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Smart Delivery Systems with Shape Memory and Self-Folding Polymers

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Abstract

New generation delivery systems involve smart materials such as shape memory and self-folding polymers. Shape memory polymers revert back to their original shape above their glass transition temperatures where this temperature change can be induced conventionally, photolytically, with a laser or magnetically depending on the composition of the material. This ability to assume original shape upon a trigger can be used in delivering drugs, DNA or cells. Self folding polymers are a new class of materials which may be composed of multilayers with different thermal expansion coefficients or with hinges that allow folding upon being triggered. These new materials allow various architectural designs of smart delivery vehicles predominantly for DNA and cells. The aim of this chapter is given shape and folding polymers and their usage for drug delivery systems.

Keywords: Polymer, Shape memory, Self folding, Drug delivery

1. Introduction

Polymers are a group of materials that are versatile in their nature spanning from industrial materials such as synthetic plastics to biopolymers. Synthetic or naturally occurring, their properties depend on the nature of the constituent monomers, the sequence of the monomers, the length of the whole polymer, and the type of bonds they contain in their structure. In the past 20 years, a new group of polymers is recognized to exhibit interesting properties, namely shape memory and self-folding. Polymers that exhibit these properties are now the subject of intensive research for their potential applications in biomedical area and drug delivery. In this chapter, we will first introduce the principles of shape memory and then give a summary of the work done in this field. In the following section, we introduce the concept of self-folding and polymer origami, which is a subsection of self-folding. Recent research done in this

exciting area is then presented, and future outlook on shape memory and self-folding polymers is specified.

2. Shape memory materials

The main characteristics of shape memory materials (SMMs) in general are that they show a plastic deformation (temporary shape) when an external stimulus is applied and are able to recover to their original shape from the temporary shape. This is also called “shape memory effect” (SME) [1].

One of the classes of shape memory materials is shape memory polymers (SMPs), which respond to external stimulus by offering mechanical action. Network elasticity of the shape memory polymer determines if SMP remembers one or more shapes [2]. Dual-shape memory polymers, which are going to be specified later on, are the first SMPs.

Until the external (shape memory-driving) stimulus is applied to trigger the shape recovery, the temporary shape of SMP is stable.

Temperature, light, electric field, magnetic field, pH, specific ions, or enzyme can be used as stimulus in order to change the shapes of shape memory polymers. The shape change can occur rapidly from temporary shape to the permanent one [3–5]. Figure 1 summarizes the relationship between polymer composition and structure, stimulus, and shape memory function.

In late 1970s, CdF Chimie Company (France) developed the first shape memory polymer called polynorbornene [6]. One year later, it was named as Norsorex by Nippon Zeon Company (Japan) and was commercialized [7]. Other commercial shape memory polymers which are named Kurare TP-301 and Asmer were produced by Kurare Corporation (Japan) and Asahi Company (Japan), respectively [8]. Widely used polyurethane (PU)-based SMP was developed by Mitsubishi Heavy Industries [4].

Another important branch of shape memory materials is shape memory alloys (SMAs). However, shape memory alloys have disadvantages among other types of shape memory materials, such as high manufacturing cost, toxicity, limited recovery, and complicated surgical problems. Shape memory polymers, ceramics, and hydrogels are preferred recently for their advantages compared to shape memory alloys [9].

3. Shape memory polymers

The shape memory effect can be originated by combining polymer structure and morphology by processing and programming methods. The material properties are not related with SME [10].

The unique properties and major advantages of SMP materials are summarized below:

- SMPs are lightweight and allow substantially higher elongations, which have properties for various technical applications [11].
- SMPs have wide range of glass transition temperatures from -70°C to $+100^{\circ}\text{C}$.
- Since they have a wide range of glass transition temperatures, their stiffness can be tailored. Also, SMPs can be processed easily [12].
- SMPs have shape recovery property up to 400% of plastic strain. (Shape memory alloys have 7–8%).
- Between the glassy and rubbery states of SMPs, large reversible changes of elastic modulus can be observed (as high as 500 times) [13].
- Shape memory polymers have high elastic deformation (strain up to more than 200% for most of the materials). They have low density and biodegradable materials.
- Most of the SMPs are biocompatible materials which allow them to be used in potential medical applications.
- SMPs are easy to process. They are applicable to molding or extrusion. They have low cost [13].
- Shape memory polymers have low thermal conductivity compared to shape memory alloys. This feature can be useful if shape memory foams are used as insulation materials [14,15].
- They can use many external stimuli and triggers. There are many alternative ways to actuate shape recovery such as light, magnetic field, electricity, and water [16].

As mentioned previously, shape memory polymers and their composites can recover their original shapes after large deformation when subjected to an external stimulus [17]. This external stimulus can be temperature [18,19], magnetism [20–22], moisture [23], or light [18,24].

Thermally Induced Shape Memory Polymers

Among these shape memory polymers, the thermoresponsive SMPs are the most common type [25,26]. Thermally induced shape memory polymers have a wide range of applications in biomedical fields, [27] such as drug delivery, implanting, suture, and wound healing [28].

The general thermomechanical cycle of thermoresponsive shape memory polymers consists of the following steps at a macroscopic level:

1. Programming
2. Storage
3. Recovery [29].

This cycle is depicted in Figure 1. The first step is the fabrication of the shape memory polymers into an original shape. Second, the polymer is heated above the thermal transition temperature (T_{trans}) (this temperature can be either melting temperature T_m or glass transition temperature T_g). When the polymer is at its T_{trans} , an applied external force deforms it, and it is cooled below

thermal transition temperature. When it is cooled, the applied force is removed in order to preserve the temporarily pre-deformed shape. In the last step, the pre-deformed shape memory polymer is heated above T_{trans} and shape recovery is observed, and SMP attains its original shape.

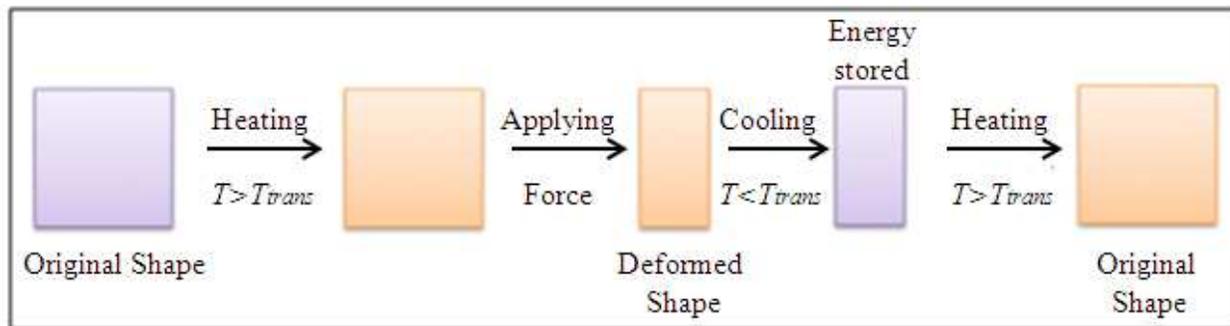


Figure 1. Thermomechanical cycle of thermoresponsive shape memory polymers.

At the molecular level, shape memory polymers offer shape memory effect by its two components, which are cross-links and switching segments. These SMPs can include chemically cross-linked networks or physically cross-linked copolymers. Physically cross-linked copolymers are usually made of linear block copolymers which have hard and switching segments. Their permanent shape is stabilized by hard segments, whereas temporary shape is fixed by switching segments [30]. Cross-links are formed by covalent bonds and physical interactions (i.e., molecular entanglements) [5,31]. For covalently cross-linked shape memory polymers, reshaping the materials is hard since the shape is fixed by covalent bonds. These types of polymers are called thermosets [32].

Polymer includes two separate domains in physical cross-linking case. The domain consists of two parts which are hard and reversible switching segments. The hard segment, which acts as net point, is related to the highest thermal transition temperature. Reversible switching segment or molecular switches are related to the second highest thermal transition temperature. These types of polymers are called thermoplastics [33]. Figure 2 shows the hard and soft segments during the shape memory process. The lines show the net points and square dots show the switching segments.

Rousseau et al. reported that epoxy polymers (neopentyl glycol diglycidyl ether NGDE) have tunable glass transition temperatures by changing the cross-link density and chain flexibility. Ranging up to 89°C, excellent shape fixity and recovery were observed [34].

Zhou et al. reported that PDLA/HA (poly D,L-lactide co-glycolide/hydroxyapatite) composites have desirable shape memory effects and the amount of HA particles in composites played an important role during the shape memory recovery. Since PDLA has remarkable properties such as shape memory effect, biodegradability, biocompatibility, easier availability, and osteoconductivity of HA, these composites have potential in biomedical applications such as minimally invasive surgery (MIS) and bone and tissue repair [35].

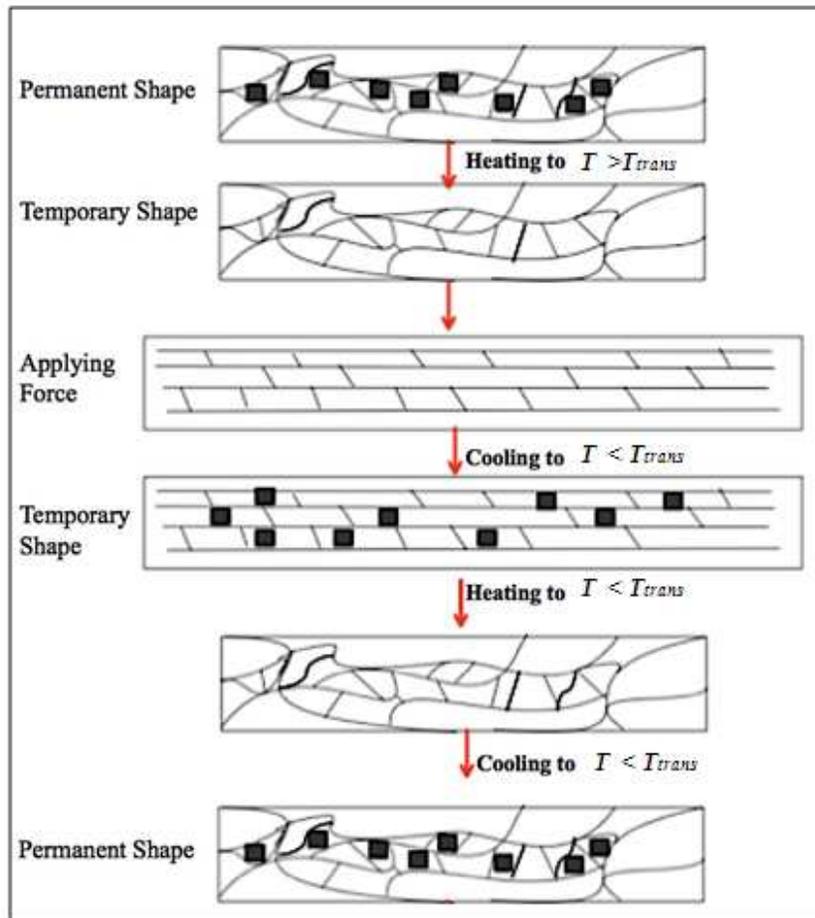


Figure 2. Hard and soft segments during shape memory effect.

Lendlein et al. developed a thermoresponsive shape memory polymer which consists of oligo(ϵ -caprolactone) diol (OGL) and crystallizable oligo(*p*-dioxanone) (ODX) as switching and hard segments, respectively. A fiber of this thermoplastic SMP was used to close the wound by loosely knotting the fiber and then when temperature increased to T_{trans} , the suture shrinks and the knot is tightened. So, they suggested that this type of material could be used in order to design new surgical devices [10].

In another study, Ashby et al. reported that poly(ϵ -caprolactone) (PCL) and poly(octylene adipate-co-meso-2,5-diazodipate) shape memory polymers were actuated by switching temperature. This new developed SMP would have potential applications in the biomedical field [36].

3.1. One-Way (Dual) Shape Memory Effect (1W-SME)

When an external stimulus is applied on SMP, the temporary shape becomes permanent shape. In order to obtain the temporary shape again, another external force or stress is required. This procedure shows that shape memory behavior is nonreversible or “one-way”, and it has a wide range of applications [37].

The most basic procedure of polymer shape memory effect is described in Figure 1. First, the shape memory polymer is heated to a transition temperature or deformation temperature (T_d), which resulted in softening of the material. Second, a deformation force is applied on SMP (i.e., loading or stress). Third, the SMP is cooled down under the load. Then, load is removed and the deformed shape is fixed, which is the temporary shape. After shape fixing, shape recovery is obtained by reheating the temporary shaped SMP to a recovery temperature (T_r) when no stress is applied on it. Finally, the original (permanent) shape of SMP is recovered [38]. If a shape memory process follows this procedure, it is called as dual-shape memory effect.

The thermal transition temperature, which is associated with switching domains, has various types. The melting transition ($T_{trans} = T_m$), liquid crystalline transition ($T_{trans} = T_{LC}$), or a glass transition ($T_{trans} = T_g$) can be taken as thermal transition temperature. However, mostly, melting and liquid crystalline phase transitions are designated to relatively small temperatures [39].

If we take a look at the macroscopic shape of shape memory polymer, when it has a permanent shape, its molecular chains are thermodynamically stable because of the highest entropy of SMP conformation. When SMP is heated above T_{trans} , chain mobility is triggered. Due to the lower entropy state and macroscopic shape change after applied stress, chain conformations of SMP are changed. Finally, when the SMP is cooled below T_{trans} , molecular chain segments freeze by kinetically trapping of lower entropy state. As a result of this, macroscopic shape fixity is obtained. In the last step, when heating the deformed SMP above T_{trans} , when there is no stress applied, the chain mobility is activated again. So, molecular chains regain their highest entropy. The one-way shape memory effect is illustrated in Figure 3 briefly.

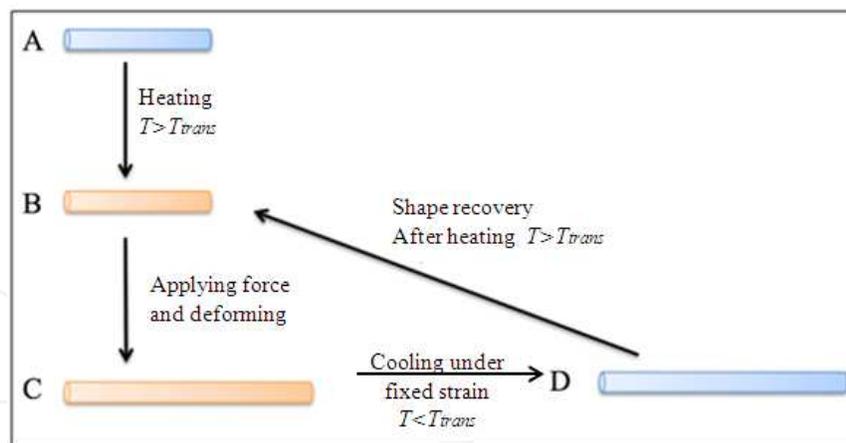


Figure 3. One-way shape memory effect.

Basically, shape memory polymers are able to change their shapes between original and temporary shape under applied stress which is a type of one-way shape memory effect. Another type of one-way shape memory effect is triple shape memory effect. The main difference of triple shape memory effect (TSME) is having one intermediate shape between its original and temporary shapes. If there is more than one intermediate shape, it is called multiple shape memory effect for a more complicated motion generation [40]. Polymers

blends, grafting and blocking copolymers, SMP hybrids, and polymer laminates are some of the ways of managing the triple shape memory effects [41]. Figure 4 shows the basic procedure of triple shape memory effect. As mentioned in the figure, there are two different thermal transition temperatures which are $T_{low,1}$ and $T_{low,2}$. This is attributed to the two segregated crystalline domains in the original shape [42].

Kumar et al. reported that grafted polymer network contains crystallizable poly(ethylene glycol) (PEG) side chains, and poly(ϵ -caprolactone) (PCL) shows triple shape memory effect [43]. The triple shape memory behavior of crystalline polyurethane was observed by Hu et al. [44]. Also, polyalkenamer and polyolefin-based polymer blends were used by Cuevas et al. in order to develop triple shape memory polymers which were two semicrystalline polymers (poly(cyclooctene) (PCO) and polyethylene (PE)) [42]. Xie et al. developed polymeric bilayers that consisted of two dual-shape memory polymers, and this new shape memory polymer bilayer shows triple shape memory effect [45]. Furthermore, Xie reported that perfluorosulfonic acid ionomer (PFSA) is able to show tunable shape memory effect which includes dual, triple, and quadruple without any change in the material composition [46].

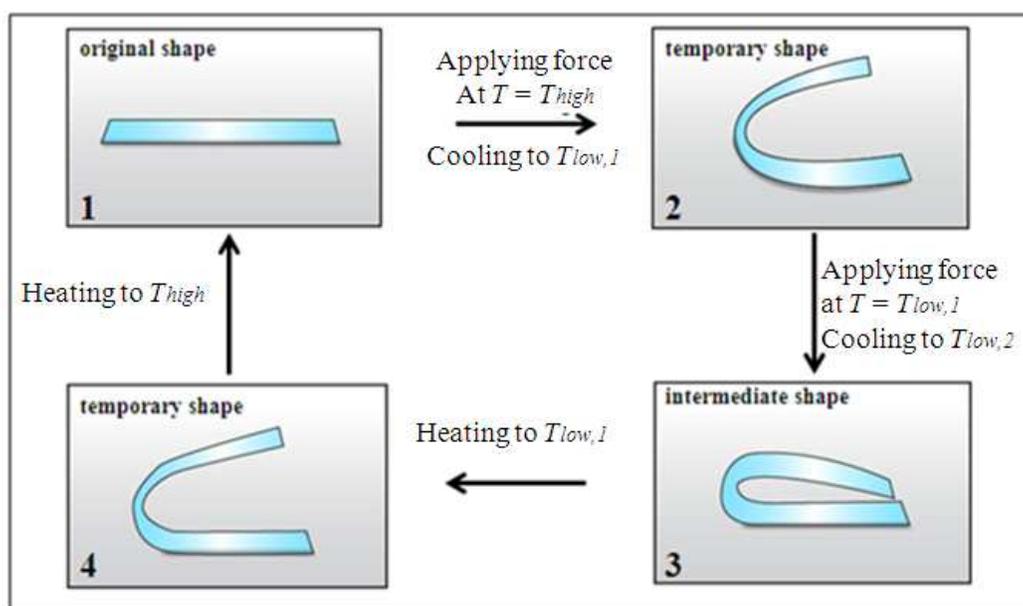


Figure 4. Triple shape memory effect.

3.2. Two-Way Shape Memory Effect (2W-SME)

Most of the typical SMPs show one-way shape memory effect. A different type of SME which is the two-way shape memory effect can be observed in liquid crystalline elastomers and photo-actuated deformation polymers [47].

2W-SME can be quite useful; however, its high cost represents an obstacle for its widespread use. In 2W-SME process, a crystallization-induced elongation and melting-induced contrac-

tion is observed during cooling and heating, respectively. This condition originated from the formation of liquid crystalline structure [48]. The comparison of 2W-SME and 1W-SME is shown in Figure 5 briefly.

Chen et al. reported that the two-way shape memory behavior of SMP laminate was observed by bending upon heating from 25°C to 60°C and reverse bending upon cooling from 60°C to 25°C. Laminated layers were prepared from shape memory exhibiting polyurethane [49].

Zhou et al. developed self-folding poly(octylene adipate) (POA). Besides showing conventional one-way irreversible shape memory, this SMP is able to form one-way reversible shape memory during heating and two-way reversible shape memory upon heating and cooling cycles. The chemical cross-links of this semicrystalline elastomer are responsible for the memorization of the original shape, whereas the physical network constructs the temporary shape [50].

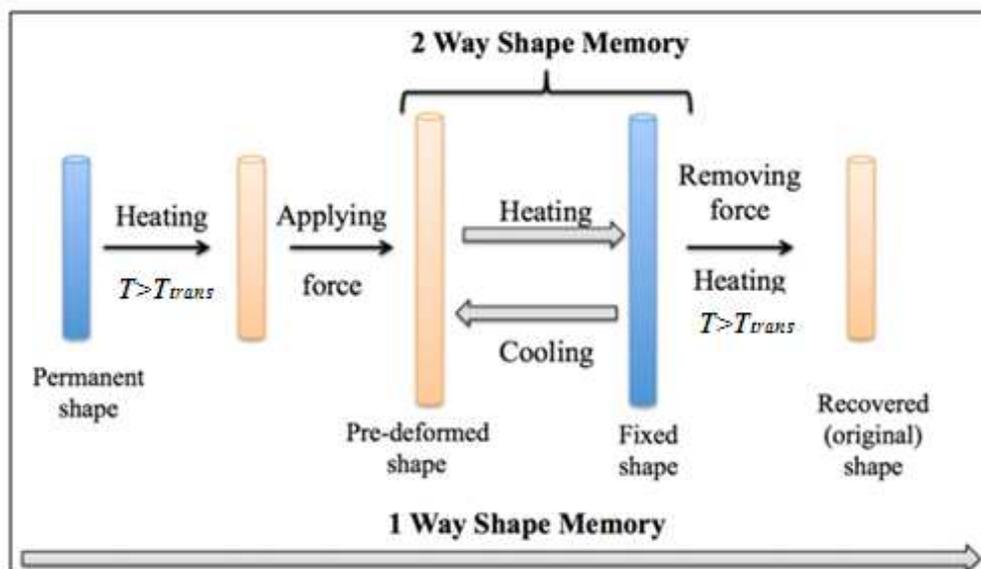


Figure 5. Comparison of two-way shape memory effect and one-way shape memory effect.

Magnetically Induced Shape Memory Polymers

Certain magnetic materials tend to respond to magnetic fields and are capable of maintaining their magnetic properties after the external magnetic field is removed. Such magnetic particles are called as ferrimagnetic or ferromagnetic materials which are iron, nickel, cobalt, and some of their alloys [51]. Some magnetic materials such as iron oxides (Fe_3O_4 , Fe_2O_3 , etc.), when below a certain nanometer size, do not have any remaining magnetization once the external magnetic field is removed. These are superparamagnetic materials and can be preferred over ferromagnetic ones depending on the application.

Shape memory can be induced by the application of an external magnetic field due to magnetic heating. So magnetic induction is a type of thermal induction, where temperature change is driven by magnetic field due to the presence of magnetic material in the nanocomposite.

The magnetic SMP has several advantages:

1. By using magnetic heating, possible danger of overheating can be eliminated.
2. Since heat is not given to the system externally, any complex-shaped device can be actuated virtually.
3. This method is convenient for medical devices which can be actuated inside the human body, since they can be controlled in a wireless manner [52].

Hilt et al. reported that magnetic field can be used in order to heat the SMPs by remote heating. This heating method relies on magnetic nanoparticles within the polymer matrix in order to create heat via power loss when exposed to an alternating magnetic field [53].

According to the study of Razzaq et al., by changing the magnetic field parameters and amount of the Fe_3O_4 in the polyurethane polymer matrix, shape recovery of the helical bended strip of polyurethane filled with 20% volume micro-sized magnetite was observed [54].

Magnetically inducing method is an indirect method. So this method can be useful if shape memory polymer cannot be actuated by direct heating methods. However, Zhou et al. reported that for cross-linked poly(ϵ -caprolactone) polymers, magnetite composite shows better reactivity to hot water than alternating magnetic field [55].

In the research study of Schmidt, polymer network composites were implemented with different contents of superparamagnetic nanoparticles (Fe_3O_4) and butyl acrylate cross-linked with oligo (ϵ -caprolactone) dimethacrylate. As it can be seen in Figure 3, the permanent shape is deformed by heating above T_{trans} . Then by cooling the temporary shape, the crystalline phase of oligo(ϵ -caprolactone) segments makes the polymer to become stable. Induction heating of magnetic nanoparticles in electromagnetic field leads to temperature increase inside the matrix. By magnetically heating above the T_{trans} , the original (permanent) shape is recovered [56].

Zhou et al. reported that poly (D,L-lactide) /magnetite (Fe_3O_4) nanocomposites show excellent shape memory effect when an alternating magnetic field was applied as a stimulus. Since PDLLA is biocompatible, these nanocomposites show potential for application as magnetically controlled smart implants in biomedical field [57].

According to the study of Puig et al., 8 wt% oleic acid-stabilized magnetic nanoparticles exhibited a temperature increase of 25°C at its surface when exposed to an alternating magnetic field in biomedical applications. Also, this temperature was enough to actuate the shape memory of the nanocomposite [58].

Electro-Active Shape Memory Polymers

As observed, shape memory effect is usually induced by thermal stimulation by heating above the transition temperature of the polymers, such as the glass transition temperature or melting temperature. However, some other stimulating sources, such as electric field, may also be used in order to trigger polymers with shape memory [59].

Electricity can be used as a stimulus which enables resistive actuation of shape memory polymer filled with conductive fillers. By passing an electrical current, shape memory effect

can be actuated easily in these nanocomposites. To date, most of the studies regarding electroactive SMPs composite are focused on thermoplastic SMP resins [60]. As a result of these, in recent studies, most of the electroactive shape memory polymers are well-dispersed carbon nanotube (CNT)-reinforced thermoplastic polyurethane (TPU) resin nanocomposites [61–63].

According to the study of Leng et al., thermoset styrene-based shape memory polymer nanocomposite filled with different amounts of nanosized carbon powder shows that with increasing nanocarbon powder amount, electrical conductivity increases. Also, it was reported that 10 vol.% nanocarbon powder shows good electroactive shape recovery property [64].

Zhou and coworkers fabricate cross-linked poly(ϵ -caprolactone) (cPCL) and conductive multiwalled carbon nanotubes (MWNTs). These nanocomposites exhibit excellent shape memory properties under the direct thermal and electrical stimulations. Therefore it was reported that this composite might be a promising prospect in biomedical applications [65].

Jung et al. obtained electroactive shape memory polymer composites by using polyurethane and three kinds of fillers. When polyurethane-multiwalled carbon nanotube composite is lightly coated with polypyrrole (PPy), new nanocomposite shows good electroactive shape memory properties when an electric voltage is applied [66].

Water-Induced Shape Memory Polymers

As a trigger mechanism, water can be used for shape transition of shape memory polymers or shape memory polymer composites. Since solvent or water molecules can penetrate into the amorphous areas of shape memory polymers, this can result in a plasticizing effect on SMP molecules. Therefore the flexibility of the molecule increases and shape recovery is observed [67].

Chen et al. reported that water-induced poly(methacrylic acid)-grafted clay and thermoplastic polyurethane composite was developed with shape memory effect. Also, this new polymer-clay composite responds to pH changes and mechanically adaptive properties when water is exposed [68].

The polymer composite composed of carbon nanotubes and shape memory polyurethane (SMPU) was developed by Luo et al. The new and developed composite has shape memory-enhanced water-sensing property which can be used in smart polymer applications such as sensory materials [69].

Aqueous environments can be used as a trigger of shape memory effect. Nöchel et al. used different grafted copolymer networks (named CLEG) which consist of different ratios of the hydrophobic cross-linker poly(ϵ -caprolactone) diisocynoethyl methacrylate (PCLDIMA) and hydrophilic poly(ethylene glycol) monomethyl ether monomethacrylate (PEGMA). The shape memory properties of this new hydrogel were studied by bending and uniaxial elongation experiments in the aqueous environments. As a result, CLEG has dual-shape capability and degradability and could be promising materials in biomedical applications [70].

Paakinaho et al. reported that the shape memory property of orientation-programmed PDLLA in an aqueous environment at 37°C was triggered by the combined effect of water molecules

and thermal activation [71]. Mendez et al. developed new water-activated biomimetic nanocomposites by adding rigid cotton cellulose nanowhiskers (CNWs) into a rubbery polyurethane matrix. At a specific concentration of CNW, aqueous swelling and shape memory behavior were observed [72].

4. Self-folding polymers

Self-folding is the ability of a material to fold and unfold without the external effects. Also without any external interference, such as human control, self-folding can be attributed to the self-assembly mechanism. These mechanisms can be patterned templates or thin films which can be folded, curved, or rolled-up to become spirals, tubes, and cylindrical tubes [73,74]. Self-folding can occur spontaneously or in response to stimuli such as light, pH [75], temperature, magnetic field, or solvent [76,77]. In Figure 6, self-folding mechanism which is provided by hinges is shown briefly.

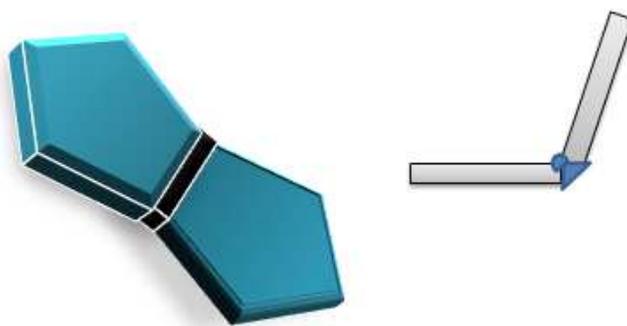


Figure 6. Illustration of 3D and 2D self-folding mechanism.

Self-folding films have become attractive recently since there is a variety of polymers which are sensitive to different stimuli, and they can fold by responding external signals. Many polymers are able to change their properties with pH and temperature. For biotechnological applications, biodegradable and biocompatible polymers are favorable choices and are frequently encountered. Polymers can also undergo considerable and reversible changes of volume that allow design of systems with reversible folding [78]. Thermoresponsive self-folding films can be designed using continuous thermal expansion, melting shape memory transition of polymers which demonstrate the low critical solution temperature (LCST) in solutions [79].

Luchnikov et al. reported that a polymer bilayer consisting of a polystyrene (PS) layer on top of a poly(4-vinyl pyridine) (P4VP) layer is formed on the polished surface on the silicon wafer or other substrates (e.g., a glass slide) by means of dip or spin coating. Rolling, in this system, is achieved due to the swelling of the P4VP in a water solution of an acid, due to protonation of the pyridine rings [80]. In another study of Ionov, self-rolling due to swelling was observed.

Fully biodegradable polysuccinimide shows self-rolling response with its polymer bilayers, and this results in the formation of microtubes [81].

Ionov et al. demonstrated a self-folding polymeric bilayer consisting of poly(methyl methacrylate) copolymer and poly(N-isopropylacrylamide) copolymer which can encapsulate an oily liquid. This new developed bilayer can be expressed as an anisotropic capsule, and the folding behavior is observed due to the swelling difference of the layers of the polymer film. Self-healing materials and drug delivery design are featured possible application areas of this approach [82]. A representative illustration of self-folding polymeric bilayer is shown in Figure 7.

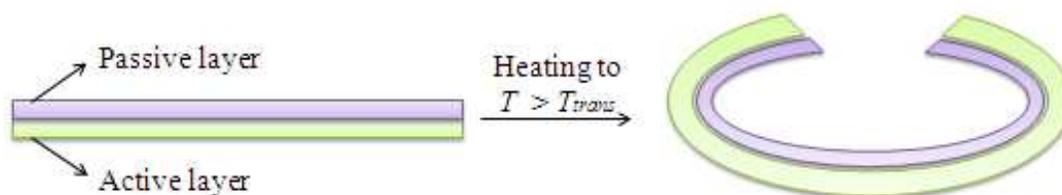


Figure 7. Self-folding procedure of thermoresponsive polymeric bilayer.

Ionov et al. studied two different sets of thermoresponsive polymeric bilayer behaviors to different stimuli. Polymeric bilayers were selected as one passive layer which is hydrophobic or random copolymer, and the active layer is the thermoresponsive hydrogel. Thermoresponsive hydrogels show swelling and shrink response to increased or decreased temperature, whereas passive layers prevent swelling of the active layer. In this manner, nonuniform expand/shrink behavior is achieved. In other words, folding and unfolding can be observed due to swelling [83].

Huang et al. developed a heat-responsive poly lactic acid (PLA) structure which would provide good uses for customized deployable/retractable and biodegradable implant devices for individual patients [84].

Lee et al. developed that self-folding oral delivery device which is capable of providing enhanced mucoadhesion, drug protection, and targeted multidirectional delivery. The device is composed of three layers which are backing layer, a foldable bilayer, and a mucoadhesive layer entrapped with drugs. The swelling bilayer was made of pH-sensitive hydrogel cross-linked poly(methacrylic acid) (PMAA) which swells during contact with body fluid whereas non-swelling layer is poly(hydroxyethyl methacrylate) (PHEMA), and it acts as a diffusion barrier in order to minimize drug leakage in the intestine. When mucoadhesive drug layer is attached on the bilayer, self-folding device attaches to the mucus first and then curls into the mucus due to the different swelling of the bilayered structure, leading to enhanced mucoadhesion [85].

Temperature-stimulated liquid crystal elastomer–polystyrene bilayers which can show complex shape changing behavior such as helical twisting, reversible folding, and patterned

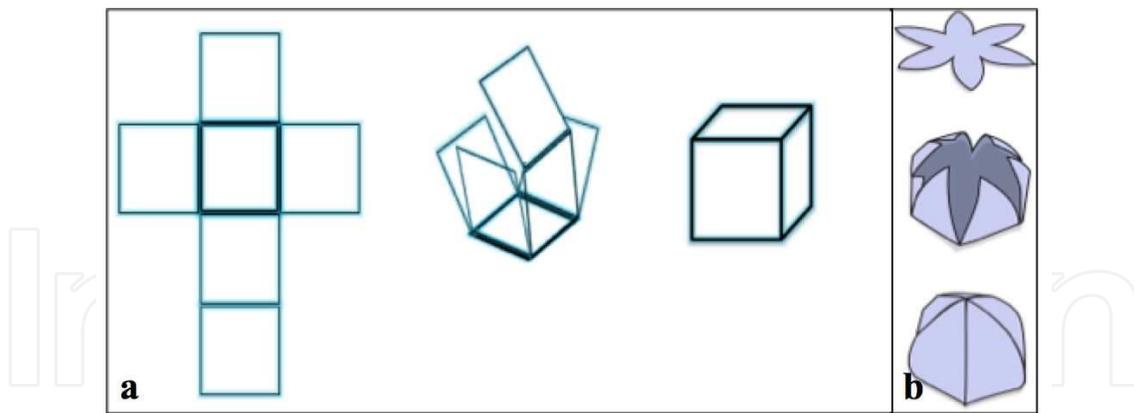


Figure 8. Origami folding sequence of a cubic structure (a), illustration of polymer origami self-folding (b).

wrinkles were developed by Agrawal et al. Tailoring was achieved by changing film thickness and overall aspect ratio [86].

Huck et al. reported that microscale, quasi-2D composite objects are fabricated which can respond to the addition of salt and pH changes [87].

Schenning et al. developed accordion-like striped actuators made of liquid crystal polymer films, which show response to the pH or temperature. These actuators would be used in medical systems and microrobotics [88]. Another liquid crystal shape memory actuator was developed by Park et al. which shows different swelling behavior between its UV exposed and non-UV exposed sides [89].

Visible light-induced graphene oxide/poly(vinylidene fluoride-hexafluoro propylene) (PVDF-HFP) nanocomposite films were produced by Yu et al. Tumbler movement was observed on the films due to the photothermal effect of graphene oxide and shape memory effect of PVDF-HFP. This behavior can be improved for full-plastic devices actuated by visible light [90].

Ionov et al. developed self-assembled porous scaffolds with uniaxial tubular pores. By producing rectangular polymer bilayers which include hydrophobic (poly methyl-methacrylate-co-benzophenoneacylate) and stimuli-responding hydrophilic polymer (poly N-isopropylacrylamide-co-acylic acid co-benzophenoneacylate), pH-dependent rolling of bilayers was observed. Also, these bilayers are capable of controlled self-assembly [91].

5. Polymer origami

Origami word is originated from the Japanese words 'ori' as in to 'fold' and 'kami' as the 'paper.' It is the art of paper folding from Japan and has been known worldwide [92]. Today, origami is not only the art of paper but also can be used for technological purposes by creating three-dimensional objects. In order to obtain these objects, fold pattern sequences should be provided to develop the desired object from a flat sheet [93].

Origami enables the creation of complex structures unlike bilayers, which can only bend in one direction or fold multiple steps. The shape of self-folded structures depends on the initial shape of the film, the radius of curvature (depending on the layer thickness), and the presence of a substrate [94]. A typical origami folding structure is depicted in Figure 8(a). Space structure solar arrays, automobile airbags, shopping bags and cartons, photovoltaic cells, and biomedical are some of the uses of polymer origami structures [93].

As mentioned above, different stimuli can be used to trigger the material's self-folding behavior as well as origami folding. Gracias et al. reported that self-folding functional microgrippers that combine a swellable, photo-cross-linked N-isopropylacrylamide-co-acrylic acid soft hydrogel with a non-swellable and hard-segmented polymer (polypropylene fumarate, PPF) show thermomechanical response to hydrogel where they can be used in surgical areas [95].

In a study, Baroud et al. manually cut geometric shape of polymethylsiloxane membrane layer placed on a hydrophobic surface. When a drop of water is added on a membrane and allowed to evaporate, as water volume decreases, thin membrane sheet wraps the liquid and forms 3D shape which shows the interaction between elasticity and capillary [96]. The illustration of this procedure is shown in Figure 8(b).

Gracias et al. developed three-dimensional (3D) microfabricated nanoliter containers by thermally actuating the 2D structure to fold into a 3D structure which is analogous to polymer origami. In this case, 2D template has smart hinges. Researchers suggested that this new fabrication method would be used for developing microscale biomedical devices in the future [97].

Ryu demonstrated photo-origami which actuates both flat and curved surfaces of polymer films in order to obtain 3-dimensional objects at a macroscopic scale via "localized photo induced stress relaxation" mechanism. Photo-origami is driven with amorphous, covalently crosslinked polymer which includes pentaerythritol tetra(3-mercaptopropionate) (PETMP), 2-methylene-propane-1,3-di(thioethylvinylether) (MDTVE), and ethylene glycol di(3-mercaptopropionate) (EGDMP)). [93]. Gracias et al. developed photo-cross-linked polyethylene glycol (PEG)-based bio-origami hydrogel bilayers which can self-fold in aqueous solutions. These new developed bilayers conserve different kinds of tissues by self-folding which would be improvable considering the tissue engineering area [98].

6. Smart polymers as drug carriers

The most important use of shape memory polymers is as drug carriers. Some drugs due to their stability of low solubility in the blood stream become more bioavailable when delivered in a carrier system. This may also allow the sustained release of the drug which can be desired if the drug is desired to be eluted over a long period of time. There are several drug delivery systems developed such as liposomal systems of biodegradable polymeric systems. Polymers offer a wide range of adjustable properties to be tailored for the desired drug elution system.

Smart polymers are a new class of materials where novel drug delivery systems can be designed with. However, there are some criteria such as drug loading capacity, aqueous environment conditions, drug release pattern, and degradation behavior which determine the suitability of shape memory polymers as matrix materials for drug release or drug carrier applications [99].

Based on the requirements defined by a specific application, such polymer systems will allow selecting one specific polymer out of a larger number of related materials without the need to change to a totally different material chemistry. In addition to adjustable thermal properties, polymer systems can also be helpful to realize demanded mechanical properties or desired degradation rates of SMP implants [100].

For biomedical applications of SMPs, the capability to change their shape should be established at relevant conditions, i.e., T_{sw} (switching temperature) of the SMP device should be close to or at reasonable levels above body temperature. To meet this goal, the thermal properties such as T_g or the melting temperature T_m that account for the shape memory effect need to be adjusted. Polymer systems as families of materials, in which different properties and functions can ideally be tailored over a wide range independent from each other, may allow the adjustment of T_{sw} by polymer chemistry, which make them good candidates as drug carriers [101].

About the controlled drug release ability of shape-memory polymers, Ohya et al. reported that chemically cross-linked networks of branched oligo(ϵ -caprolactone) polymer can perform sustained release of theophylline drug over a month without initial burst release in Phosphate Buffer Saline (PBS) at 37°C [102].

According to the study of Ameer et al., hydroxyl-dominant (HD) polydiolcitrate (HD polymers) can perform the subsequent release of hydrophobic dichlorofluorescein (DCF) drug. This means polydiolcitrate elastomers could benefit from smart biodegradable materials for tissue engineering applications [103].

Such systems are ideal for minimally invasive surgery where implants are inserted through a small incision, and after self-anchoring, they start to release a pharmacological agent. Dobrzyński et al. developed a shape memory polymer based on L-lactide, glycolide, and trimethylene carbonate in order to obtain double layer systems for paclitaxel drug delivery that paves the way for drug eluting stents [104].

Lendlein et al. reported that oligo (caprolactone-co-glycolide) dimethacrylate was combined with drug, and its activation was obtained between 28-42°C where shape memory effect was pronounced at body temperature. In this study, diffusion-controlled drug release was observed independent from polymer degradation [105].

Gong et al. reported that biodegradable polymeric cross-linked poly(ϵ -caprolactone) (cPCL) and poly(sebacic anhydride) (PSA) were developed, and release accumulation of drug can be enhanced by adding PSA into cPCL matrix. This shape memory polymer could be used as potential drug-eluting stents in biomedical field [106].

7. Potential biomedical applications of smart polymers

During the past decade, biomedical applications of shape memory materials became a very active area of research [107].

As mentioned in the previous section, the progress in surgical techniques, especially in minimally invasive surgery, allows these materials to be used widely in biomedical applications of polymers.

These smart materials are enabled to insert a bulky device in the body through a small keyhole incision in a temporarily fixed shape. After a precise position by the surgeon, such smart materials gain their application-relevant shape on demand [108].

Zhang et al. demonstrated a new nanofibrous, biomimetic, shape memory, and biodegradable poly(D,L-lactide-co-trimethylene carbonate) by electrospinning which would be applicable for MIS implantation [109].

Nelson et al. developed hydrogel bilayers composed of N-isopropylacrylamide with polyethylene glycol diacrylate. By using the expansion difference of these layers due to swelling, self-folding behavior was observed. These new devices are switchable and show reversible shape transition against external stimuli. These layers were designed for different purposes in order to demonstrate microstructures which can preserve magnetic alginate microbeads when they have folded structures. After exposing to NIR laser source, microbeads are capable of being released from the microstructures. So, this method offers a solution for drug and cell delivery systems [110].

Tai et al. demonstrated an origami technique by constructing 3D spherical structure from 2D parylene-C (PA-C) film for intraocular implantation application [111]. Maitland et al. developed an SMP adapter in order to reduce the hemodynamic stress which arises from impingement of dialysis needle in an arteriovenous graft [112].

The most effective areas of biomedical applications of shape memory polymers are intravascular stents, treating aneurysm occlusion and clot removal.

7.1. Intravascular stents

Intravascular stents are predominantly used in main arteries or peripheral arteries, in the treatment of cardiovascular diseases (CVDs) which is the number one cause of death globally: more people die annually from CVDs than from any other cause [113]. First-generation stents are metallic, whereas second-generation ones are polymer-coated drug-eluting metallic stents. New-generation stents are biodegradable polymers that are also drug eluting. The potential advantages of pure polymer stents compared to bare metal stents include increased biocompatibility, biodegradability, increased drug loading, enhanced compliance matching, reduced cost, ease of fabrication for patient-specific devices, molecular surface engineering, and the use of shape memory effect [114].

Metallic stents are effective in hindering acute occlusion and reducing late restenosis after coronary angioplasty; however, many concerns still remain. Compared with metallic stents,

poly-L-lactic acid (PLLA) stents are biodegradable and can deliver drugs locally, and these were developed by Igaki and Tamai. It was reported that feasibility, safety, and effectiveness of PLLA-biodegradable stents were verified in humans [115].

Wagner et al. reported that shape memory thermoplastic polyurethane is developed as a self-expandable stent, and it can be used as a drug delivery system [116].

A polymer system consists of *tert*-butyl acrylate, and poly(ethylene glycol) dimethylacrylate is improved which meets specific needs of minimally invasive cardiovascular devices by Gall and his coworkers. In this study, it was found that 10 wt% cross-linked polymer network can be stored unconstrained at room temperature and can be activated at body temperature which can be fabricated as a stent [117].

Chen et al. developed shape memory chitosan-based films (chitosan/PEO/glycerol) which are used to produce biodegradable stents. Chitosan cross-linked with epoxy compound stent's most remarkable property shows rapid expansion from a crimped state by using the hydration in an aqueous environment as a stimulant. By using minimally invasive surgery techniques, this stent can be placed into an artery. In another study of Chen and coworkers, genipin cross-linked chitosan-based stents were developed. The possibility of using this newly developed genipin stent as a drug delivery vehicle was also examined by loading an anti-proliferation drug, sirolimus. Findings showed that the genipin stent with enhanced mechanical strength can be used as an attractive stent platform for local drug delivery [118,119].

Maitland et al. performed the design and fabrication of an SMP stent (MM5520 thermoplastic polyurethane) which was triggered by photothermal actuation at 40–45°C [120].

Wang and coworkers developed fully biodegradable polymeric stent that can self-expand at body temperatures (37°C), using the concept of elastic memory. This self-expansion is necessary in fully polymeric stents, to overcome the problem of elastic recoil following balloon expansion in a body vessel. Bilayered biodegradable stent prototypes were produced from poly-L-lactic acid and polyglycolic acid (PLGA) polymers [121].

7.2. Aneurysm treatment

An aneurysm is a formation of balloon-like bulge in an artery. This bulge is formed when a part of artery wall becomes weak which results in unusual widening. Aneurysms can occur in any of the artery; however, the most common ones are aortic, cerebral (in the brain), popliteal (in the leg, behind knee), mesenteric (in the intestine), and splenic artery aneurysm (in the spleen). Almost 13,000 Americans die annually from aortic aneurysms. Surgery is the possible option for the treatment of large aortic aneurysms [122,123].

Shape memory polymer foams are the most attractive materials for aneurysm treatment by using them as a filling device in the artery [124]. Wilson and his coworkers showed that the shape memory polymer foam which includes hexamethylene diisocyanate (HDI), N,N,N',N'-tetrakis(2-hydroxypropyl)ethylenediamine (HPED), and triethanolamine (TEA) can be laser deployed in an *in vitro* aneurysm model. In this study, 10-mm aneurysm was treated with a new developed device [125].

In the study of Wong et al., shape memory polymer Calomer™ was investigated as a candidate for aneurysm coils. In this work, shape memory polymer coils spread inside a simulated aneurysm model proved that the typical hemodynamic forces do not prevent the shape recovery process [126].

Maitland et al. developed shape memory polyurethane foam with high porosity which makes it convenient for intracranial aneurysm treatments. Adding 4% tungsten into this foam improves radioopacity. Inherent radioopacity makes the material to be visualized by using conventional patient imaging modalities such as fluoroscopy in order to deliver it safely [127].

Another shape memory polymer foam based on hexamethylenediisocyanate, triethanolamine, and tetrakis(2-hydroxyl propyl)ethylenediamine was developed by Maitland et al. which is found to be suitable for aneurysm treatment [128].

Raymonda et al. developed a non-cytotoxic, non-mutagenic, and poorly thrombogenic polyurethane-based foam called cold hibernated elastic memory (CHEM) for endovascular procedures. The shape memory property and possibly modifying T_g or the size of the pores let this material for developing new tools including embolic agents that could completely replace the aneurysmal cavity, without intervening thrombus, to prevent recanalization and recurrences after the endovascular treatment of aneurysms [129].

7.3. Clot removal

When blood does not flow smoothly in the blood vessels, it can begin to coagulate and/or blood clots. A blood clot, or thrombus, may continue to grow, blocking the blood supply to certain parts of the body and causing damage to tissues and organs. Some medical intervention is often required to remove the clots. It is estimated that each year thrombosis affects as many as 900,000 people in the USA and kills up to 100,000 [130,131].

Maitland et al. reported that a prototype endovascular electromechanical clot extraction device was fabricated using a combination of shape memory polymer and shape memory nickel–titanium alloy (nitinol). This preliminary study suggests that SMP–nitinol device may have an application in the treatment of acute stroke or other thromboembolic diseases [132].

Also, Maitland and coworkers aimed to evaluate the feasibility of utilizing a system of SMP acrylates for a thrombectomy device by determining an optimal cross-link density that provides both adequate recovery stress for blood clot removal and sufficient strain capacity to enable catheter delivery. They have reported an acrylic SMP system with glass transitions above body temperature in the range of 65–75°C with tailorable recovery stresses that were controlled by varying the cross-link density. From the four different material compositions evaluated, devices with 15 mole% bisphenol A(BPA) gave the most favorable outcome [133].

Wilson et al. reported that coil, umbrella, and microgripper-shaped polyurethane microactuators are used to treat stroke by activating this shape memory polymer with laser to remove clots. The actuation of the devices was obtained between 65 and 85°C [134].

8. Conclusion and future outlook

In this chapter, novel smart polymeric materials, i.e., shape memory polymers, self-folding polymers, polymer origami structures, and their potential applications are summarized. Shape memory polymers are the class of smart materials which can fix their shape after applying a deformation by cooling below their transition temperature. Then, by reheating the above transition temperature, shape recovery to the original shape is observed. They can be produced from polymer material or blending with network-based polymers.

Due to their excellent biocompatibility, SMPs are promising building blocks of biomedical applications such as polymer vascular stents with shape memory polymers as the drug delivery system, smart surgical suture, laser-activated SMP microactuators to remove clots in a blood vessel and implants for minimally invasive surgery.

Today, SMP development continues rapidly, in the case of clinical applications. Enhancing biomedical applications beyond medical devices would be achieved by blending the shape memory polymers with compatible materials.

When minimally invasive surgery application is taken into account, implants should be able to carry out complex movements. These movements have to be performed by a material which can perform predetermined shift many times such as SMPs. Also, SMPs would be required for individual patients since they are compatible against specific conditions.

Shape memory polymers are considered to be a future strategy which may prevent undesired complications during the treatment in biomedical applications compared to shape memory alloy-based materials due to their biodegradability. Since SMPs are versatile materials, they would continue to develop as a result of their promising potential applications.

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