol (PTMEG) with a potential application as artificial tendon.[184]

Their system was based on a switch and spring mechanism, which is schematically demonstrated in **Figure 12**, with the crystalline PCL network being responsible for reversible shape shrinkage at high temperatures, through melt-induced compression, and the compressed elastomeric PTMEG network being responsible for the elongation upon cooling by triggering the shape to expand. With this system, the authors provide a toolkit to easily convert existing shape-memory polymers toward two-way, reversible, shape-memory polymers by making use of an IPN with a "switch-spring" mechanism.

All things considered, truly reversible, freestanding, shape-memory polymers are a novel field that still requires a lot of exploration in the biomedical field. It is, nonetheless, very promising in this regard. An excellent review about reversible shape-memory polymers was published earlier by Lendlein and Gould.[185]

10.1. Other Reversibly Actuating Polymer Systems

Systems that can perform reversible actuation are however not limited to the reversible shape-memory polymers. Other systems such as liquid crystalline elastomers and hydrogel actuators have also been reported.[186] The difference between these materials and reversible shape-memory polymers is that the shape-memory polymers can be programmed in both the permanent and the temporary shape by processing of the material, which is not possible to the same extent for liquid crystalline elastomers or hydrogel actuators, of which the shape change is dependent on the original 3D shape of the material.[187]

Hydrogel actuators are based on differences in swelling between different regions in the material. These differences in swelling can result from local heating caused by light[188] or external fields,[189] or are caused by subjecting a homogeneous hydrogel film to a pH- or a temperature-gradient. Alternatively, by making use of two materials that exhibit various volume increases upon hydration, a reversible actuation can also be achieved. A recent communication by Wang et al. discusses these bilayer hydrogels.[190] Another method to obtain a reversible hydrogel actuator is through ionoprinting, as demonstrated earlier by Lee et al. By incorporating Fe^{3+} ions in certain regions of the hydrogel film, a pH-responsive actuation can be obtained caused by reversible crosslinking. A change of the local crosslink density in the material results in an altered swelling behavior causing actuation of the hydrogel.[191]

Liquid crystalline elastomers (LCE) are materials that couple the properties of liquid crystals with those of elastomeric polymers. These materials are able to anisotropically stretch or shrink as a result of a change in temperature,[192,193] light,[194] and external fields.[195] These materials contain elongated, anisotropic groups (mesogens) that are covalently linked to polymer chain backbones that are further crosslinked. Their shape changing behavior is based on a change state between an ordered, anisotropic (nematic or smectic) state in which the mesogens are loosely aligned along a common axis and a disordered, isotropic state with random orientation of the mesogens.[196] It has to be noted however, that when processed under the right conditions, LCE can also exhibit a shape-memory behavior as already demonstrated by Rousseau et al.[197] A recent review by Sabine et al. explains the concept behind LCE and touches upon applications while going into depth on certain synthetic strategies to produce LCEs.[196] An interesting review about these materials and their potential biomedical applications was published earlier.[198]

11. Conclusions and Future Perspectives

In the present review, the general principle behind a variety of shape-memory polymers was discussed. In addition, recent and established literature was covered featuring shape-memory polymers exploiting different triggers for the recovery of the permanent shape together with their respective applications in the biomedical field. Moreover, novel, reversible shape-memory polymers were discussed.

Shape-memory polymers form an active field of research with a lot of application potential in the biomedical field. However, while progress is being made toward commercial applications of shape-memory polymers for nonbiomedical applications such as heat shrink tube, the use of shape-memory polymers in the biomedical field remains limited to date. Models have been developed to facilitate the design of shape-memory polymers for certain biomedical applications while the range of available triggers has widened, rendering remote triggering of shape-memory polymers possible, as well as exploiting physiological conditions as trigger.

Additionally, progress has been established in the development of reversible shape-memory polymers, allowing for actuation of shape-memory polymers or devices thereby paving the way toward a broader range of applications such as self-expanding stents and minimally invasive surgery, which was previously not within reach.

While current developments have mainly focused on designing new polymers with novel triggers as well as tuning the polymer properties, future research will have to focus more on in vivo studies and medical trials if shape-memory polymers need to find their entry in the clinic. Indeed, a lot of work still needs to be done in bringing the materials closer to the biomedical market. Additionally, focus on and improvement related to reversible shape-memory polymers will result in new applications such as artificial muscles that were previously not within reach with conventional shape-memory polymers.

Taken together, the promise of shape-memory polymers to serve biomedical applications is great. It can therefore be anticipated that in the forthcoming decade substantial progress will be realized that will feed new applications of shape-memory polymers in the biomedical field while the technology readiness level is likely to advance towards effective clinical applications.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

biomedical applications, shape-memory polymers, stimuli-responsive materials

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