A Review on Additive Manufacturing of Shape-Memory Materials for Biomedical Applications

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Shape-memory materials (SMMs) are characterized by their unique ability to remember and recover their shape in response to external stimuli. Over recent decades, the use of SMMs in biomedical areas such as tissue engineering, drug delivery, endovascular surgery, orthodontics, orthopedics, etc. has attracted significant attention from both academia and industry. Recently, additive manufacturing (AM) has also attracted growing interest for biomedical applications because of its ability to produce on-demand, patient-tailored devices for medical treatments. This article provides a review of current state-of-the-art AM techniques for producing SMMs for biomedical applications. First, both shape-memory alloys and shape-memory polymers are discussed regarding their fundamental characteristics and compositions, and the general principles governing their shape-memory effects. Next, current and potential biomedical applications of SMMs are presented, then available AM techniques that have been used for the fabrication of SMM-based medical devices are discussed and explored. Finally, an outlook on AM of SMMs for biomedical applications is provided.

INTRODUCTION

Shape-memory materials (SMMs), also sometimes known as smart materials, are stimulus-sensitive materials that can be deformed and fixed into a temporary stable shape under specific conditions of mechanical deformation and temperature, then recover their stress-free original shape upon exposure to an appropriate stimulus such as temperature, electric field, magnetic field, pH change, or near-infrared light.¹ Shape-memory alloys (SMAs) and shape-memory polymers (SMPs) are the two most important and widely used classes of SMMs.

SMAs were first discovered by Arne Olander in 1932,² and the unique shape-memory effect in nickel-titanium (NiTi) alloys was first discovered by Buehler et al.³ in 1963. Since then, the demand for SMAs has increased in engineering fields, driven by various commercial applications. There are three main types of SMAs, based on NiTi, Cu, and Fe. NiTi-based SMAs have been the preferred choice for

biomedical applications due to their excellent functional properties, fatigue resistance, and biocompatibility, although patient allergies to nickel remain a concern.^{4,5} While Fe-based SMAs (such as FeMnSi) and Cu-based SMAs (such as CuZnAl and CuAlNi) are relatively low cost and commercially available, their poor stability, low corrosion resistance, and poor thermal mechanical performance limit their potential applications in the biomedical field.^{6–8} Therefore, this review article focuses on the properties and additive manufacturing of NiTi alloys rather than Fe-based or Cu-based SMAs.

SMPs have been utilized commercially since the late 1990s and are similar to SMAs in their ability to change shape in response to stimuli. Compared with other external stimuli, thermally induced SMPs have been the most extensively studied by academia and used in industry.^{9,10} For thermally induced SMPs, the transformation (switching) temperature of polymers plays a vital role in their shape-memory effect and is most commonly associated with the glass-transition temperature (T_g) or melting temperature (T_m). From a molecular architecture point of view, there are two important requirements for thermally induced SMPs

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to demonstrate a shape-memory effect (SME): (1) the presence of permanent crosslinks which act as netpoints and form the fixed phase, and (2) the presence of stimulus-sensitive segments which form the reversible phase.¹¹ The netpoints and reversible segments connect to create the polymer network. The permanent crosslinks (i.e., netpoints) can be categorized as either chemical (i.e., covalent bonds) or physical (i.e., ionic or hydrogen bonds). Thermoset SMPs are chemically crosslinked, whereas thermoplastic SMPs are physically crosslinked.¹²

In comparison with SMAs, which exhibit high strength but recoverable strain of only around 1–8%, SMPs possess low strength and higher shape deformability, generating recoverable strains of up to more than 200%.¹³ SMPs also enjoy the advantages of being low cost, light weight, and easy to process, with excellent potential for biocompatibility and biodegradability. Nevertheless, material selection for biomedical applications is most often driven by the unique mechanical and stimuli responsive properties required for particular applications.

In recent years, additive manufacturing (AM) has been introduced as a class of innovative advanced manufacturing techniques that can enable the design and fabrication of highly customized medical devices with enhanced functionality. AM is a layerwise manufacturing technique in which a computer-aided design (CAD) solid model is first produced using three-dimensional (3D) modeling software, mathematical equations,¹⁴ or tomographic imaging data,¹⁵ e.g., x-ray computed tomography (CT), magnetic resonance imaging (MRI), etc. The AM equipment then reads the data from the CAD file and lays down or adds successive layers of resin liquid, powder, filament, or sheet forms of material, in a layer-by-layer fashion, to fabricate a 3D object. The ability to directly use CT and/or MRI data renders AM attractive for the fabrication of customized medical devices including prosthetics, implants, tissue grafts, etc.

The main aim of the present review is to provide an overview of the most common SMAs and SMPs applied in the biomedical field and their key properties when fabricated using different AM techniques. The fundamental characteristics, compositions, and general shape-memory mechanisms are presented, together with the biomedical applications of both SMAs and SMPs. AM techniques which have been used to fabricate these materials and the corresponding properties of the fabricated parts for biomedical applications are also highlighted. Finally, challenges in designing and manufacturing SMAs and SMPs for biomedical applications are discussed.

GENERAL MECHANISMS OF SHAPE-MEMORY ALLOYS AND SHAPE-MEMORY POLYMERS

Mechanisms and General Principles for SMAs

SMAs can exist in two different phases (i.e., martensite and austenite) with three different

crystalline structures (i.e., twinned martensite, detwinned martensite, and austenite), resulting in six possible phase transformation routes.¹⁶ Among them, martensite transformation is one of the most important phase transformations in SMAs, being a diffusionless transformation characterized by the well-coordinated and shear-dominated movement of atoms. During the martensite transformation, only the crystalline structure changes while the local chemical composition remains unchanged. As depicted in Fig. 1, the martensite transformation starts from the austenite phase (a stable phase at high temperatures), which transforms upon cooling to the martensite phase (a stable phase at low temperatures). M_s denotes the temperature at which the parent phase (austenite) starts converting to martensite, while M_f denotes the temperature of complete martensite transformation.³ During the heating process, the crystalline structure can recover its original shape upon conversion back to austenite. A_s and A_f describe the start and finish temperatures of this reverse transformation, respectively.¹⁷ The martensite transformation can also be mechanically induced between the temperatures M_d and M_s , where M_d is defined as the highest temperature at which martensite can no longer be stress induced.¹⁸ The shape-memory properties of SMAs can be classified into two categories: (1) the shape-memory effect (SME, one and two way) and (2) pseudoelasticity (or superelasticity), as shown in Fig. 1.^{19,20} The key martensite phase responsible for these effects in NiTi is the B19' monoclinic phase, although the existence of the rhombohedral R-phase often complicates the design of NiTi alloys.^{21–24} In general, M_s increases with decreasing content of Ni for the B19' martensite transformation.²⁵ The unique properties of SMAs make them ideal materials for many biomedical applications, including in dental, orthopedics, vascular, neurological, surgical, and other fields.

One- and Two-Way Shape-Memory Effect (SME)

Upon cooling from A_f to M_f , the austenite phase in a SMA transforms into a heavily twinned martensite phase, and below the temperature M_f this martensite can be easily deformed to produce a detwinned martensite state. Provided that the yield stress for dislocation motion is not exceeded, the detwinned martensite can recover its original shape on heating without any external force. This is called the one-way SME. Using compression testing, Haberland et al.²⁶ studied the stability of the SME effect for NiTi alloys. Figure 2a shows typical stress–strain hysteresis diagrams for NiTi samples. Upon loading, the inflection and change of slope during loading can be attributed to detwinning of the martensite and the reverse transformation, respectively. This inflection point represents a critical stress where the detwinning of the martensite begins. The material was further stressed to a

Fig. 1. Crystalline structures, phase transformation routes, and shape-memory properties in SMAs. Reprinted with permission from Ref. 19.

maximum value of 400 MPa before being unloaded and heated up to 120°C (30°C higher than A_f) to achieve one-way shape recovery. This process was repeated for 15 cycles, and some accumulation of nonrecoverable strain was observed, illustrating that the one-way SME is not always perfectly reversible.

After a careful “training” procedure, some SMAs can memorize the shape of both the austenite and martensite phases, which is called the two-way SME. An example of two-way SME can be seen in Fig. 2b. In this case, the specimen was first deformed in tension to 6.2% and then heated to 346 K. Figure 2b shows that 4.88% of the strain was recovered. Upon cooling to 270 K, a strain of 1.44% was induced, which was fully recovered upon reheating to 346 K. Once “trained” by the initial deformation, this strain hysteresis requires only heating and cooling as the material cycles between austenite and a single variant of detwinned martensite. This effect is called the two-way SME. However, the two-way SME effect is not as widely used in industry due to the additional “training” requirement and lesser strain recovery than the one-way SME for the same material.^{27,28} Moreover, the strain recovery in two-way SME is often unstable and tends to deteriorate at higher temperatures.²⁹

Pseudoelasticity (PE) or Superelasticity (SE)

When the temperature is higher than A_f , the transformation to twinned martensite can be induced by mechanical stress (loading) and the crystalline structure can return to its original austenite state after unloading.³³ The strain can be fully or partially recovered, and this effect is called the pseudoelasticity or superelasticity effect of SMAs. Unlike the SME, this transformation process does not require any temperature change. The amount of strain recovery can be affected by the ambient temperature, alloy composition, and microstructure texture. For example, Dolce and Cardone³¹ studied the superelasticity response of NiTi samples at different temperatures. At each temperature, they evaluated the critical stresses relevant to the forward and reverse phase transformation and reported different mechanical properties (starting and completing transformation stresses and strain recovery) at different temperatures (Fig. 2c). Omori et al.³² compared the superelastic properties of both ferrous polycrystalline SMA and NiTi alloys and found that they showed similar stress-strain curves but NiTi was superior to Fe-based SMAs (Fig. 2d).

Fig. 2. Functional properties of SMAs: (a) shape-memory behavior for conventionally fabricated NiTi (reprinted with permission from Ref. 26), (b) two-way shape-memory effect obtained after a single deformation by 6.2% of NiTi (reprinted with permission from Ref. 30), (c) stress-strain curves of NiTi in tension as a function of temperature (reprinted with permission from Ref. 31), and (d) tensile stress-strain curves at different temperatures obtained in a ferrous superelastic SMA alloy compared with NiTi (reprinted with permission from Ref. 32).

Mechanisms and General Principles of SMPs

In the case of polymers, the SME is an entropy-driven phenomenon involving an initial programming step to freeze in a lower-entropy state. The shape is then recovered upon reheating as the polymer disorders back to its original high-entropy state. There are many different types of polymers, and almost all of them exhibit shape-memory behavior to some extent. Schematic diagrams of the SME and molecular mechanisms in physically and chemically crosslinked polymers are depicted in Fig. 3. The programming step is achieved by first heating the polymer above a transformation temperature, T_{Trans} . This leads to material softening and triggers high polymer chain mobility. While the polymer temperature is maintained above T_{Trans} , an external load is applied to the polymer, which leads to rearrangement of the polymer chains into a more highly ordered configuration and thus a lower-entropy state. Following this process and maintaining the applied force, the polymer is cooled below the transition temperature. Then, the molecular chain segments freeze, and this lower-entropy state is kinetically trapped. This new and temporary shape of the SMP is retained after unloading. However, a considerable amount of elastic energy

is stored in the programmed SMP, which provides a driving force to remember the original shape. Finally, when the SMP is heated up again above T_{trans} , the molecular mobility is reactivated and the polymer chains return to their higher-entropy structural state. Consequently, the original shape of the polymer is recovered.

Most thermally activated SMPs are hot programmed (HP), meaning that the programming step is started by heating the polymer above the glass-transition temperature for shape-memory thermosets or the melting temperature for semicrystalline SMPs.³⁴ The important benefit of HP is achieving a large shape fixity with negligible springback; moreover the SMP can be easily deformed into a designed temporary shape with a small stress. However, there are a few studies in which the polymer is deformed below its glass transition (cold programming, CP). In many cases, CP means programming the polymer at room or ambient temperature. As the SMP should be deformed beyond the yield point, in contrast to HP, CP is not always possible. Some shape-memory thermosets are very brittle in the glassy state and tend to fracture before yielding, particularly under tension. However, some thermoset or thermoplastic SMPs can be deformed under cold compression

Fig. 3. (a) The general shape-memory mechanism in SMPs. (b) Schematic of the molecular mechanism of SME in thermally sensitive SMP for physically crosslinked copolymer. (c) Chemically crosslinked SMP (reprinted with permission from Ref. 1).

Fig. 4. Schematic of cold compression programming and free shape recovery of a shape-memory thermoset.

programming. Figure 4 shows a schematic of cold compression programming and free shape recovery of a shape-memory thermoset. The programming steps include cold compression at temperature below T_g , stress relaxation while keeping the strain constant at that temperature, unloading, and then the structural relaxation or resting step.^{34–36} Note that the unloading step is accompanied by spring-back. Also, in cold-programmed SMPs, there will be an immediate recovery of elastic deformation, hence 100% shape fixity cannot be obtained.

The shape (strain) fixity (R_f) and shape (strain) recovery ratio (R_r) are two important factors that quantify the ability of an SMP to fix the mechanical deformation and recover the original shape. Using cyclic thermomechanical testing, these two parameters are defined as¹:

$$R_f = \frac{\varepsilon_{temp}}{\varepsilon_{load}} \times 100\%, \quad (1)$$

$$R_r = \frac{\varepsilon_{load} - \varepsilon_{rec}(N)}{\varepsilon_{load} - \varepsilon_{rec}(N-1)} \times 100\%, \quad (2)$$

where ε_{temp} is the final strain of the temporary shape after programming, ε_{load} is the maximum strain applied during programming, and ε_{rec} is the recovered strain after one full programming and heating cycle. In Eq. 2, the different values of ε_{rec} refer to the current (N) and previous ($N-1$) thermomechanical cycles. The shape fixity and shape recovery ratio for cold-programmed SMPs can be defined by Eqs. 3 and 4³⁴:

$$R_f = \frac{\varepsilon_{res}}{\varepsilon_{pr}} \times 100\%, \quad (3)$$

$$R_r = \frac{\varepsilon_{rec}}{\varepsilon_{res}} \times 100\%, \quad (4)$$

where ε_{res} is the residual viscoplastic damage strain (which can be obtained by subtraction of the spring back strain from the total programming strain), ε_{pr} is the total programming strain, and ε_{rec} is the recovered strain.

For all the articles reviewed in “AM Techniques for SMP-Based Medical Devices” section, the HP is conducted on 3D-printed SMP devices. More examples from past research and detailed explanation about R_f and R_r are included in “AM Techniques for SMP-Based Medical Devices” section.

Classification of SMPs Based on Crosslinks

Physically Cross-Linked SMPs Multiblock copolymers obtained by the synthesis of a segmented polyurethanes or melt blending techniques are an important class of physically crosslinked SMPs. Thermoplastic polyurethanes (TPUs) contain segregated hard and soft domains.¹¹ The three main chemical compounds contributing to the synthesis of TPUs are diisocyanate, macroglycol (polyester or polyether diols, triols, polyols), and a low-molecular-weight chain extender.³⁷ The chemical reaction between diisocyanate (-NCO) and the hydroxyl functional molecules (macroglycol) leads to the creation of urethane linkages (-NHCOO-). For polyester urethanes, the urethane linkages act as netpoints and form the hard segments,¹ while polyesters form the soft and switching segments. The transition temperature of these physically crosslinked SMPs can be either the melting temperature ($T_{\text{Trans}} = T_m$)¹ or the glass-transition temperature ($T_{\text{Trans}} = T_g$)³⁸ of the soft switching segments.³⁹ TPUs with different properties can be obtained by using different chain extenders, different diisocyanates (e.g., aromatic versus aliphatic), and/or different soft segments.^{40–43} Most commonly in the field of shape-memory polyurethane (SMPU) synthesis, semicrystalline poly(ε -caprolactone) (PCL) is used as the switching soft segment with $T_{\text{trans}} = T_m$.^{44–47} Alternatively, Lee et al. synthesized a SMPU with $T_{\text{trans}} = T_g$, composed of poly(tetramethylene glycol) (PTMG) as the soft segments and 4,4-diphenylmethane diisocyanate (MDI) and 1,4-butanediol (BD) as the hard segments.⁴⁸ They found that the quantity of hard segments severely affected the shape-memory behavior and mechanical properties of the synthesized SMPUs. In another study, Lin and Chen⁴⁹ synthesized SMPUs using poly(tetramethylene oxide glycol) (PTMO) as soft segments. They stated that using a greater content of hard domains (MDI + BD) led to higher T_g and better compatibility between the soft and hard domains. It is worth noting that the entropy change caused by the glass to rubber phase transition is much lower than that of the solid to liquid phase change, so using T_m as the switching temperature is preferable for achieving larger strain recovery.³⁹

Physically crosslinked thermoplastic SMPs can also be obtained by melt blending a thermoplastic

SMP with a miscible polymer or directly blending an amorphous polymer with a semicrystalline polymer. The most common examples are TPU/phenoxy resin⁵⁰ and TPU/polyvinyl chloride (PVC)⁵¹ blends, in which the polycaprolactone (PCL) segment of TPU is miscible with phenoxy resin and PVC. In the obtained compounds, the PCL/phenoxy resin and PCL/PVC regions acted as reversible soft segments and the ratio of their composition affected the switching temperature. Additionally, Mather et al.⁵² developed new SMPs by blending a semicrystalline polymer [PLA or poly(vinylidene fluoride) (PVDF)] with an amorphous polymer [polyvinyl acetate (PVAC)]. All the blends ratios showed only a single T_g and demonstrated good shape-memory properties.

Some semicrystalline homopolymers such as PCL and polylactic acid (PLA) are also candidates for physically crosslinked SMPs. The crystals and amorphous domains of these polymers serve as hard and switching segments, respectively. Using the melt blending technique, researchers produced PLA/TPU blends at different weight ratios and studied the shape-memory properties of the developed materials.^{53,54} They found that, compared with pure PLA, the blended composition exhibited improved shape-memory properties. A schematic of the polymer network architecture for physically crosslinked SMPs is depicted in Fig. 3b.

Covalently Cross-Linked SMPs Unlike thermoplastic shape-memory polymers, chemically cross-linked polymers (thermoset polymers) generally cannot be reshaped after curing, because their primary shape is fixed during processing. In contrast to physically cross-linked polymers, these chemically cross-linked materials have a better degree of shape recovery. This is because the covalent bonds are stronger than ionic or hydrogen bonds and no slippage (creep) occurs between polymer chains in SMPs with covalent crosslinks. Thermoset SMPs can be obtained by synthesis or postpolymerization techniques including ionizing radiation and chemical cross-link creation.⁵⁵ However, ionizing radiation may cause chain scission rather than crosslinking. Zhu et al.⁵⁶ studied the effect of γ -radiation on the formation of crosslinks in PCL polymer with different molecular weights. They found that increasing the radiation dose led to bond cleavage in the polymer chains, which severely degraded the mechanical properties.

Shape-memory thermosets with $T_{\text{Trans}} = T_g$ are often called glassy thermosets, and an example is a soybean oil polymer obtained by a cationic copolymerization and chemical cross-linking procedure of natural soybean oil with styrene (crosslinking agent) and ethylvinylbenzene.^{57,58} Fengkui and Larock⁵⁷ found that only soybean oil polymers with stable crosslinks and T_g higher than ambient showed good shape-memory properties. Since these polymers are derived from natural sources, they

have potential for use as biomaterials in biomedical applications.

In shape-memory thermosets with $T_{\text{trans}} = T_m$, the reversible phase is fixed by crystallization, resulting in faster shape recovery compared with those glassy shape-memory thermosets in which the secondary shapes are fixed by vitrification. Three important materials in this category are bulk polymers, hydrogels with separated crystalline regions, and semicrystalline rubbers. By applying ultraviolet (UV) radiation, Lendlein et al.⁵⁹ synthesized a biodegradable multiblock copolymer with shape-memory properties consisting of two different biocompatible compounds: oligo(ϵ -caprolactone) dimethacrylates with different molecular weights as crosslinkers and *n*-butyl acrylate as a comonomer. In this system, the oligo(ϵ -caprolactone) acts as the reversible segments and can fix the secondary shape, while the *n*-butyl acrylate comonomers with methacrylate end groups of PCL diol form the permanent covalent crosslinks, giving rise to the permanent shape. In this SMP developed by Lendlein et al., the melting temperature of the PCL segments defines T_{Trans} and controls the shape recovery temperature. Another example in this category of SMPs is chemically crosslinked transpolyisoprene (TIP), exhibiting a degree of crystallinity of 40% and melting temperature of 67°C.⁶⁰ By adding peroxide compounds, this polymer was chemically cross-linked into a three-dimensional network which was responsible for maintaining the permanent shape. A schematic of the polymer network architecture in chemically crosslinked SMPs is depicted in Fig. 3c.

BIOMEDICAL APPLICATIONS OF SMMS

Biomedical Applications of SMAs

NiTi SMAs are the most widely used SMAs in the biomedical field due to their excellent functional properties (SME and PE), including large recovery strains up to 8% by unloading and heating.⁶¹ In addition, NiTi is a suitable material for biomedical applications due to its excellent biocompatibility,^{62,63} high corrosion resistance,⁶⁴ low stiffness,⁶⁵ and good compatibility with magnetic resonance imaging and computer tomography scanning.⁶⁶ NiTi also has a lower elastic modulus compared with other conventional metallic biomaterials. Thus, the modulus is more similar to human bones, which is important for minimizing bone stress shielding and promoting bone healing. Figure 5 shows a comparison of the stress–strain curves of two commonly used metallic biomaterials with human bone.⁶⁷ It can be clearly seen that NiTi shows similar deformation behavior to bone and is capable of high recovery strain up to 8%. This illustrates that NiTi implants can exhibit biomimetic behavior under loading–unloading conditions in the human body. Moreover, NiTi exhibits excellent corrosion behavior due to a self-repairing passive film that is not

Fig. 5. Schematic stress–strain curves of stainless steel, Nitinol, and bone (reprinted with permission from Ref. 72).

substantially affected by deformation in the pseudoelastic and plastic regimes.⁶⁸ Finally, the human body is an ideal isothermal environment for controlling the occurrence of the SME and PE.⁶⁹ Therefore, NiTi alloys have been used in many biomedical fields including orthopedics, endodontics, orthodontics, neurology, vascular, and medical instruments.^{70,71} Table I lists some major biomedical applications of NiTi, and some typical applications are shown in Fig. 6.

In 1971, the first orthodontic archwires made from NiTi were introduced by Andreasen and Hilleman.^{125,126} They were identified as a more effective alternative than traditional stainless steel and Co-Cr wires for teeth alignment due to the pseudoelasticity properties of NiTi. Since then, extensive research has been published on the properties and clinical use of NiTi.^{124,127} Nowadays, the main applications of NiTi in orthodontics focus on archwires, palate expanders, as well as dental drills and fixators. Results from these applications show that NiTi improves the clinical performance of these devices. Additionally, it is well known that high-magnitude, discontinuous forces can cause hyalinization, a deleterious process resulting from tissue disintegration.⁶⁹ In this regard, the success of NiTi in orthodontic applications largely stems from its ability to generate constant and lighter forces during the insertion and positioning process. This is mainly because NiTi can be used in its pseudoplastic state where stress is not significantly increased by strain increments, and this unique property of NiTi can help protect the underlying equipment and reduce patient discomfort.

In the orthopedic field, essential requirements for effective connection between two disjointed bone segments are stable fixing and proper compression between the bones. Fixation devices are introduced to treat fractured bones by helping to support the bones as well as maintain correct and stable alignment during healing.¹²⁸ Fixation devices should also be minimally invasive and biocompatible. NiTi can meet all these requirements, and the SME of NiTi has been exploited extensively in applications such as staples and plates. At ambient temperature

Table I. Current and potential applications of NiTi

Field	References	Field	References
<i>Orthodontics</i>		<i>Orthopedics, bulk devices</i>	
Archwires/braces	73,74	Staples	75,76
Palatal expander	17	Plates	77
Dental drills	78	Intramedullary nail	79
Fixators	80	Patellar concentrator	81
Dental prostheses and implants	82	Spinal vertebrae spacer	77,84
Distracters	83	Correcting rod to treat scoliosis	85–87
<i>Neurosurgery</i>		Rings	88
Stents	89	<i>Orthopedics, porous devices</i>	
Coils	17,90	Bone implant	63,92
Microguidewires	17,91	Colorectal surgery	
Microforceps	93	expansion device	95
Brain spatulas	94	ColonRing	96,97
<i>Vascular</i>		Artificial muscles (actuated device)	100,101
Devices for closing ventricular septal defects	98,99	<i>General surgery</i>	
Venous filter	102–104	Radiofrequency interstitial tissue	78
		ablation device	
Percutaneous treatments for valve disease	105	Tools for laparoscopy	108
Stent graft	106,107	Retrieval basket	111
Self-expandable vascular stents	109,110	Catheters/snares	113
Membranes (eNitinol)	112	<i>Urology</i>	
<i>Otolaryngology</i>		Urethral and prostatic stents	116
Stapes prosthesis	114,115	SMA-activated sphincters	118
Ear reconstruction framework	117	<i>Ophthalmology</i>	
Tracheal cartilaginous framework	119	Clips	120
<i>Gynecology and andrology</i>		Dynamic plug for extremely complicated	122
		myopia	
Homer Mammalok used to locate breast tumors	121		
Coil in conceptus	123		
Needles in prostate ablation device	78		

T ($T \leq M_f < A_f$), NiTi plates are in the martensite phase and can be easily deformed and inserted into the body. When installed and maintained at body temperature, the device takes advantage of the phase transformation into austenite to produce a constant stress which consequently closes and compresses the two fractured bones. In addition to bulk NiTi devices, porous NiTi has been considered as a promising candidate for orthopedic applications. Porous NiTi is characterized by low density, high surface area, and high permeability, which are beneficial characteristics to enhance bone growth and improve fluid transportation.¹²⁹ The high strength and high toughness of NiTi also help prevent undesired deformation and avoid brittle failure of porous NiTi devices. Although the toxicity of Ni in NiTi has been under debate for some time, it has been reported that the Ni content released from NiTi remains in a safe range in tissues and no significant increase is observed in blood, demonstrating the good biocompatibility properties of NiTi without any cytotoxicity or genotoxicity reactions.¹³⁰ Porous NiTi exhibits relatively lower stiffness (lower effective elastic modulus), which is critical to minimize the risk of stress shielding.¹³¹ However, due to the poor machinability and

compositional sensitivity of NiTi, fabrication of porous NiTi is challenging using conventional processing techniques.

The application of NiTi SMAs has also made great contributions to the vascular surgery field and boosted the development of noninvasive surgery. The main applications of NiTi in this field are catheters and guidewires, embolic filters and stents.¹⁷ The SME of NiTi alloys has been used in numerous applications of self-expandable vascular stents. They are superior to conventional stainless-steel or Cr-Co stents due to their easier operation and lower risk of damage to vascular tissue. One challenge in this field is the occurrence of fatigue fractures resulting from systolic pressure cycles and leg movements. However, the nonlinear nature of the pseudoelastic effect and the unique surface condition and material characteristics arising from the manufacturing methods for these NiTi devices have made it difficult to investigate their fatigue behavior in vivo.⁷¹ Therefore, further efforts are needed to understand and thereby improve the fatigue resistance of NiTi devices.

Finally, the neurosurgery field also makes use of NiTi in coils, stents, and microguidewires. Clinical neurosurgery requires the exploitation of new

Fig. 6. Typical biomedical applications of NiTi: (a) orthodontic NiTi archwires (1) before and (2) after bracket engagement (reprinted with permission from Ref. 124), (b) NiTi self-expandable neurosurgical stent (reprinted with permission from Ref. 17), (c) NiTi plate for mandible fracture (reprinted with permission from Ref. 17), and (d) NiTi palatal expander (reprinted with permission from Ref. 17).

materials and novel structures to adapt to their small-dimension operation environment. In other words, instruments should be as small as possible and be able to eliminate unnecessary components as a consequence of simple design.⁶⁹ Due to the higher strain recovery and torsion resistance of NiTi, NiTi microguidewires have an advantage over other guidewires which suffer from severe kinking problems.

Biomedical Applications of SMPs

SMPs have a broad range of applications such as smart textiles,¹³² temperature sensors and actuators,¹³³ photonic nanostructures,¹³⁴ and micro foldable vehicles.¹³⁵ In recent years, more attention has been paid to the use of these smart polymers in the biomedical field including tissue engineering, drug delivery, endovascular surgery, orthodontics, and orthopedics. Biomedical polymers must be designed and synthesized from highly biocompatible and nontoxic compounds so that they can perform their functions without any immune-inflammatory reactions. The other considerations for designing biomedical SMPs are their biodegradability/biostability, mechanical properties, and activation mechanisms. Among different activation mechanisms, thermo-induced SMPs with transition temperatures near the human body temperature (37°C) are the most widely investigated polymers for biomedical

applications.^{136,137} Use of biomedical SMPs with switching temperature above or below body temperature will result in suboptimal performance of the implanted medical devices. Alternatively, remote triggering mechanisms such as infrared (IR), laser, ultrasound, etc. can be used to overcome this obstacle and stimulating the SME.^{138,139} Other approaches such as incorporating functional fillers and magnetic nanoparticles into the polymer matrix are also available, so that (by using an external magnetic field) the implanted device can be triggered inside the human body at the desired temperature and location.

Aliphatic polyester-based SMPs are widely used for various biomedical applications, such as resorbable implants, sutures, and wound closures due to their tunable physical and mechanical properties.¹⁴⁰ One application of SMPs is in biodegradable smart sutures for wound closure (Fig. 6a).¹⁴¹ In endoscopic suturing, defect closure has long been a significant obstacle, as the wound's edges must be brought together with an optimal stress to achieve ideal primary wound closure. If the knot of the suture is fixed by a force stronger than this optimal value, tissue necrosis may occur,¹⁴² while exerting weaker forces will lead to formation of scar tissue and potential hernias.¹⁴³ As a possible solution to achieve ideal wound healing in endoscopic surgery, Lendlein and Langer¹⁴¹ introduced a biodegradable

smart thermoplastic suture based on oligo(ϵ -caprolactone) diol which can be first stretched outside the body at a controlled force and then tied inside the wound and finally shrunk and tightened at body temperature (Fig. 7a).

The unique characteristics of SMPs provide a tremendous opportunity for the design of self-fitting tissue scaffolds to treat irregularly shaped bone defects. Zhang et al.¹⁴⁴ fabricated a PCL diacrylate-based SMP scaffold with the ability to conform to a craniomaxillofacial bone defect (Fig. 7b). By heating

the scaffold to a temperature above T_{Trans} (55°C), the scaffold first became soft and malleable. Then, the scaffold was fit into a model defect using manual pressure. After removing the exerted force, the scaffold was expanded to fill the irregular shape. Following this, the scaffold returned to its rigid state upon cooling, and finally the scaffold was locked within the irregular defect.

The application of biodegradable SMPs for the treatment of vascular diseases such as aneurysms has attracted increasing attention in recent years.

Fig. 7. Applications of SMP-based medical devices: (a) (1) tightening the biodegradable suture when heated up to 40°C , (2) wound closure in animal experiment (reprinted with permission from Ref. 175); (b) (1) the malleability of self-fitting foam after heating up to its T_{trans} , (2) the foam is fit into the irregular defect model, (3) after cooling the foam is removed from defect area (reprinted with permission from Ref. 144), (c) (1) SMP foam before and after being expanded into an aneurysm sac, (2) healing process of a vein pouch aneurysm model (reprinted with permission from Ref. 145), (d) orthodontic archwires (reprinted with permission from Ref. 148).

An aneurysm is a balloon-like bulge on a blood vessel wall which is at risk of rupture and uncontrolled internal bleeding in patients. One of the most common endovascular methods for the treatment of these arterial abnormalities is to use a soft platinum coil to fill the aneurysm area and isolate it from the normal blood circulation.¹⁴⁵ However, there are some problems associated with these coils, including lower filling volume compared with the total aneurysm volume, an immune reaction to the bare platinum coils, and unstable placement of the coil in the aneurysm sac, which makes such coils beneficial only for the treatment of small-sized aneurysms (smaller than 4 mm).^{146,147} Thermally sensitive shape-memory polyurethane foams have been recently introduced as an alternative to platinum coils to eliminate the risks associated with the material type and coil design. By using a catheter, a temporary and small-sized foam can be positioned in the aneurysm sac. Then, via thermal stimuli, it can be expanded to fill the cavity. Rodriguez et al.¹⁴⁵ implanted a shape-memory polyurethane (SMPU) foam into a porcine cerebral aneurysm model (Fig. 7c). Their pathological results showed that, compared with other materials such as platinum, silk, or polypropylene, the shape-memory polyurethane-based filling devices exhibited only a mild chronic inflammatory response, proving their satisfactory biocompatibility.

SMPs are also used as archwire materials for orthodontic applications. Compared with metallic orthodontic wires, transparent PU polymers offer an improved esthetic effect as well as biocompatibility. Jung and Cho¹⁴⁸ prepared a PCL-based SMPU wire and studied its orthodontic behavior using a dental model. First, the polymeric wire was stretched at 65°C to a length of 1.5 times longer than its original length, then it was cooled down to room temperature. Following this, the elongated wire was attached to the brackets and heated above T_{Trans} (40°), which triggered the shape recovery of the wire (to its original length) between the brackets, leading to the movement of teeth to achieve acceptable alignment (Fig. 7d). A summary of current and potential applications of SMP-based medical devices is presented in Table II, while several applications of SMP-based medical devices are depicted in Fig. 7.

ADDITIVE MANUFACTURING OF SMMS FOR BIOMEDICAL APPLICATIONS

Additive manufacturing (AM) is a layerwise material processing technology which can build net-shaped and geometrically complex components. In contrast to conventional subtractive and formative manufacturing technologies, AM produces components by incrementally building hundreds or thousands of layers.¹⁷⁶ AM was initially considered as an innovative prototyping technique but has now moved into the mainstream for product design and

fabrication in the biomedical field after a decade-long development period.^{177–179} In addition to its ability to produce customized and complex structures,¹⁸⁰ AM is also a fast production route from computer-aided design (CAD), which results in reduced resource and material usage. Therefore, it is considered to be a cost-effective, energy-effective, and environmentally friendly manufacturing process.¹⁸¹

Using SMMs as the layering material in AM has driven 3D printing to another level, known as four-dimensional (4D) printing,^{182,183} defined as “3D printing + time,” with the fourth dimension being time. While most 4D printing methods to date have used polymers,¹⁸⁴ 4D printing of nickel-titanium shape-memory alloy parts via multiple shape recovery stages with the capability of being activated at different temperatures was reported very recently.^{185,186}

AM Techniques for SMA-Based Medical Devices

Current AM techniques for producing NiTi-based SMAs used for biomedical applications can be categorized into two groups: (1) powder bed fusion-based technologies, e.g., selective laser melting (SLM), selective laser sintering (SLS), and electron beam melting (EBM), and (2) directed energy deposition methods, e.g., laser engineered net shaping (LENS). Powder bed fusion techniques use a laser or electron beam as the energy source to fuse powder particles of a material in selected areas on the powder bed. In general, these techniques have an advantage over other metal AM techniques in manufacturing small and complex parts with high dimensional accuracy. Therefore, powder bed fusion techniques have been considered to be very promising to achieve the highly complex and fine structures with strictly controlled mechanical and functional properties required for biomedical applications.¹⁸⁷

The emergence of AM techniques for SMAs is anticipated to boost the application of SMAs in orthopedic and dental fields; for example, AM enables the production of SMA devices that mimic the porous and permeable hierarchical architecture of bone via porous scaffold structures, which are very difficult to fabricate using conventional manufacturing techniques.⁹⁰ Such porous scaffold structures can provide suitable spaces for cells to attach, grow, and differentiate into functional tissues or organs, resulting in better bone ingrowth and osseointegration.¹⁸⁸ In addition, dense metal implants usually demonstrate highly homogeneous and isotropic stiffness (Young's modulus) which result in lower load transfer to surrounding host bones. This phenomenon is described as stress shielding and causes weakening of adjacent bones, which can lead to premature implant loosening or failure.¹⁸⁹ By designing and producing porous

Table II. Current and potential biomedical applications of SMPs

	Materials	References
<i>Tissue engineering</i>		
2D and 3D scaffolds	PCL, PLA, PU, poly(D,L-lactic acid-co-ethylene glycol-co-D,L-lactic acid) (PELA), poly(lactic-co-glycolic acid) (PLGA) + poly (lactide-co-caprolactone) (PLCL) blends	144,149–152
Cell culture platforms	PCL	153,154
<i>Stents</i>		
Tracheal stent	PCL dimethacrylate	155
Neurovascular stent	PU	156,157
Coronary stent	PLLA, PLGA, PCL + PU blends, PU	54,158–160
Ureter stent	Oligo[(ϵ -caprolactone)-co-glycolide]-dimethacrylates	161
Biliary stent	PLLA	162
<i>Wound closure</i>		
Bioabsorbable suture	Multiblock copolymer consisting of oligo(ϵ -caprolactone) and oligo(p -dioxanone) diols	141
Surgical staples	Poly(L-lactide-glycolide-trimethylene carbonate)	163
Annulus fibrosus closure device	Crosslinked poly(D,L-lactide-co-trimethylene carbonate) diols with methacrylate groups	164
<i>Embolization</i>		
Aneurysm occlusion	PU	145,165–167
Vascular occlusion	Polyethylene glycol (PEG), PU	168
Fallopian tube occlusion	PDLLA-based PU	169
<i>Orthodontics</i>		
Arch wires	PCL-based TPU	148
<i>Orthopedic</i>		
Spinal disc	PLGA-PEG-PLGA	170
<i>Others</i>		
Nerve conduit	PLGA	171
Clot removal devices	PU	172
Drug delivery devices	PU, PLGA	173,174

structures for metal implants, their stiffness can be reduced to a value similar to bone, leading to improved load transfer between implants and bones, mitigation of the stress shielding problem, and ultimately increased service efficiency of the fabricated metal implants. To improve the interfacial bond strength and reduce the Young's modulus mismatch between bones and implants, as well as better match the mechanical properties of human bone, porous NiTi should be designed with an optimized porosity level, pore size, shape, and distribution. Examples of how these can be controlled with AM are shown in Fig. 8, while Table III highlights some studies generating different NiTi porous structures and their key properties using various AM methods. The following sections discuss the most widely used AM techniques for producing NiTi implants: SLS, SLM, and LENS. Due to the high-vacuum condition inside EBM machines and considering the high affinity of NiTi to oxygen, EBM may be a promising AM technique to fabricate NiTi with minimized oxygen influence. However, to date, no studies on EBM of porous NiTi for biomedical applications have been reported. However, some studies have been conducted to explore various aspects of dense NiTi manufactured by the EBM

process. Zhou et al.¹⁹⁰ investigated the microstructure, phase transformation, and mechanical properties of EBM-printed NiTi parts and reported excellent and stable superelasticity for the printed samples. It is worth noting that EBM-NiTi has superior tensile performance compared with the NiTi parts fabricated by SLM or LENS.

Selective Laser Sintering

A schematic illustration depicting the selective laser sintering (SLS) technique is shown in Fig. 9a. In the SLS process, powder particles in each layer are selectively sintered together by using a scanning laser. Shishkovsky et al. produced NiTi implants by the SLS technique (Fig. 9c) with an energy input of 100–300 J/cm².^{198,199} Figure 9b shows the microstructure of the SLS-fabricated NiTi samples after cell infiltration for 3 months using scanning electron microscopy (SEM). It was found that the bone closely bonded to NiTi and the controllable open-cell structure of the porous NiTi implant promoted the ingrowth of the surrounding bone tissue into the implant, resulting in good tissue tolerance and firm fixation to the bone.¹⁹⁸ Nickel was not observed on the surface of NiTi, and there

Fig. 8. (a) Porous NiTi structures and their octahedron cell design (reprinted with permission from Ref. 197). (b) Porous NiTi structures and their unit cell design (1) octahedron, (2) cellular gyroid, and (3) sheet gyroid (reprinted with permission from Ref. 194). (c) Optical microscopy for NiTi porous structures: (1) dense, (2) 32%, (3) 45%, and (4) 58% (reprinted with permission from Ref. 192). (d) Images of NiTi porous structures: (1) SC-58% porosity, (2) SC-45% porosity, (3) SC-32% porosity, (4) BCC-Z, and (5) BCC (reprinted with permission from Ref. 193).

Table III. Previous studies on mechanical properties of NiTi porous structures fabricated by different AM methods

Material	AM methods	Type of unit cell	Porosity (%)	Mechanical properties	Refs.
Ni55.2-Ti44.8 (wt.%)	SLM	Octahedron	56-78	—	191
Ni50.8-Ti49.2 (at.%)	SLM	Simple cubic (SC)	32/45/58	Young's modulus: 9–18 GPa Recoverable strain: 1st cycle: 2.7–4% Last cycle: 1.75–2.75%	192
Ni50.1-Ti49.91 (at.%)	SLM	SC, BCC, BCC-Z	32/45/58/65/69	Elastic modulus: 16.5–41.2 GPa Recoverable strain: First cycle: 3.4–5.07% Last cycle: 0–1.95%	193
Ni-55.2 wt.%	SLM	Octahedron, cellular gyroid, sheet gyroid	74.8/74.8/73.4	Yield strength: 21–44 MPa	194
NiTi	LENS	—	12–36	Young's modulus: 2–18 GPa Recoverable strain: 2–4%	195
Equiatomic (50:50 at.%) NiTi	LENS	—	2/10/20	0.2% proof stress: 368 ± 60 to 971 ± 20 MPa?	196

Fig. 9. (a) Schematic illustration of SLS (reprinted with permission from Ref. 201). (b) Microstructures of NiTi implants after 3 months of bio-integration experiments (reprinted with permission from Ref. 198). (c) NiTi implant fabricated by the SLS technique (reprinted with permission from Ref. 199).

was pronounced cell adhesion and a high density of cells in the presence of the implant, proving that SLS can produce NiTi implants without cytotoxicity.²⁰⁰

Selective Laser Melting

Selective laser melting (SLM) is very similar to SLS (Fig. 9a). The main difference is that SLM has a much higher laser energy density, which enables full melting of the NiTi powder.²⁰¹ Both dense and porous NiTi has been produced by SLM, and the mechanical properties such as elastic modulus and ductility are highly dependent on the porosity and pore structures.¹⁹³ Figure 10a shows the stress-strain curves of NiTi with 32%, 45%, and 58% porosity. The elastic modulus of NiTi decreased with increasing porosity. After cycling, all the porous samples showed stabilized SME with recoverable strain of 5%. Saedi et al.¹⁹² tested the pseudoelastic response of porous NiTi at body temperature. NiTi with porosity of 32% and 45% showed strain recovery of 3.5% and 4% in the first cycle, respectively,

and both showed full strain recovery of 2.75% in the last cycle. In comparison with the elastic modulus of 47 GPa for SLM-fabricated dense NiTi, the elastic modulus of SLM-fabricated porous NiTi structure was reduced to 9 GPa by introducing 58% porosity. Apparently, the higher mechanical strength and continuous connectivity between adjacent unit cells rendered porous NiTi with good SE property and reduced elastic modulus. However, the presence of pores can decrease the strength of the fabricated NiTi porous structures.¹⁹² SLM is also capable of processing layer-structured NiTi alloys in which an alternating austenite/martensite microstructure can be obtained in a specified temperature range. The gradual transformation of austenite phase into martensite during cooling results in high damping performance of printed samples.²⁰² The potential application of this unique property in the biomedical field is worth further investigation.

Additionally, the assessment and improvement of fatigue life is critical for many biomedical applications of SLM-fabricated NiTi. Speirs et al.¹⁹⁴

Fig. 10. (a) Stress–strain curves of cycling tests of NiTi with 32%, 45%, and 58% porosity (reprinted with permission from Ref. 193). (b) Absolute (1) and normalized (2) S–N curves for sheet gyroid, octahedron, and cellular gyroid (reprinted with permission from Ref. 194), (c) Fluorescence micrographs of porous NiTi with incubation of hMSC (green = living cells, red = dead cells, scale bar 1 mm) (reprinted with permission from Ref. 204).

studied the fatigue behavior of different NiTi porous structures and found that the triply periodic unit cell presented superior resistance compared with

the octahedron unit cell (Fig. 10b). Triply periodic minimal surfaces (TPMS) are minimal surfaces which necessarily have zero mean curvature and

periodic structures in three coordinate axes.²⁰³ Hence, this result can be attributed to the removal of nodal points which can be regarded as stress concentrators for crack initiation.¹⁹⁴ Furthermore, other adverse stress-concentrating defects such as residual particle attachment and the staircase effect can also be minimized by TPMS designs.

Ni is a known toxic element. Therefore, it is important to minimize Ni release from the fabricated NiTi structures inside the human body after implantation, and the concentration of Ni should be well controlled to a level which is significantly lower than the cytotoxic concentration of 25×10^6 ng/ml.⁶¹ Habijan et al.²⁰⁴ studied the response of human mesenchymal stem cells (hMSC) when cultivated on SLM-fabricated NiTi (Fig. 10c). It was found that, after 8 days of incubation, a large number of viable cells were observed not only on the surface of implants but also inside the pores. These results showed that the Ni ion release was drastically below the cytotoxic level, indicating that SLM is an attractive manufacturing technique for NiTi structures for biomedical applications.

Laser Engineered Net Shaping

Laser engineered net shaping (LENS) is a directed energy deposition technique. In a LENS machine, a laser beam acts as the energy source to generate a melt pool on a substrate. A specified amount of material is injected into this melt pool and solidifies rapidly as the laser beam moves away, leading to the formation of a thin layer of material that is strongly attached to the substrate. After the formation of each layer, the laser head moves up vertically, leading to the creation of a new layer. Similar to SLS and SLM, the LENS process is characterized by a high solidification rate in the range of $\sim 10^3$ – 10^5 K/s and is able to produce fully dense products containing strongly bonded particles.¹⁸⁷ Also, LENS is believed to enable the fabrication of porous and functionally graded parts for use as biomedical implants.¹⁹⁵ A schematic illustration of the LENS system along with some examples for LENS fabricated NiTi parts are shown in Fig. 11. LENS has been used to produce NiTi parts with porosity of 12–36%. These porous NiTi alloys samples exhibited low Young's modulus between 2 GPa and 18 GPa as well as high compressive strength and up to 4% recovery strain.¹⁹⁵ The porosity has a significant effect on the maximum recovery strain, which decreases from 6% to 4% with an increase in the pore volume from 12% to 36%. Furthermore, LENS-produced samples with varying porosity (1%, 10%, and 20%) have been found to maintain cyclic compression fatigue stresses up to 1.4 times their yield strength for 10^6 cycles without failure (Fig. 11c).¹⁹⁶ In terms of biocompatibility, LENS-fabricated NiTi was anodized for different lengths of time in H_2SO_4 at different pH values and then assessed for in vitro cell–material

interactions using a human fetal osteoblast cell line (hFOB). This anodization treatment was found to successfully improve the cell–material interactions and also reduce the Ni release (Fig. 11b).²⁰⁵

AM Techniques for SMP-Based Medical Devices

The main AM techniques that have been used for fabrication of smart polymer-based medical devices are stereolithography (SLA) and fused deposition modeling (FDM). Schematic representations of the SLA and FDM fabrication processes are shown in Fig. 12.

Stereolithography

SLA is based on photopolymerization of a liquid thermoset resin. In the SLA process, a UV laser beam is controlled by a computer to scan predefined paths and, then 2D pattern is cured and hardened on the surface of the resin. Once the first layer has polymerized, the platform (z-axis) is lowered by 50–200 μ m, allowing the cured layer to be recoated with liquid resin. This process (curing each layer and platform movement) is repeated until the whole 3D object has been printed. Depending on the resin used, a postpolymerization process may also be required. Different types of thermoset photopolymers can be used for both SLA and micro-SLA printers, all of which are based on multifunctional and low-molecular-weight monomers (normally reactive oligomers).²⁰⁸ The most commonly used photosensitive monomers are low-molecular-weight acrylates and epoxy monomers.²⁰⁷ The resins also include an inhibitor, photoinitiator, and light absorber to prevent over curing of the resin and control the depth of polymerization. In recent years, researchers have developed various types of synthetic resins for biomedical applications, including thermoset biopolymers with shape-memory properties.

For example, Zarek et al.¹⁵⁵ synthesized a PCL dimethacrylate shape-memory resin. Using a UV-LED SLA printer and an MRI scan to provide anatomical data, they fabricated a personalized tracheal stent (Fig. 13a). When the ink was exposed to a UV laser beam, a cross-linked network containing both crystalline and soft domains was formed. The melting temperature of the crystalline segment was 55°C, dropping to 47°C after crosslinking. For the printed endoluminal device, the authors reported a strain fixity rate of 99% and a strain recovery rate of 98% after three cycles. Another medical application proposed by Zarek et al.²⁰⁹ for SLA printing of SMPs was cardiovascular stents (Fig. 13c). Firstly, they synthesized PCL-based macromethacrylates with different methacrylation degrees, all of which exhibited strain fixity and recovery rates greater than 98% and 93%, respectively. Using a high-resolution SLA technique, they successfully fabricated different vascular stents

Fig. 11. (a) Schematic illustration of LENS (reprinted with permission from Ref. 205). (b) Ni ion release from NiTi alloys with and without anodization (reprinted with permission from Ref. 205). (c) Results of fatigue testing for LENS-fabricated NiTi (porosity 1%, 10%, and 20%) (reprinted with permission from Ref. 196). (d) LENS-fabricated NiTi samples (reprinted with permission from Ref. 206).

with intricate designs and strut thicknesses of about $600\ \mu\text{m}$.

Miao et al.²¹⁰ developed a novel renewable soybean oil epoxidized acrylate resin with two types of chemical groups, hydroxyl and ester groups. They used the liquid resin for multidimensional SLA printing of biomedical bone scaffolds (Fig. 13d). First, they optimized the SLA process by studying the effect of the laser frequency and printing speed on the geometric properties of the cured soybean oil-based ink. Then, by performing Fourier-transform infrared (FTIR) analysis, the polymerization of the synthesized resin was confirmed. Their study on the shape-memory properties of this synthesized thermoset indicated that the polymerized resin showed an excellent thermally sensitive SME. The temporary shape of the printed scaffolds was fixed at -18°C , and the permanent shape was fully

recovered after being immersed in 37°C phosphate-buffered saline (PBS). Cytotoxicity analysis also indicated the biocompatibility of the synthesized SMP with human bone marrow mesenchymal stem cells (MSCs), proving the potential for scaffold-assisted tissue applications.

In another study, Miao et al.²¹¹ proposed a novel sacrificial molding method for processing unprintable shape-memory thermosets. First, they mixed a specified amount of PCL triol, castor oil, and a crosslinker, to achieve a series of PCL-based polyurethane resins with tunable shape-memory properties. Following this, the sacrificial PLA molds with different infill density were FDM printed then filled with a heated mixture for curing and synthesizing the polymer. The PLA mold was then dissolved in dichloromethane, leaving behind the interconnected scaffolds with graded porosity (Fig. 13e). Using

shape-memory tests, the authors found that the smart scaffolds exhibited rapid and full shape recovery at physiological temperature and shape fixity greater than 92% at temperature of -18°C or 0°C . MSC colonization results also showed that the SMP scaffolds exhibited better biological properties (cell attachment and proliferation) compared with the PCL scaffolds.

In another example, Lantada et al.²¹² used a shape-memory epoxy resin known by the trade name Accura[®] 60, and optimized the SLA technique for fabrication of intricate microvascular actuators (Fig. 13b) in a single-step SLA process. Finally, a shape-memory polyurethane acrylate and acrylate-based tBA-co-DEGDA network has recently been synthesized and fabricated using SLA.²¹³ The results demonstrated excellent shape-memory performance, high printability, and good UV-curing behavior for the developed shape-memory thermosets.

Fused Deposition Modeling

Fused deposition modeling (FDM), also known as fused filament fabrication (FFF), is another AM technique suitable for thermoplastic SMPs. FDM technology is a relatively user-friendly, simple, and low-cost 3D printing method based on the extrusion of a polymeric filament through a heated nozzle to deposit layers on a substrate. Hence, a 3D object can be printed layer by layer (Fig. 12b). A wide range of both pure polymers and polymer-based composites can be melt-extruded and used as a filament for FDM of implants and medical devices.²¹⁴ In the field of SMPs, FDM printing of PLA and polylactide-co-

Fig. 13. (a) (1) MRI scan of tracheobronchial tree in a middle-aged male and SLA-printed tracheal stents, (2) SME of a personalized endoluminal stent (reprinted with permission from Ref. 155). (b) SLA-printed microvascular SMP device (reprinted with permission from Ref. 212). (c) Stages of shape recovery for a cardiovascular stent model upon heating above 70°C (reprinted with permission from Ref. 209). (d) (1) SEM and optical images of soybean oil-based scaffolds, (2) confocal microscopy of seeded hMSCs on scaffolds (reprinted with permission from Ref. 210). (e) SMP scaffold fabricated by sacrificial molding method: (1) printed scaffold compared with a cent, (2) SEM image of the pore distribution in the scaffold, (3) varied pore diameters in different directions, (4) potential for minimally invasive application, and (5) confocal microscopy of seeded hMSCs on scaffolds compared with PCL control scaffold (reprinted with permission from Ref. 211). (f) (1) PLA and (2) PLA/HA porous scaffolds after the second and third heating-compression cycle, respectively (reprinted with permission from Ref. 215), (3) optical microscopy of MSC colonization on the surface of PLA/HA scaffolds (reprinted with permission from Ref. 149).

poly(ethylene glycol) (PELA) has been reported by various research groups.

Senatov et al. conducted a series of research studies on the shape-memory and mechanical properties of both pure PLA and PLA/15 wt.% hydroxyapatite (HA) composite bone scaffolds (Fig. 13f) fabricated by FDM.^{149,215,216} The average porosity and pore size of the scaffolds was 30 vol.% and $700\text{ }\mu\text{m}$, respectively. They indicated that the physical entanglement of long PLA chains acts as netpoints to fix the permanent shape. Furthermore, the polymer chains between the physical entanglement can be stretched during the deformation step and form the temporary shape. Hydroxyapatite is the type of calcium phosphate naturally occurring in bone and teeth and is extensively used in bone scaffolds for regenerative medicine due to its

Fig. 12. Schematic illustrations of (a) the stereolithography (SLA) additive manufacturing process and (b) the fused deposition modeling (FDM) additive manufacturing process (reprinted with permission from Ref. 207).

Fig. 13. continued.

outstanding bone-bonding ability, biocompatibility, bioactivity, and osteoconductivity.²¹⁷ Senatov et al.²¹⁵ indicated that the presence of dispersed HA particles in the PLA matrix acted as nucleation sites and additional rigid phases, affecting the ordering of the PLA molecular chains during the heating process and governing the thermal and mechanical properties of the material. The authors also reported a larger storage modulus for composite scaffolds, indicating that a larger shape fixity and shape recovery would be obtained during the shape-memory activation mechanism. Using the cyclic thermal mechanical compression test, they concluded that the PLA/HA composite could withstand three compression-heating-compression cycles with shape recovery of 98%, while the pure PLA samples failed at the second cycle. Furthermore, it was found that, when the composite scaffold was under cyclic loading, the presence of HA particles decreased the defect accumulation rate and prevented crack propagation. Senatov et al.¹⁴⁹ seeded mesenchymal stem cells (MSCs) onto pure PLA and PLA-HA composite scaffolds and found that the FDM-printed PLA/15%HA scaffolds exhibited excellent cell adhesion and proliferation properties (Fig. 13f-3) and could be used as clinically viable self-fitting implants for bone tissue regeneration.

In another study, Kutikov et al.¹⁵¹ synthesized a thermoplastic amphiphilic triblock copolymer poly(D,L-lactic acid-co-ethylene glycol-co-D,L-lactic acid) (PELA) by a melt ring-opening polymerization method. Then, they prepared PELA and HA-PELA composite films and studied the shape-memory and thermomechanical properties of the developed thermoplastic polymer. Furthermore, PELA and HA-PELA filament was extruded, and porous 3D scaffolds were printed by FDM. Amphiphilic polymers composed of hydrophobic and hydrophilic blocks exhibit shape-memory properties due to the phase segregation between the hydrophobic and hydrophilic phases.²¹⁸ The phase with higher thermal transition forms the hard segments and creates the physical crosslinks, while the other phase forms the switching soft segments. For the developed polymer, the melting temperature of the PEG component

defined the transition temperature, which was around $T_{\text{Trans}} = 50^{\circ}\text{C}$. The authors stated that incorporation of < 10 wt.% HA into the PELA had a negligible impact on the shape-memory properties. However, when adding a greater amount (about 20 wt.%) of HA, both high shape recovery ($> 90\%$) and tensile modulus were achieved. Both monolithic PELA and composite HA-PELA were deformed and programmed into temporary shapes at room temperature and exhibited rapid (< 3 s) shape recovery when immersed in 50°C deionized water. The same group studied the biological properties (adhesion and proliferation of MSCs and fibroblast cells) of shape-memory PELA and HA-PELA scaffolds fabricated by FDM.²¹⁹ They demonstrated that adding hydrophilic osteoconductive HA particles to the polymer matrix could improve the interfacial adhesion properties of the printed scaffolds. Hence, they concluded that FDM-printed PELA-HA scaffolds are a suitable candidate for minimally invasive biomedical applications.

Polyetheretherketone (PEEK) is another organic semicrystalline thermoplastic with excellent biocompatibility and mechanical properties. PEEK biomaterials are considered to be inert in biological environments, and their mechanical properties are not significantly affected by long-term exposure to the physiological environment, even under cyclic conditions,²²⁰ enabling their acceptance as alternatives to implantable metal materials.^{221,222} PEEK composites can also be used for both hip and knee bearing applications.²²³

A group of researchers studied the shape-memory properties of a commercial PEEK and reported a maximum recovery rate of 90% for a residual programming strain of 30%.²²⁴ So, they concluded that PEEK can be considered as an excellent high-temperature shape-memory polymer. Regarding processing PEEK with additive manufacturing techniques, successful FDM printing of PEEK structures was reported by Vaezi and Yang.²²⁵ By optimizing the FDM process, they studied the possibility of fabricating porous structures without delamination or polymer degradation and with appropriate mechanical properties. However, to

the best of the authors' knowledge, the SME in additively manufactured PEEK-based medical structures has not been investigated.

SUMMARY AND OUTLOOK

SMAs and SMPs represent viable shape-memory materials (SMMs) for additive manufacturing of medical devices. Both SMAs and SMPs exhibit the unique ability to recover their original shape under external stimuli. This review introduces the shape-memory mechanism of SMMs and their past and current biomedical applications including orthopedics, orthodontics, tissue engineering, drug delivery, and general surgery. Furthermore, the main AM techniques for fabrication of SMM-based medical devices are highlighted in this review, along with the material systems that have generated the most interest to date. Previous experimental studies have shown that AM techniques have great potential for producing complex and customized structures made from SMMs. Some future perspectives on AM of SMMs are provided below:

- For the most widely used SMAs medical devices, i.e., NiTi-based SMAs, while there is concern over the release of Ni into the patient's body which causes toxic and allergic response in human body,²²⁶ AM processes coupled with surface treatments have been demonstrated to mitigate this issue.²²⁷ Therefore, the development of new surface treatment strategies suitable for AM-fabricated NiTi SMAs to enhance their properties, e.g., minimized Ni release, excellent wear and fatigue properties, etc., is of great importance for their wider implantation in the biomedical sector in the near future. Also, the development of NiTi SMAs has enabled great progress in minimally invasive surgery, but there is still some space for enlarging and optimizing current SMA devices.
- Future development trends in AM of other SMAs can be expected in three different regards: (1) development of new SMAs suitable for various AM techniques, e.g., Ni-free Ti-based SMAs, to further extend the current material palette to include more SMAs with new and desirable mechanical and functional properties; (2) optimization of current AM techniques for various SMAs to further unlock their potential for wider biomedical applications; and (3) exploration of novel biomedical applications of current and newly developed SMAs and integration of the unique materials properties of these SMAs with the structural properties endowed by AM techniques. Moreover, modern computer design and analysis tools such as CAD and finite element analysis (FEA) are required to cooperate with the development of innovative SMA applications, which can reduce the high risks of costly research and development activities in the biomedical sector.
- Most additively manufactured SMP-based medical devices produced to date have been thermally actuated. Thus, an important area of future development will be the synthesis and processing of different stimulus-sensitive SMPs, including smart polymers that can be triggered upon exposure to light, water, electric fields, magnetic fields, etc. Very recently, there has been interest in the development of multiple stimulus-responsive SMPs, particularly in composite form. The possibility of processing these materials via AM techniques and their bioapplications requires further investigation. There is also a great need for advanced in vivo evaluation of additively manufactured shape-memory medical devices in order to determine their tissue compatibility, potential inflammatory response, and other body reactions. For tissue engineering applications, further work is needed on 3D scaffolds seeded with human cells prior to shape change; for example, the effect of temperature changes and mechanical strains applied to the cells during shape transformation on their attachment, proliferation, and migration should be investigated. Moreover, the development of SMPs with controlled shape recovery speed is required for specific biomedical applications such as artificial muscles. Finally, for some biomedical applications such as wound suturing, scaffold-assisted tissue engineering, etc., the next step is to process and develop SMPs that can degrade after performing their functions. Additive manufacturing of bioresorbable medical implants with tunable biodegradation rate and nontoxic released degradation products are other underexplored research topics.

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