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Review

Shape memory polymers and their composites in biomedical applications

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ABSTRACT

As a kind of intelligent material, shape memory polymer (SMP) can respond to outside stimuli and possesses good properties including shape memory effect, deformability and biological compatibility, etc. SMPs have been introduced for medical applications such as tissue engineering, biological sutures, stents and bladder sensors. Due to the shape memory effect, the medical devices based on SMP can be implanted into body through minimally invasive surgery in contraction or folded state and recovered to their requisite original shapes at target position. In this paper, a review of SMPs utilized in biomedical applications and their actuation methods are listed. Various biomedical applications and potential applications based on the beneficial properties of SMP are also summarized.

1. Introduction

As an intelligent material, shape memory polymer (SMP) can keep its temporary state and recover to its initial state under different stimuli such as solution, light, electricity, etc. [1–5]. The most favorable characteristic of SMP is that its stiffness is adjustable. SMP is in rubber state when ambient temperature is higher than transition temperature (T_g). When the temperature decreases, stiffness and storage modulus of the material increase gradually [6]. SMP is in a two-phase structure, fixed phase and reversible phase, which possesses inseparable synergy to maintain the initial shape and contribute the shape-shifting ability. The fixed phase plays a significant role in maintaining and recovering original shape and preventing flow deformation of polymer. This stationary phase has a higher crystal melting temperature or T_g. However, the reversible phase is characterized by a lower crystalline melting temperature or a lower T_g. In this phase, SMP may undergo reversible changes of softening and hardening by altering external conditions (for example temperature), which contribute polymer deformability. Based on active response and deformation, SMP has a potential development in novel biomedical applications especially the devices for minimally invasive surgery.

Compared with traditional materials, SMP possess many advantages, such as light weight, low cost, large deformation, adjustable glass transition temperature [7–10]. Other characteristics of SMP including biocompatibility and biodegradability are valued to biomedical applications. In addition, advanced science provides possibilities to adjust the glass temperature by controlling the chemistry of the structure of SMP according to different applications. This greatly broadens the range of potential biomedical applications.

Though temperature is the common stimulus to trigger SMP, it has limitation to provide shape-memory switching in SMP under specific conditions. In this case, SMP is usually filled with particles, such as carbon nanotubes, carbon nanofibers, silicon carbide, nickel powder and ferroferric oxide nanoparticles to provide shape changing effects under stimuli with mechanical, electrical and magnetic properties [11,12]. By adding different particles into SMP, this process can achieve different driving methods to satisfy different requirements, which enrich its range in specific applications. This review summarizes the promising biomedical applications of SMP, such as bone tissue, cardiac valve repair, tissue engineering and other specialized fields as well as the driven methods being used in biomedical applications.

2. Actuation methods in biomedical field

SMP absorb energy to overcome the internal stress and recover to its original shape. Therefore, how to efficiently and controllably drive shape recovery of SMP becomes the focus of research. At present, there are many stimulus methods such as magnetic driving, optical driving, solution driving, water driving and pH driving etc. Though body heat may be the most important driving method for biomedical application, by mixing different polymer or appropriate dopants with SMP to expand its actuation methods can realize specific function such as

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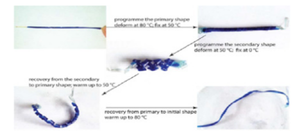
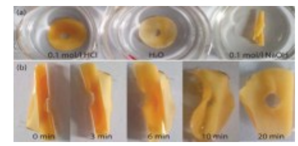
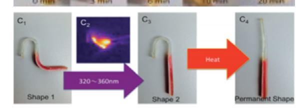
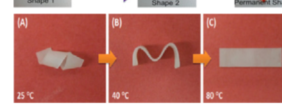
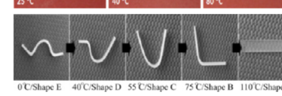
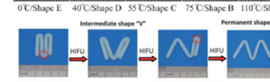
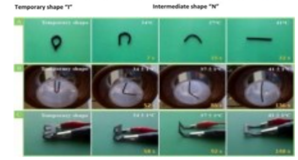
Table 1
Several of multi-shape memory polymers.

Polymer types	Driven methods	Transition temperature	Process of shape memory cycle
Polyurethane/poly(methacrylic acid) [31]	Thermal stimuli	50 °C/80 °C	
Polyurethane/poly(methacrylic acid) [31]	Water/pH		
Epoxy based on shape memory polymer [32]	UV and temperature	60 °C	
Epoxy resin/PCL fibers [33]	Temperature	40 °C/80 °C	
Polymer (methylmethacrylate)/polyethylene glycol [34]	Temperature	35 °C/50/70 °C/110 °C	
Crosslinked poly(methyl methacrylate-*co*-butyl acrylate copolymer [35]	High-intensity focused ultrasound	47 °C	
Chemically cross-linked poly(3-caprolactone) composite [36]	Magnetic field, electric field, and temperature	About 40 °C	

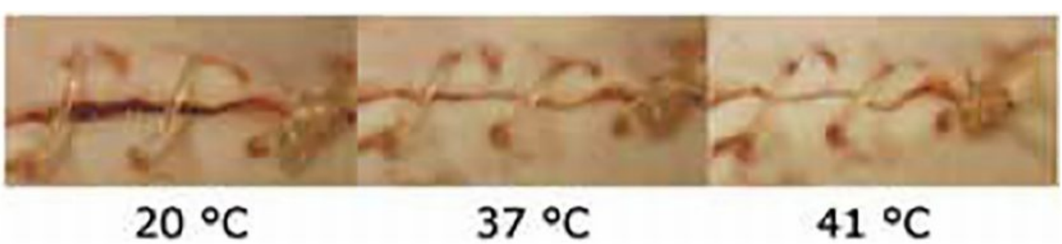


Fig. 1. Process of shrinks of degradable suture for wound closure based on SMP in order to optimal healing [38].

selectively heating by light, magnetic, etc. These techniques broaden its application in medical devices based on SMP.

SMP containing photo-response functional groups can produce reversible cross-linking and decomposition reaction when exposed to a specific wavelength of light. However, this driving mode is limited to a few SMP [13]. For heat-sensitive SMP driven by photo-thermal, its shape memory effect (SME) can be driven by absorbing heat from laser waves. If optical fibers are embedded into SMP, optical energy with specific wavelength can be delivered to polymer by optical fiber. The optical energy gradually heats polymer to above its transition temperature, then shape memory effect is triggered. It will be significance for laser treatment and photodynamic therapy. If a SMP device triggered by a laser is embedded into blood vessels, it can be used as a thrombus removal [14]. Besides, by adding particles such as carbon black, carbon nanotubes into SMP devices accelerate the heat diffusion. And most importantly, this way make the non-contact actuation a reality [15,16]. In addition, Liu et al. gave in-depth discussions of coating light-absorption materials to surface of SMP can realize locally self-folding [17,18]. Zhang et al. developed a photic driving SMP by coating gold nanoparticles, which can finish its shape recovery under remote controlling [19].

Wang et al. firstly discovered and confirmed that water or moisture can actuate shape recovery of some polyurethane [20,21]. Further, Wang et al. presented a new type of sodium dodecyl sulfate/thermosetting epoxy driven by water [22]. For biomedical application, this stimulus may be more significant considering the body fluid.

The magnetic remote control shows up its prospect in biomedical application as well, because most of living system is not sensitive to magnetic field which has relatively small threat to human beings. To realize remote control through magnetic field opens a new window for telemedicine and diagnostic equipment. Besides, due to the SME, the magnetic response of nanocomposite has a potential application in intravenous and localized administration by minimally invasive approach [23–25]. The magnetic stimuli is considerably expanded its application range in bionic medicine and creates breakthroughs in the field. For instance, magnetic responsive SMP composites provide new means for drugs and hormones delivery in vivo. And it can enhance the surgical effect of non-invasive and minimally invasive surgery. Magnetic and electromagnetic responsive SMP composites are manufactured by adding magnetic particles into SMP. Ding et al. adopted vinyl-capped

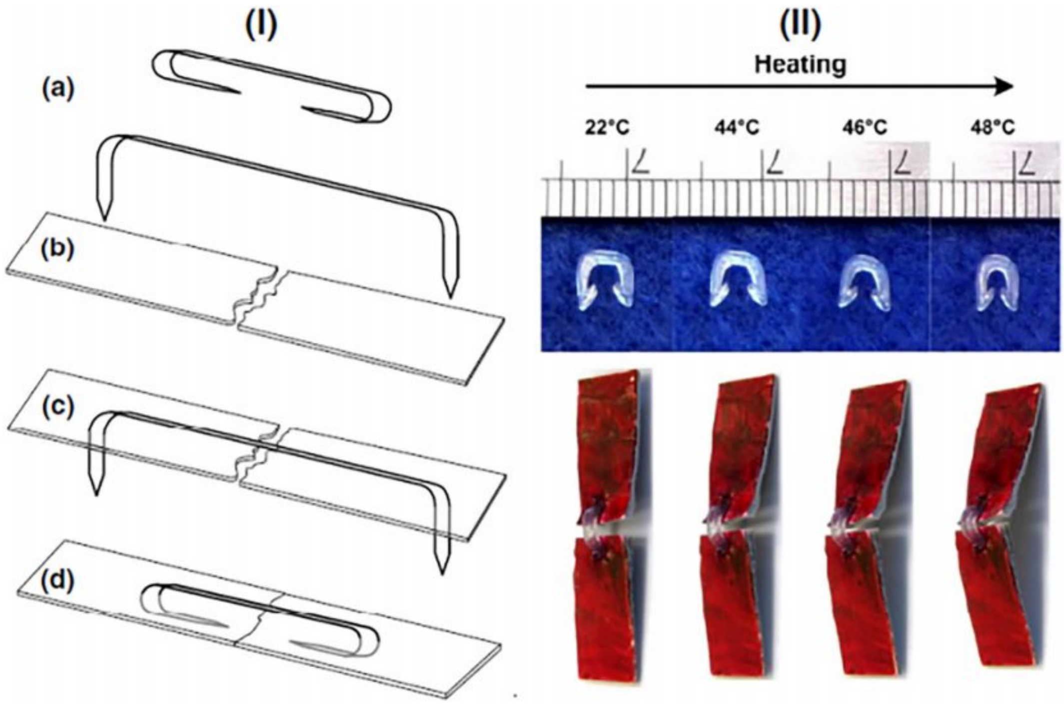


Fig. 2. Self-tightening staple based on shape memory PLA (I) concept. (a)–(d) Working principle of self-tightening staple (II) evaluate of self-tightening staple by bringing two pieces of tissue closer [40].

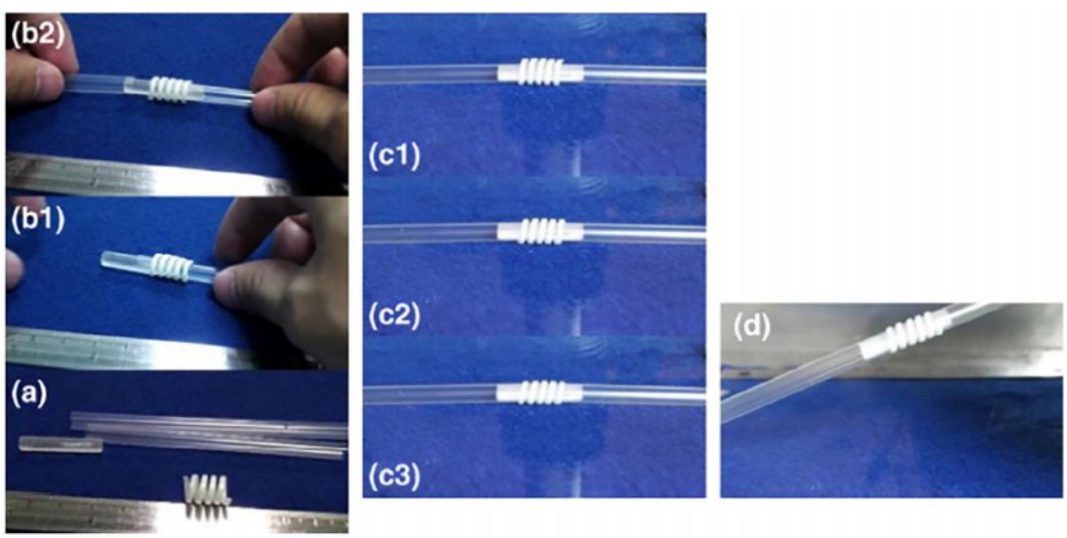


Fig. 3. Evaluate of a spring based on shape memory PLA for sutureless anastomosis [40].

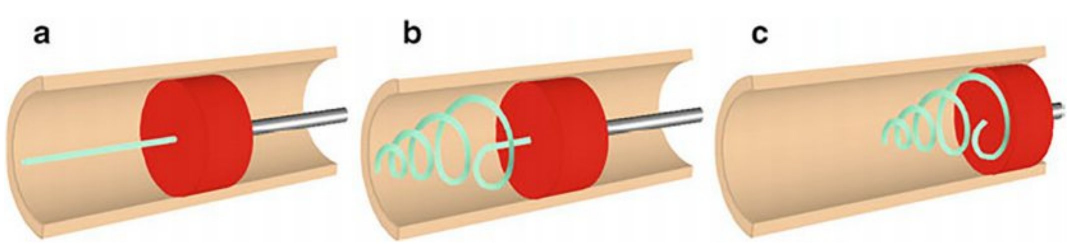


Fig. 4. Concept of operating principle of thrombectomy device based on shape memory polymer. (a) The clot is first punctured by device (b) then device is activated to form a coil shape (c) both the device and clot is pulled to remove simultaneously [43].

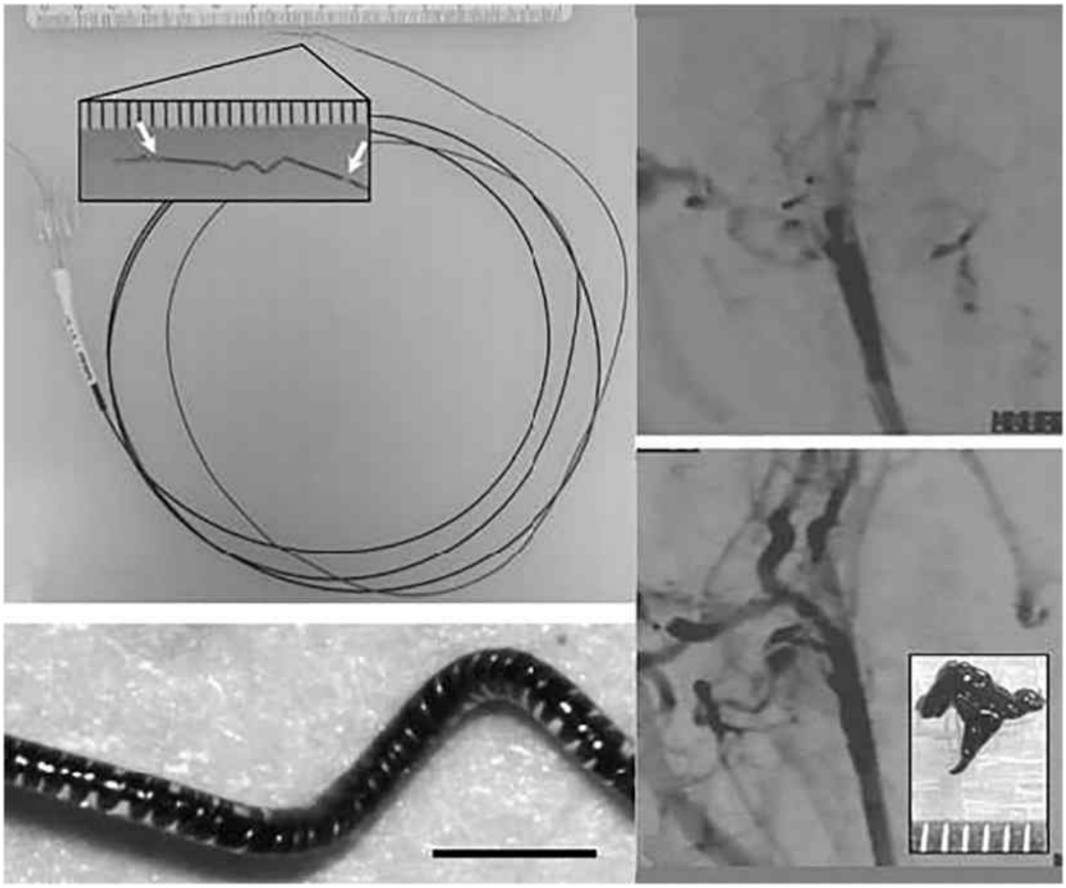


Fig. 5. Clot microactuator based on shape memory polymer [45].

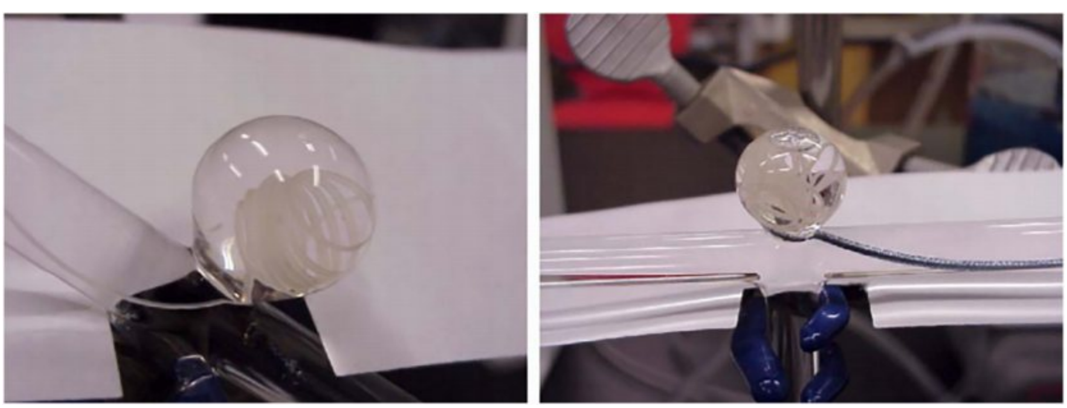


Fig. 6. Deployment processes of aneurysm occlusion devices based on SMP [49].

Fe_3O_4 nanoparticles as net-points putting forward a novel magnetic responsive SMP network [26]. Lendlein group have developed a complex system driven by ambient temperature and magnetic field work together [27].

For applications of SMP, the ideal driving methods must be selected according to physiological environment. In human body, physiological pH is variational in different regions. In addition, different from physiological environment, pH changes usually occur in the whole biological systems. Zhou et al. immersing SMP into acid and alkaline solution verified that SMP can complete a full shape memory cycle in pH solution [28]. Li et al. developed a SMP which can finish its shape memory behavior in human pH environment [29]. Chen et al. synthesized a new type of hydrogel which can complete its shape memory behavior induced by pH and sugar [30].

3. Multi-shape memory polymer composites

Duo to potential applications, intelligent multi-SMPs have attracted more attention and got rapid development. Multi shape memory effect is obtained due to SMP which has a broad phase transition. Biomedical application based on them can address more complex applications to realize complex functions.

Using polyurethane (PU) and poly(methacrylic acid) (PMAA), Zhang et al. synthesized a novel polymer composite, which possessed triple-shape memory effect. Applying thermal stimuli and water/pH to PU/PMAA, the triple-shape memory effect can be triggered. After experiencing two deformations, its initial shape will recover [31]. This type of SMP with remote actuation possibilities make the application in vivo is more feasible [32]. Hu et al. developed a SMP composite

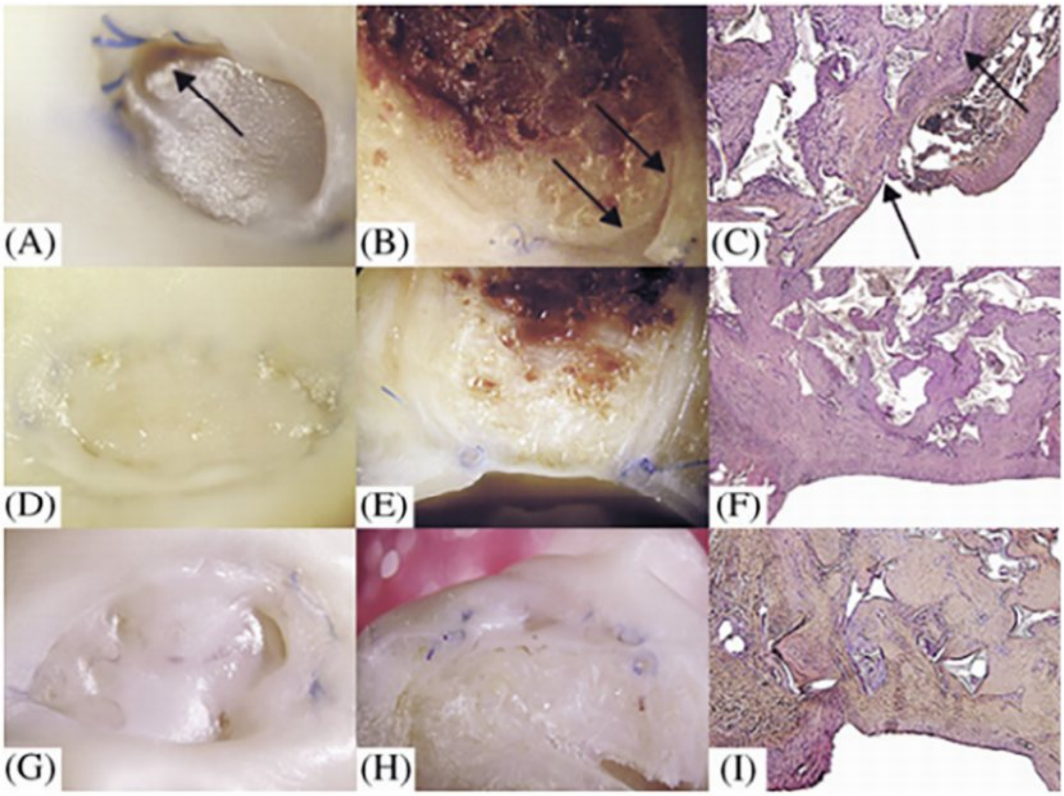


Fig. 7. The lateral wall common carotid aneurysm embolized of a dog by shape memory foam (A–C) only a small crescent of recanalization is shown (D–I) aneurysms are perfectly healed [50].

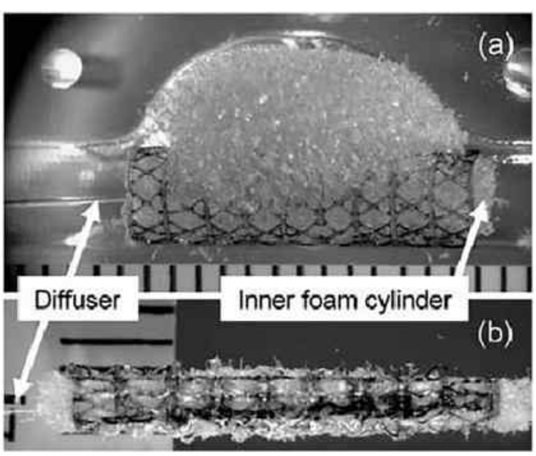


Fig. 8. Stent-foam device based on SMP [51].

possessing triple shape memory effect simulated by UV and heat [32].

Any of the multiple switching transitions SMP can gradually exhibit shape memory behavior under a reasonable stimulus. Luo and Mather made the thin shape memory polycaprolactone (PCL) fibers by dipping them into epoxy resin. After curing it was demonstrated that the material exhibited two thermal transition processes [33]. Li et al. developed a SMP with a broad T_g by introducing an additional melting transition into it, which has quintuple-shape memory effect [34].

High-intensity focused ultrasound techniques making inroads as treatment tool for tumor in vitro duo to its thermal effect. Li et al. have experimentally confirmed that high-intensity focused ultrasound can be used for stimulating SMP and achieve shape recovery [35]. Process of shape transition could be realized by selectively controlling the ultrasound exposure time and its acting position. Therefore, SMP can be given multiple temporary shapes and it can be release the drug in specific areas if used in a drug delivery system.

Leng et al. have proposed a SMP composite, which mixed with Fe_3O_4 nanoparticles decorated multiwalled carbon nano-tubes, and can be actuated by magnetic and electric [36]. As such this nanocomposite can utilize multiple stimuli, such as magnetic field, electric field, and temperature. Besides, it has been proved that this new SMP material possesses a good biocompatibility and has a high potential to use in smart medical devices.

At present, many researchers are focus on multi-functional stimuli-responsive intelligent devices based on polymer for invasive surgical. To meet the complex operating requirements, multi-shape memory effect attract more and more attention. Table 1 list several multi-shape memory polymers mentioned above.

4. Applications in biomedicine

4.1. Suture less anastomosis based on SMP

Traditional surgical suture needs a doctor to possess adept knot tying technique. If the force of tying is relatively high, it will cause the surrounding tissue necrosis. On the other smaller forces will also leave scars. Therefore traditional sutures can potentially cause wound infection. In recent researches have shown that the surgical sutures based on biodegradable SMP can provide a steady, uniform restoring force [37].

In 2002, Lendlein et al. reported a kind of surgical suture made by biodegradable shape memory polyurethanes (SMPU). This suture had shape memory function and was biodegradable (Fig. 1). They used SMPU monofilament which is in slack state to suture wound. When the temperature rose to body temperature, the suture returned to its original shape and automatically triggered by restoring force and the wound gap is closed [38].

Besides, in terms of wound closure, shape memory alloy (NiTi) has certain advantages. However, some drawbacks of limited deformation,

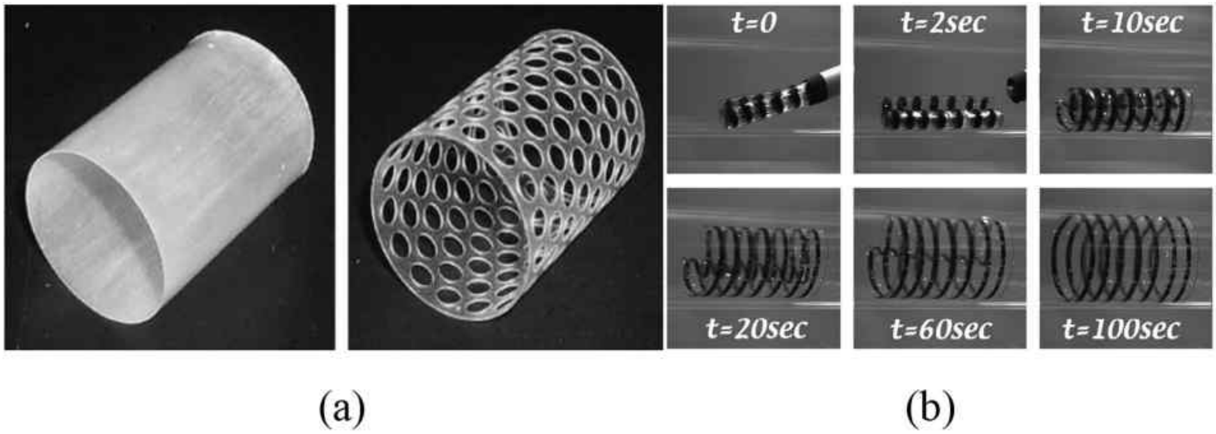


Fig. 9. The drug-eluting stents of SMP. (a) The prototype of vascular stents based on SMP. (b) Recovery of shape memory polymer stent [53].

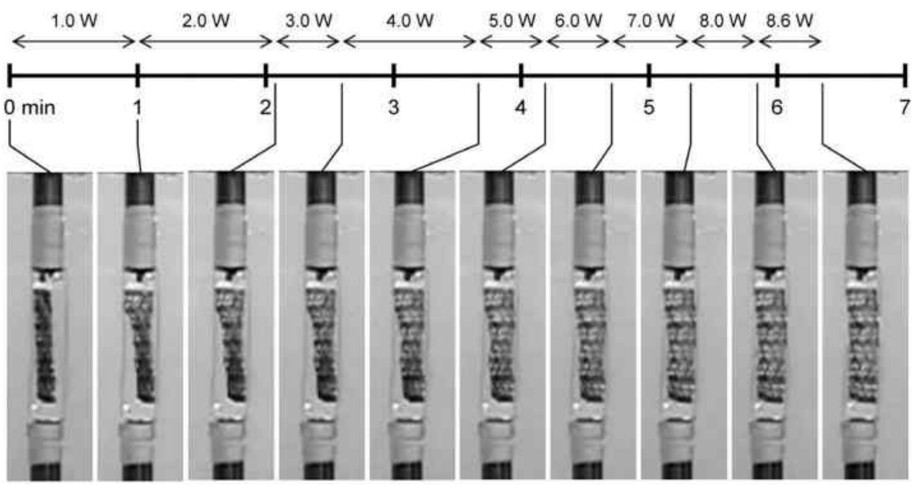


Fig. 10. Process of shape memory polymer stent deployment in the mock artery with the increase of laser power [54].

non-biodegradable greatly limit its development in biomedical application [39,40]. Recently, biodegradable stapler has attracted more and more attention in minimally invasive surgery. Various staples can be emitted continuously and relatively easy to reach the depths of human body by minimally invasive surgery. However, it does not mean that this method is used for wound closure without any problems. To meet the requirement of different tissues, varisized staples are needed. Staples that made up with SMP can shrink to achieve the most suitable locked state by applying certain stimuli on it, which can meet different needs of sizes with just only one dimension. The SMP staples are able to exert gentle force for wound closure [40]. The self-locking function of SMP staple has been successfully demonstrated in vitro (Fig. 2).

A compression method has been developed for a long time for wound sutured anastomosis. Spring of shape memory polylactic acid has been fabricated for suture less anastomosis. As shown in Fig. 3, the spring was pre-expanded to a certain extent, and then placed it into intersection of the two tubes. When it was heated to body temperature, the spring tightened up gradually and frapped the two tubes together. Furthermore, the possibilities for application in bleeding control are greatly extended due to its degradable function [40].

4.2. Clot removal devices based on SMP

Stroke is a common disease. Nerves and blood vessels atherosclerosis is the main cause of Stroke. Hemagglutination and blood clots occurs with the blood vessels become narrow, and when blood clots start to block the flow of blood, stroke will happen. The ischemic of brain cells caused by thrombus will lead irreversible damage to brain within short time. Such circumstance is life-threatening if left untreated. However, medication treatment for stroke will waste too much time, and those drugs are strictly controlled. Therefore, many researchers have proposed a non-drug treatment method for stroke patients. Compared with drug treatment, non-drug treatment method can quickly restore blood flow.

Using shape memory thermoset polyurethanes, Maitland research group developed a thrombectomy device for stroke patients [41,42]. As illustrated in Fig. 4, firstly, the thrombectomy device is guided into the thrombus accumulation area via tube. After puncturing the clot, the device recovers to its coil shape. And then it collects thrombus and pulls it out [43]. The prototype of thrombectomy device has been demonstrated under pressure over ten times of neurovasculature.

In the following research, the laser-driven SMP is applied to the thrombectomy device, and novel “umbrella” extraction devices and embolic coils are improved [42]. Since the laser-driven thrombectomy devices can be heated above the body temperature, the transition temperature of selected SMP for thrombectomy devices can be operated in a higher temperature than body temperature. Therefore, SMP which has higher stiffness can be used to remove thrombus.

Later, during nickel-titanium alloy in the shell of thermosetting polyurethane, the hybrid thrombectomy device has been fabricated by Maitland group [44,45]. Compared with thrombectomy device of pure SMP, the hybrid device has a higher restoring force. In the process of working, SMP-Nitinol hybrid wire is preset as straightened state, and SMP in glass state suppresses the recovery of alloy. By heating Ni—Ti

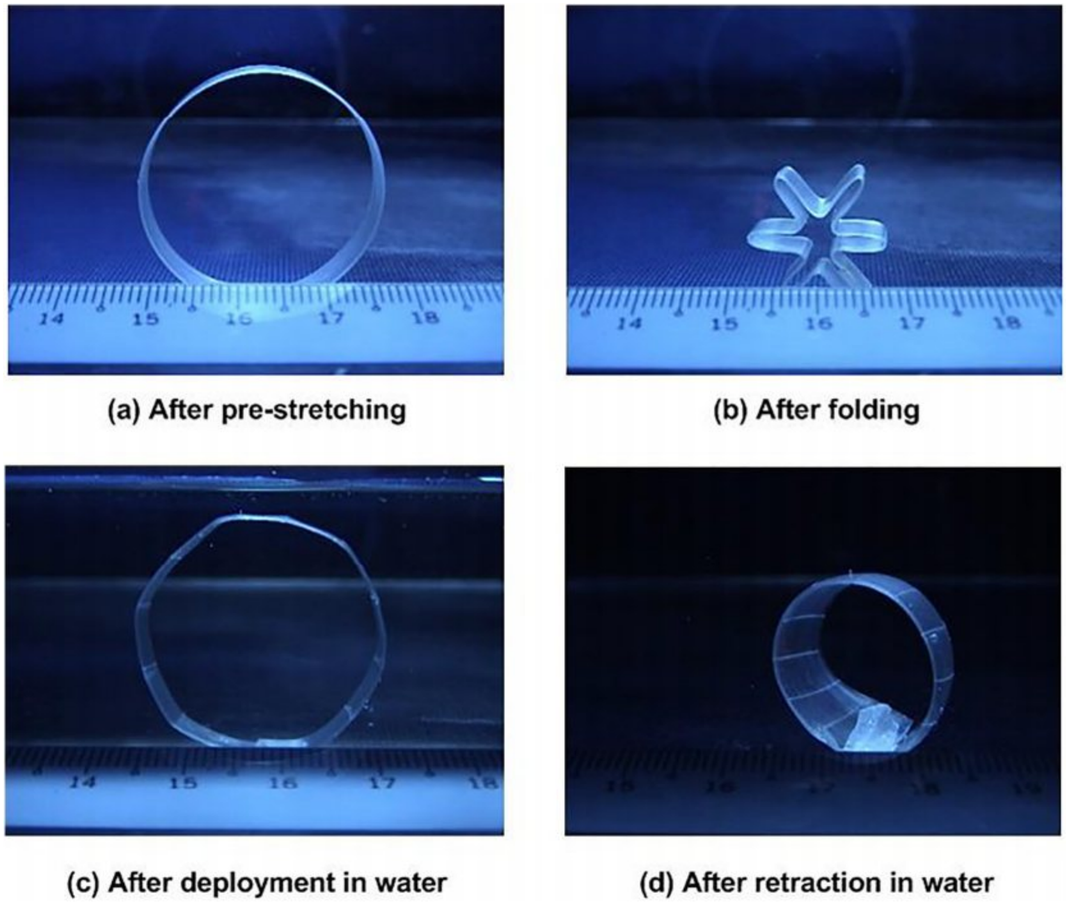


Fig. 11. Star-shaped stent based on film polyurethane shape memory polymer [55].

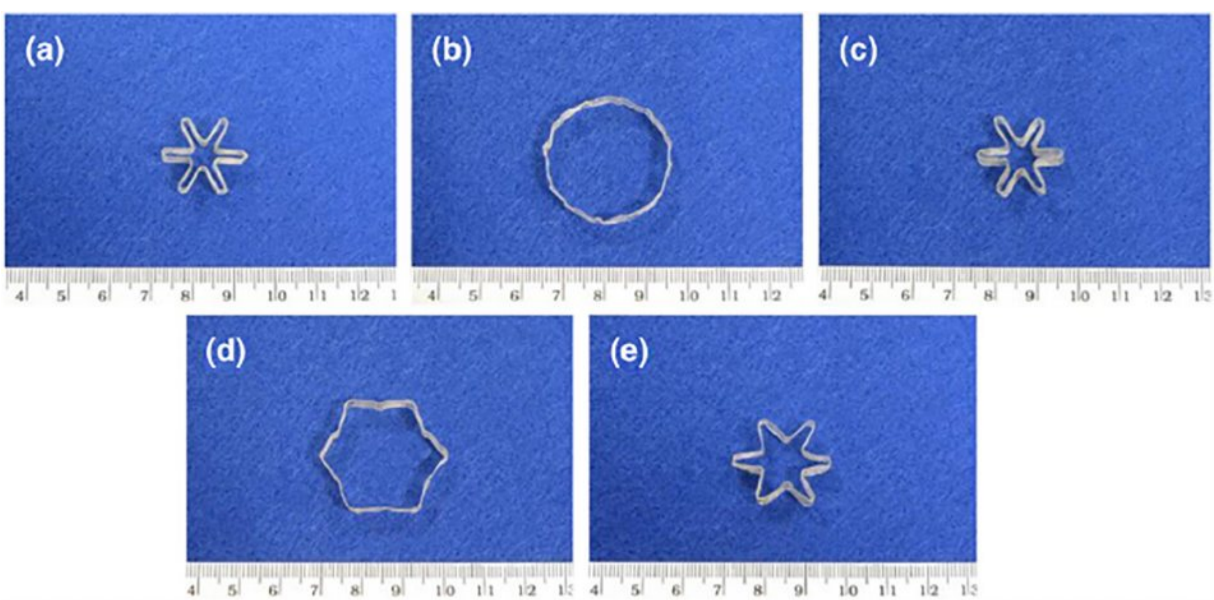


Fig. 12. Demonstration of instant retraction property of a polyurethane SMP stent. (a) Original shape, (b) expansion state, (c) mechanical folding, (d) heating for deployment and (e) heating for retraction [59].

alloy wire, both of the shape memory effects were triggered and initial shape were recovered [44]. This device has been verified in a rabbit acute arterial occlusion model, and the results investigated that four-fifths of clot was cleared (Fig. 5) [45].

4.3. Aneurysm occlusion devices based on SMP

Intracranial aneurysms are balloon-like bulges in cerebral artery, which is caused by weak vascular. It will lead to intracranial hemorrhage when it's ruptured, which maybe result in hemorrhagic stroke brain damage even death. Metal coil was first used as implants for

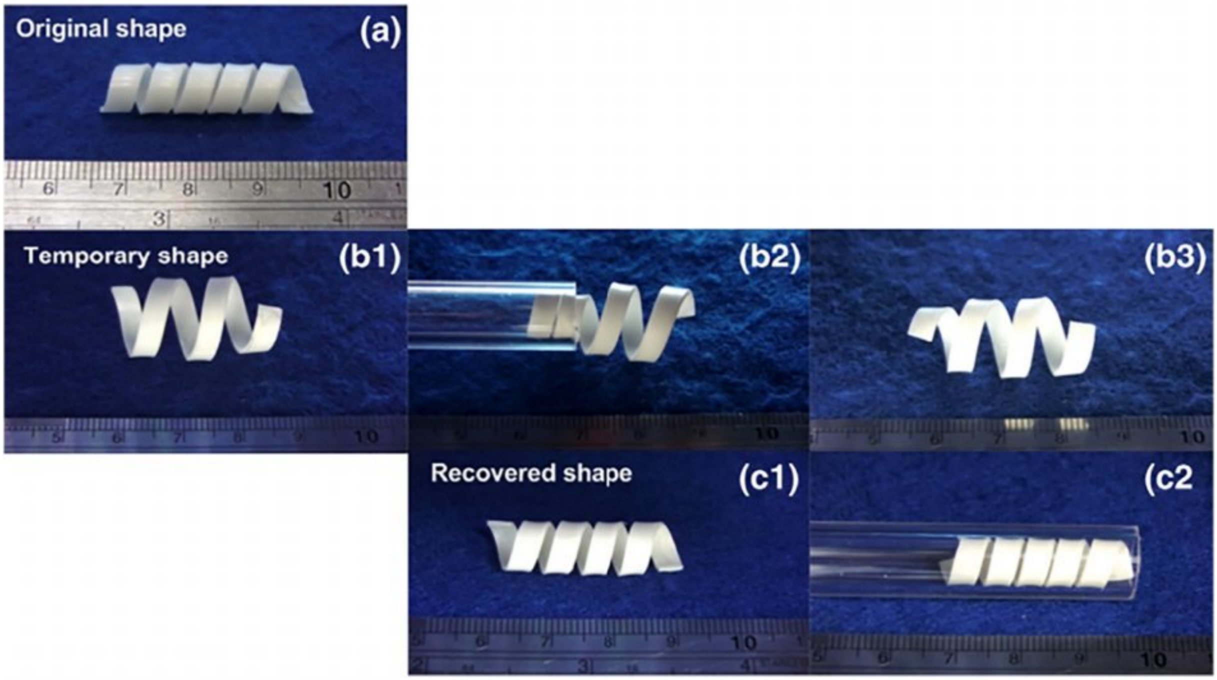


Fig. 13. Demonstration of instant removal of a PLA stent. (a) Original state, (b1) temporary state, (b2) push out of tube, (b3) deployed, (c1) shape recovery and (c2) back into tube [40].

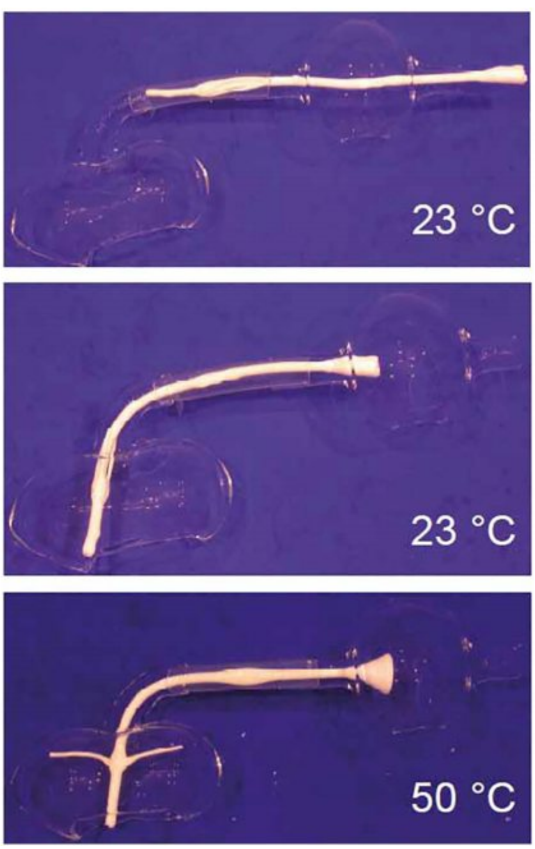


Fig. 14. Working principle of a ureteral stent based on shape memory polymer [60,61].

treatment of intracranial aneurysms, and then it was sealed off. In 1995, detachable coil technique was put forward by Guglielmi. It works by guiding a deployable coil into aneurysm to induce the coagulation. However, this therapy has some problems, such as operational difficulties, easy rupture, and incomplete blocking.

In the following research, bioactive coils based on SMP are developed to replace metal coil. When contact with blood, platinum coils with polymer coated will swell. Finally, the coils could expand to nine times of their original state. Thus, this technique can maximize the volume of coil while reduce the number of coils required and shorten the treatment time [46]. Compared with metal coil, hybrid-hydrogel coil show a better performance in inducing aneurysm occlusion, which has been verified by animal experiment [47]. However, along with the absorption of polymer coating, it may cause coil compaction and aneurysm recanalization.

Afterwards, coil of shape memory polyurethane was developed and verified using in vitro experiment [48]. Additionally, Hampikian et al. designed a radiopaque SMP embolic coil of SMP which increased the likelihood of forming a stable tissue matrix. It reduces the risk of aneurysm recanalization comparing with biologically inert platinum coils. The deploying process of SMP coil in an intracranial aneurysm is shown in Fig. 6. The hot water used in simulation process has the same velocity and pressure with the flow in vivo. The helical coil was implanted to an aneurysm model as verticality status. Once exposing to hot water, the coil will recover its original state inside the glass aneurysm. Results indicated that recovery of coil did not prevented by hydrodynamic forces. At the same time, coils remained stable in aneurysm dome without migrating in the cavity [49].

In the following research, SMP foam is proposed for aneurysm treatment. After compaction, SMP foam is planted into the aneurysm, and due to the shape memory effect, it can gently fill the aneurysm during its expansion. The method can reduce the complexity of the operation obviously and avoid the coil-induced rupture. Metcalfe et al. proposed that polyurethane-based SMP foam was used for treatment of carotid aneurysm. After three weeks, angiographic scores are improved by SMP. Histological results showed: there is a layer of thick neointima in surface of foam; most of aneurysm neck is sealed by thrombus and connective tissue.

However, the authors commented that the SMP foam does not deploy completely in body temperature, due to the T_g was 60 °C. Thus it just only sealed most of the aneurysm neck. If the T_g is lowered nearby the body temperature, it will have a better effect [50]. The healing

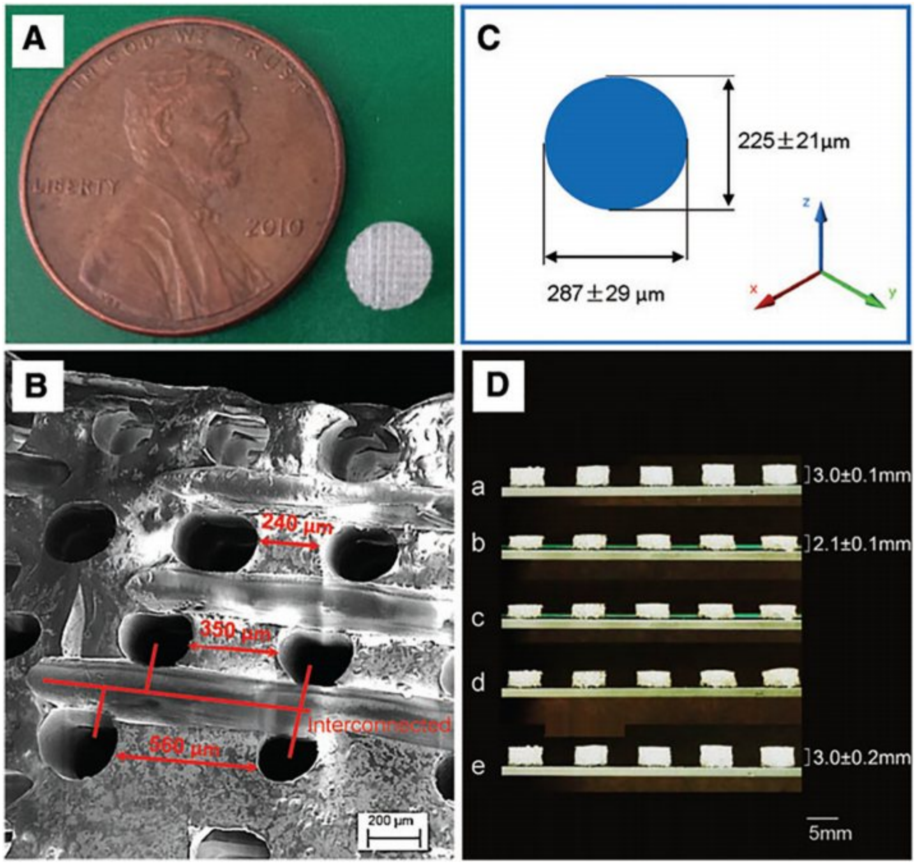


Fig. 15. The biomedical scaffolds fabricated by 4D printing technique. Figure (A) compared the scaffold with a cent, (B) the distribution of pores in scaffold, (C) the pore size of scaffold and (D) (a)–(e) recovery process of the scaffold [64].

Fig. 16. Arch wire based on shape memory polymer installed in a dental model [66].

Fig. 17. Evaluate of cylindrical device expanding for soft tissue fixation based on SMP [67].

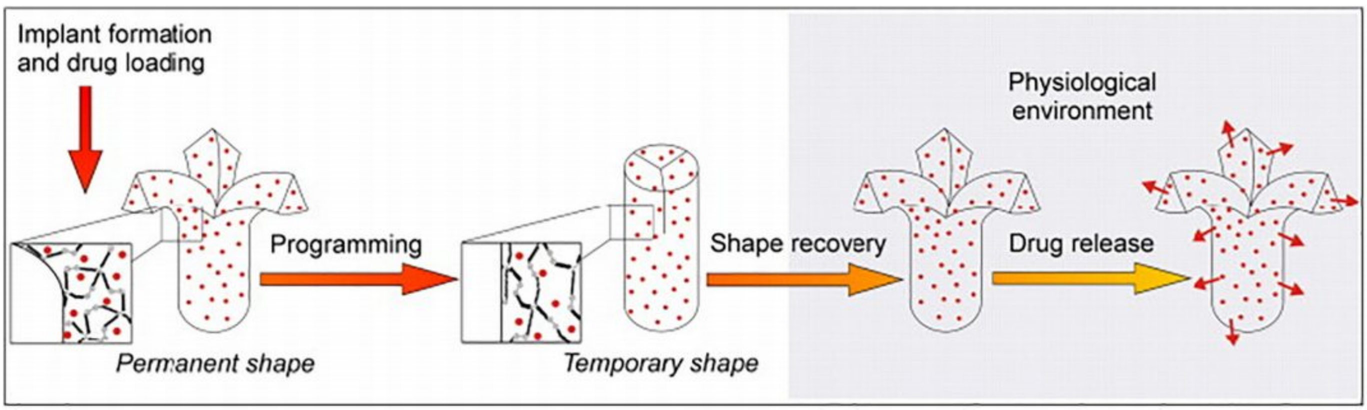


Fig. 18. Operating principle shape memory polymer drug loaded devices [74].

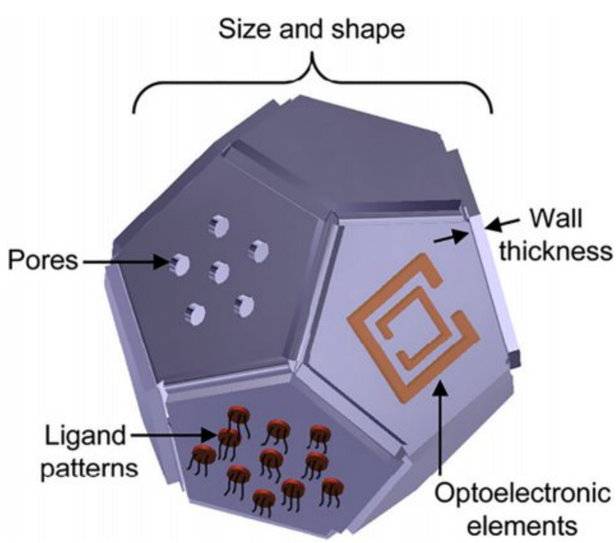


Fig. 19. Important characteristics of a drug delivery device [75].

process of embolism was shown in Fig. 7.

Additionally, light-driven SMP foam was also used for the treatment of embolism by Maitland et al. In this research, the transition temperature of SMP foam is 45 °C. Its feasibility has been verified through experiment in vivo. Under arterial flow conditions, foam deployed completely by applying a light stimulus.

In clinical medicine, the treatment for wide-necked aneurysms will be more different. It always needs staged treatment methods during curing process, including stent-assisted coil embolization. These methods are demonstrated successfully for wide-necked aneurysms, however, they are lacking in the treatment of fusiform aneurysms with a clear identifiable neck. Small et al. reported a prototype device for the treatment of fusiform (non-necked) aneurysms (Fig. 8). Two main parts of the device are SMP scaffold and SMP embolic foam. A light diffusing fiber is compressed into the device for photo-thermal actuation. Its functionally has been investigated by in vitro model: finally, the aneurysm lumen was successfully filled by foam, meanwhile, shape memory scaffold keep a flow channel [51].

4.4. Biomedical scaffolds based on SMP

Stents are a kind of tubular scaffolds, which are widely used to prevent acute vascular closure and vascular restenosis of various kinds of large vessel. Percutaneous interventions have got a great development, since the stents was proposed. DESs got a breakthrough in stent technology firstly, and later by adding polymer coating to surface of stent, vascular compatibility and elute anti-proliferative agents were improved. Additionally, the proliferation caused by proliferation of smooth muscle cell is reduced, due to the release of drug. Inspired by development of DESs, the design philosophy of pure polymer scaffold was proposed by many researchers. The vascular stent based on SMP possess more advantages compared with metal stents, such as biocompatibility, biodegradability, more drug loading, lower costs. Besides, it can also offer same percutaneous, and can be implanted into body through minimally invasive surgery. Triggered by body temperature, SMP vascular stent can gently deploy and get a larger volume.

Wache et al. first proposed such a drug-eluting stents of SMP. Based on thermoplastic polyurethane, the prototype of stent was obtained by injection molded. Its feasibility has been verified by experiment in vitro. In this experiment, the driving temperature of SMP was around body temperature [52]. Later, Gall and Yakacki et al. started to use thermoset (meth) acrylates to fabricate SMP stent. And under the drive of heat, it finished its deployment. Illustrated in Fig. 9 is its design prototype and recovery process. Under stimuli of body temperature, this stent automatically expanded without any restrictions [53].

Afterwards, the same group developed a stent of SMP triggered by photo-thermal, which a light diffusing fiber was embedded into it. A laser beam was launched from a diode laser for deployment. Just as shown in Fig. 10, the SMP stent deployed gradually with laser power from zero flow to 8.6 W in 6.3 min [54].

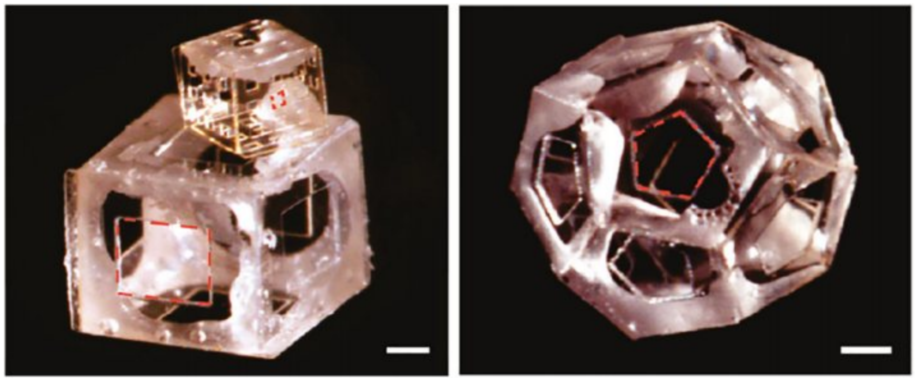


Fig. 20. Self-assembled of polyhedral from a 2D template based on SMP PCL hinges [78].

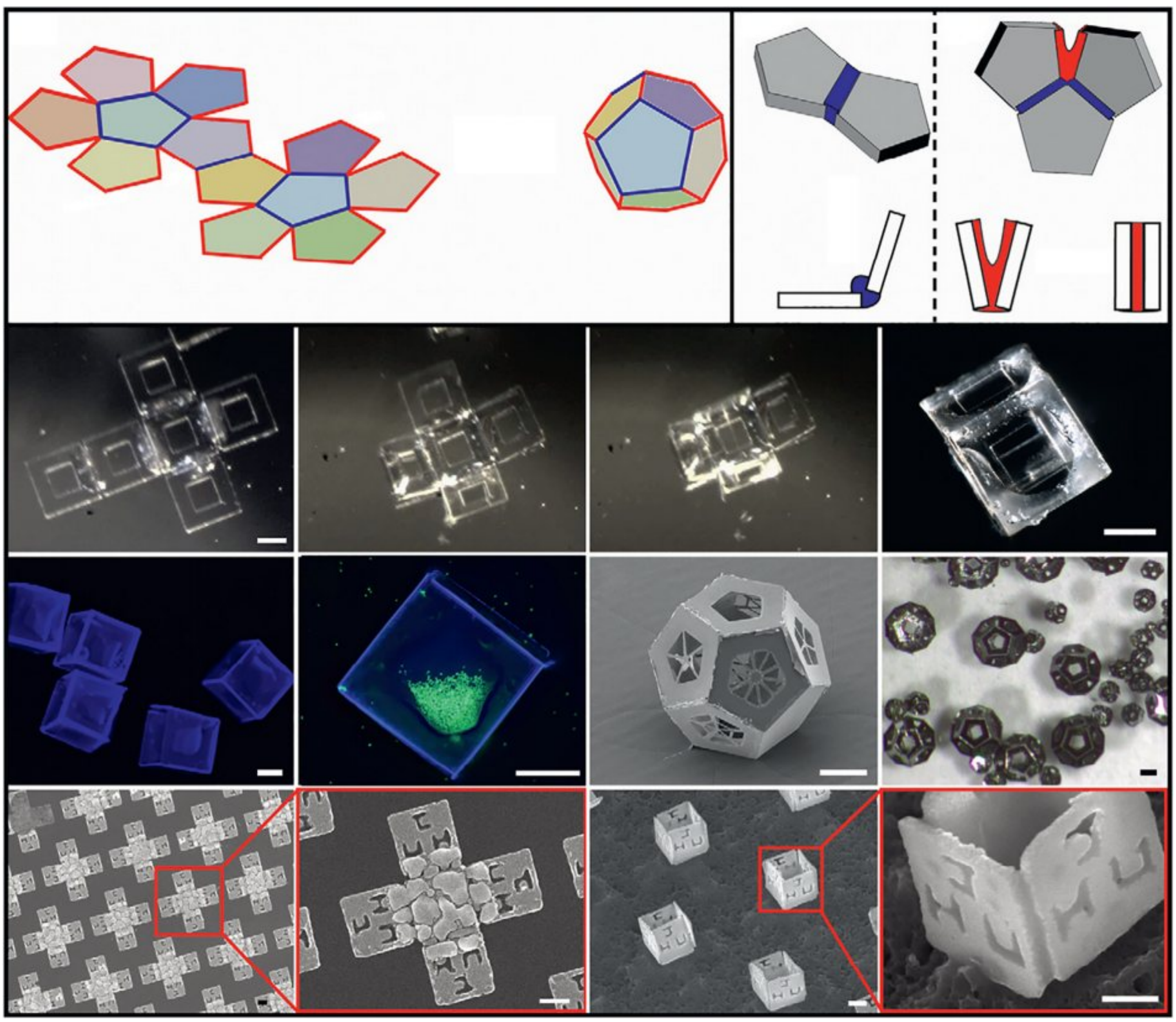


Fig. 21. Several of hollow polyhedral containers and schematic of self-folding method [79].

Recently, stents based on SMP get a new breakthrough. Generally, a stent is guided into target location through a catheter and then it was released. Stent in contraction state can deploy by mechanical expansion method due to its SME. However, once it deploys in the fixed position, it will be a trouble to remove. Huang et al. reported a novel SMP stent to solve this problem. Firstly, the shape memory polyurethane was pre-stretched, wrapped into tube and folded to a star state. The volume of stent in fold state was small, so it can be guided into any part of the body easily and recovered its initial shape under the driving of water in human body. Hence, it is easy to take out [55]. Fig. 11 is the working principle of the stent prototype.

The adopting of biodegradable SMP stent reduces the chance of suffering blood clot greatly [56–58]. Sun et al. fabricated a stent based on triple SMP, which possessed function of instant retraction (Fig. 12). Allowing for various unforeseen factors during surgery, the instant removal of stent brought convenience for operation [59].

In addition, Sun et al. developed a biodegradable spiral stent based on PLA. Once the spiral stent was heated to body temperature, it would

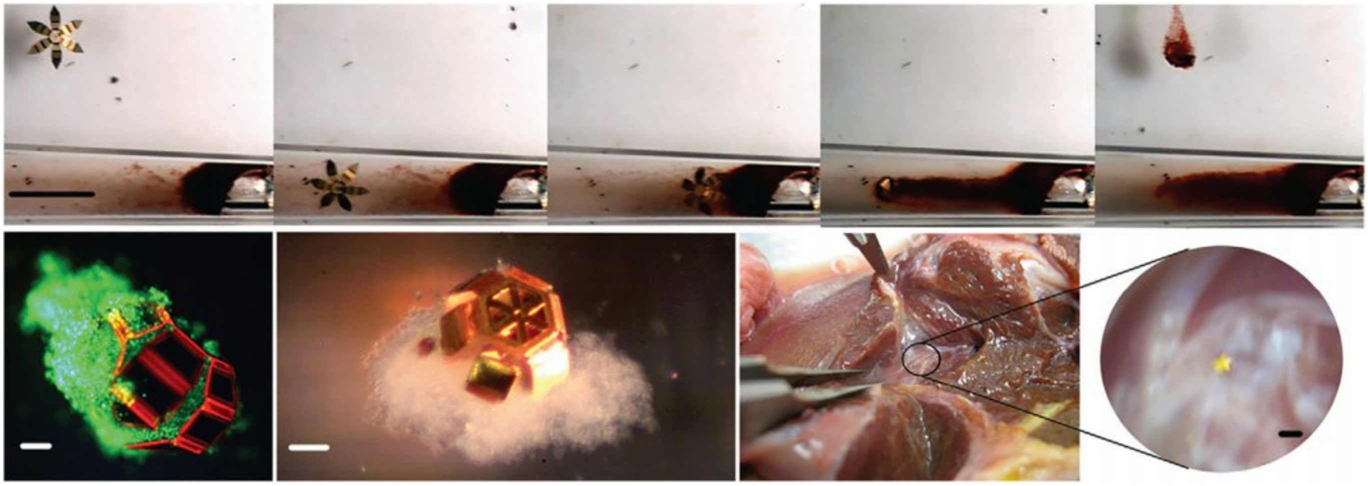


Fig. 22. Reconfigurable self-folding miniaturized tools for surgery [80].

Fig. 23. Mitral ring based on shape memory polymer [81].

recover its original shape. Its function of instant removal was verified by experiment in vitro (Fig. 13) [40].

Vascular stents of SMP can release drugs. Besides, they can be removed gradually from a body by biodegradation process. It provides mechanical stabilization for a tissue, but in many cases it might be considered as pharmaceutical product for drug reservoir. Drug-loaded SMP has a great potential in application of drug release, however, only a limited number of practical examples have been given. One application is ureteral stent used for keeping the ureter open in patients with abdominal tumors (Fig. 14) [60,61]. Besides, the intelligent drug release system based on SMP has been proposed, include self-anchoring implant rods and all sorts of reservoir systems [62,63].

With the developing of Four-Dimensional Printing technique, the future design and development of novel and functional biomedical scaffolds will be significantly advanced. Leng and Zhang et al. developed a novel smart biopolymer for biomedical SMP scaffolds which exhibit excellent shape memory effects and shape recovery at physiological temperature (Fig. 15) [64]. Experiments revealed that this scaffold possesses extraordinary biocompatibility and exhibit excellent cell attachment and differentiation of mesenchymal stem cells. By 4D printing technique, the porous SMP scaffold was readily obtained. Due to modify the layer infill density, the alterations in porosity was realized. Fig. 15A illustrated a porous scaffold with a diameter of 5 mm. The distribution of pores was showed in Fig. 15B, and the pore size can be seen from Fig. 15C. And then the possibility of this SMP scaffold used in a minimally invasive surgical was evaluated. Fig. 15D illustrated its recovery process exposed to physiological temperature.

4.5. Orthodontics based on SMP

Because of esthetic appeal and shape memory effect, SMP also has a great potential in application of orthodontics [65]. Compared with traditional orthopedic fixation materials, SMP possesses more advantages, such as easy to install and easy to adjust shape, light weight and comfortable. The essential requirements for orthopedic fixation material are excellent shape fixed rate and shape recovery ratio. Nakasima, a dentist, first proposed the concept of using thermal SMP as orthodontic arch wire for teeth, which not only can provide sufficient restoring force, and looks more aesthetically appealing than conventional arch wires [66].

In 2010, Jung et al. reported a kind of shape memory polyurethanes which can provide more stable recovery force for teeth and can be last for three months at 50 °C [67]. The fixed effect of shape memory polyurethanes was demonstrated in vitro dental model. As shown in Fig. 16, orthodontics based on shape memory polyurethanes looked more aesthetically appealing.

It is common that the anterior cruciate ligament is torn partially or completely in athletes, which will lead to destabilization of knee. Yakacki et al. developed a copolymer, and its modulus is range from 9.3 MPa to 23 MPa in rubbery state [68]. The fixed effect based on SMP for soft tissue is proposed in Fig. 17.

4.6. Reconfigurable self-folding devices

Many drugs developed in laboratory always can't get ideal clinical effect, such as too large volatility along with blood concentration and too fast degradation velocity, side effects caused by drug residues and inconvenience caused by long-term medication [69].

Thus, the dynamic behavior of drug release in vivo as well as its absorption, distribution and metabolism must be considered in modern design and development of pharmaceutical preparations in addition to pharmacological properties of the drug itself. In the early 1970s, drug delivery system has been put forward, in terms of the shortcomings of the traditional cyclical mode of administration. Researches developed

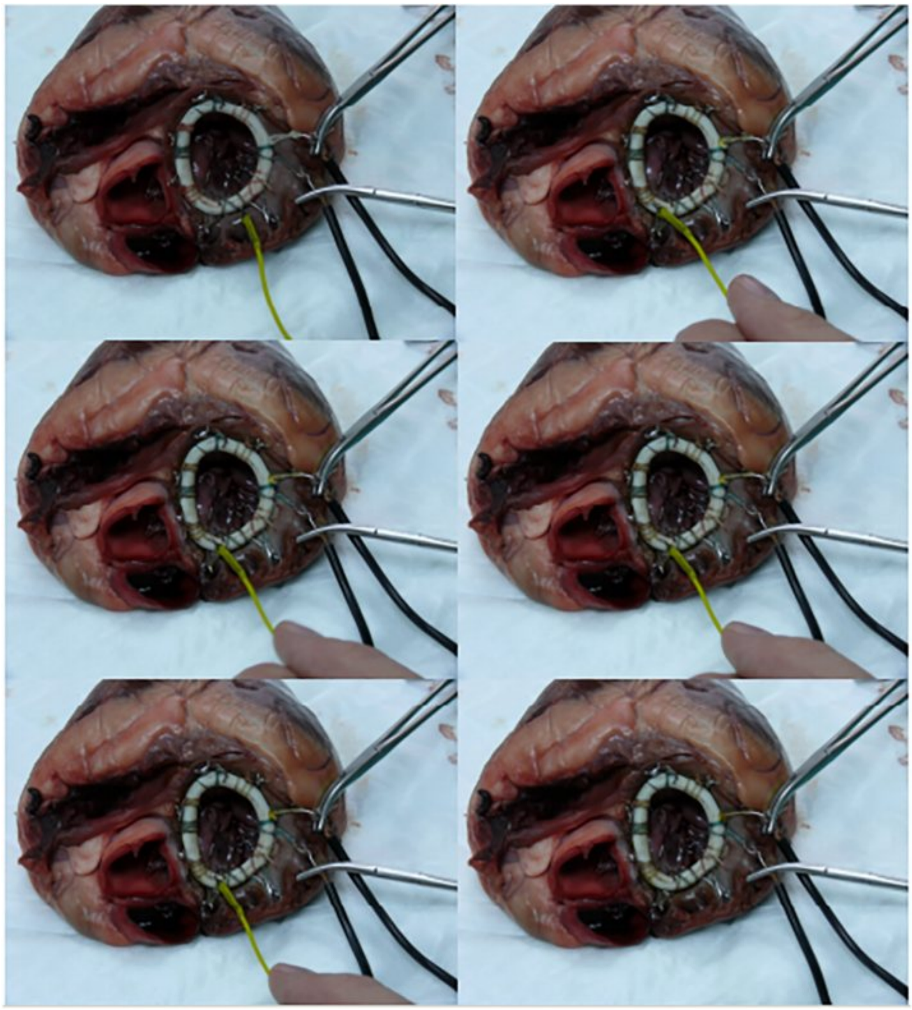


Fig. 24. Process of shape recovery using heating resistances [81].

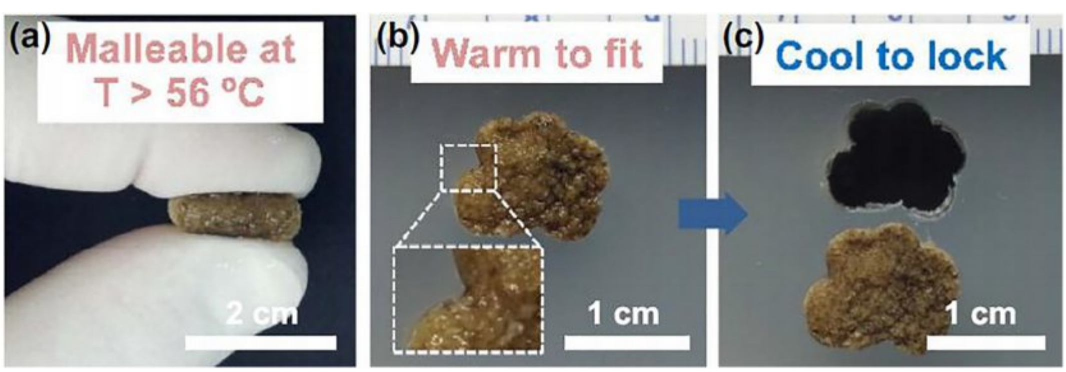


Fig. 25. Self-fitting behavior of scaffold based on shape memory PCL [82].

many controlled release pharmaceutical with different controlled drug delivery mechanisms. In recent years, micro-sized pharmaceutical controlled release system attracted much attention in medical research. It will play a great role in improving oral absorption of poorly soluble drugs, enhancing targeting and stability of drugs, prolonging the time of drug action, increasing its utilization efficiency as well as lower the adverse reactions [70–74].

Lendlein et al. applied SMP to drug delivery system and achieved controllability of the drug release [75]. Firstly, the drugs were implanted in surface of SMP. Later, SMP wrapped them completely by deformation. When drug delivery system entered the organisms, a certain dose of drug appeared in specific place with a controlled speed by controlling the shape recovery speed to realize purpose of controlling drug release intelligently. Shown in Fig. 18 is the working principle of drug delivery system.

Recent years, the development of self-assembly techniques makes the drug delivery get a further development. Self-folding is also known as self-assembly of interconnected planar templates or thin films, such as cylindrical tubes, which fold into three-dimensional structures. This method achieves the change from two-dimensional to three-dimensional structures, and the structures possess properties of biocompatible, well-tailored composition function, such as size, shape and wall

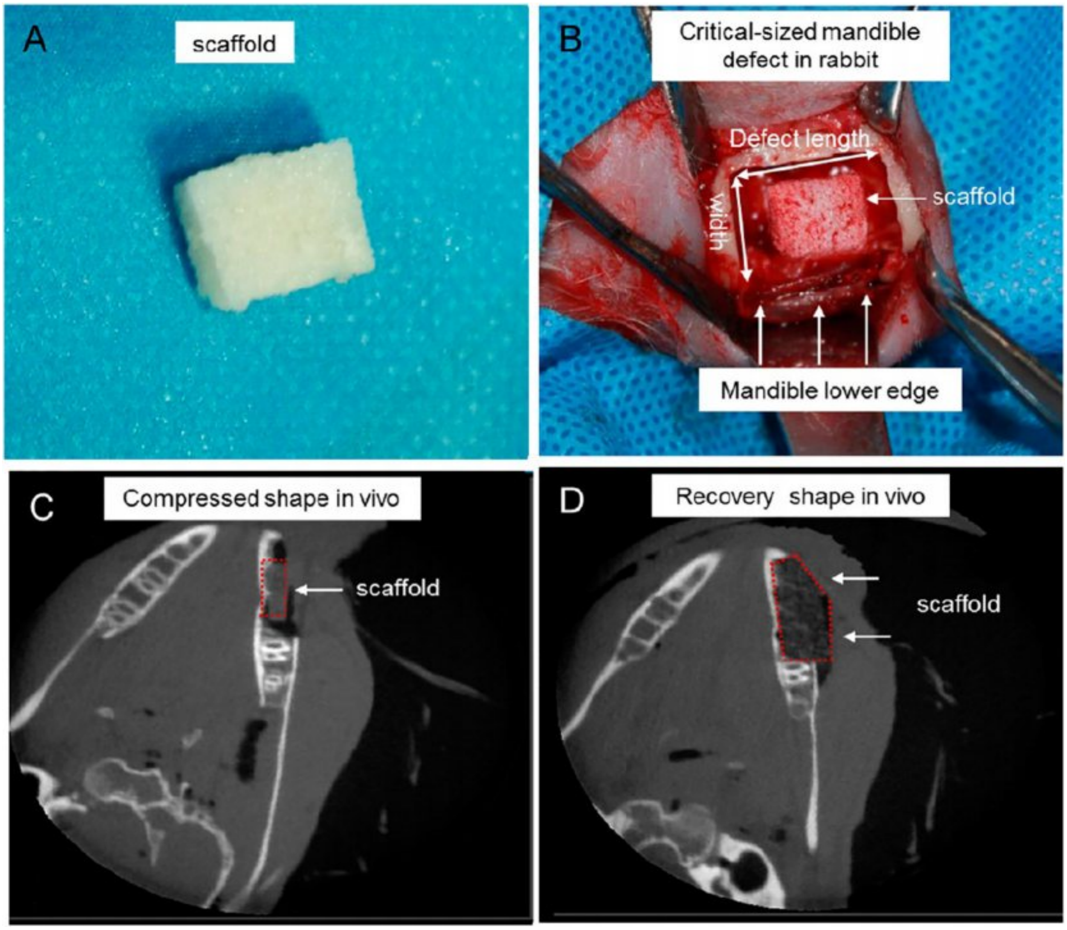


Fig. 26. Recovery process of shape memory polymer scaffold in vivo (A), scaffold in state of compression (B), implanted in bone defect (C) and recover to its original state (D) 10 min later [83].

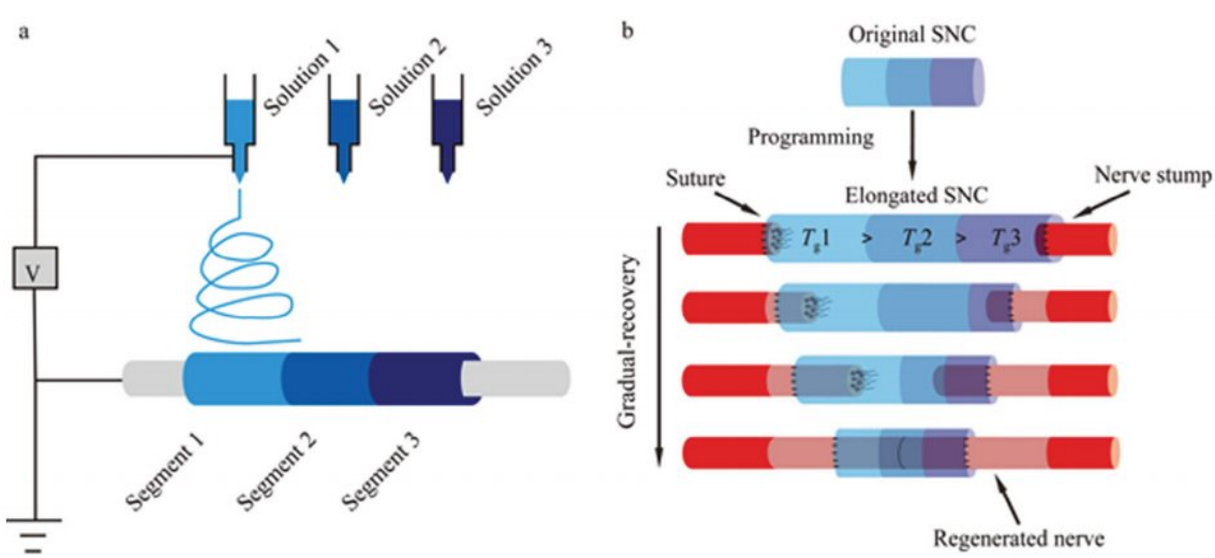


Fig. 27. a) Fabrication process for smart-nerve-conduit: injected different polymer solutions with different T_g via syringe in sequence. b) Nerve repair process [84].

thickness. These properties make self-assembly techniques more suitable for the application of drug delivery [76].

There are several important attributes about drug delivery device, as shown in Fig. 19, such as material composition, some structural parameters, surface functionalization; reconfigurability and manufacturability [77,78].

David H. Gracias et al. have developed a nanoscale structure. Its self-assemble completed actuated by PCL hinges. Fig. 20 is the all-polymeric submillimeter scale polyhedral [79]. Due to the biocompatibility of these structures, they can be used for diagnostic and drug delivery. With the drug reserving in the structure, self-folding containers can be expand by surface tension for the delivery of drugs and

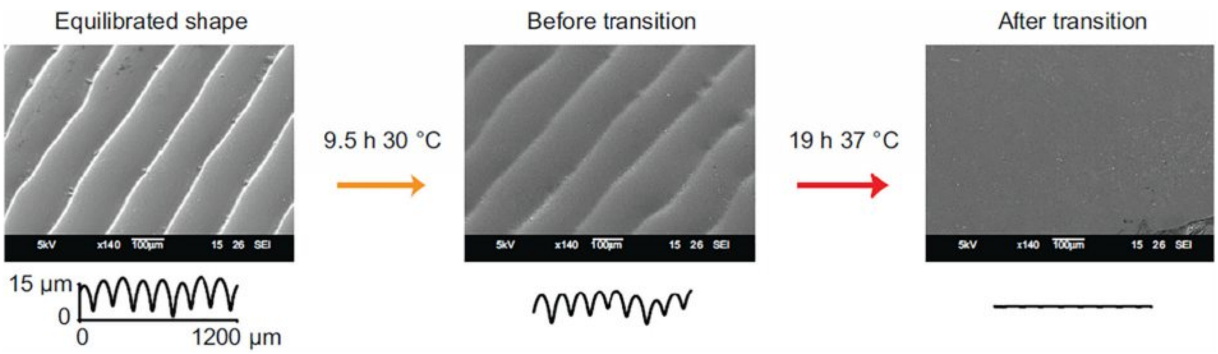


Fig. 28. Transition process of cell culture substrate [85].

other biological factors.

In this technique of self-folding methodology, lithographically patterned pores are essential for polyhedra to realize chemical release. It needs to deposit low melting point between the two panels in the process of creating a 2D template. As shown in Fig. 21, these polymeric containers have similar miniaturized 3D parishes and possess properties such as bioinert, optically transparent and easily observing encapsulated cells. Additionally, these containers can disintegration, which provides the possibility for applications of some parts of body [80].

In addition to permanent bonds structures, self-folding method could be used to create reconfigurable 3D structures. At present, many researchers focus on development of smart tools for less invasive surgery. Due to this treatment method shorten the amount of time patients must spent in hospital, lower the medical cost, reduce the postoperative pain, it gradually gain a dominant position in the surgical treatment. The development of surgery gradually in to less invasive methods, the size of the surgical tools always determine the size of the incision. As such the developments of less invasive surgery are closely associated with micro-/nanoengineering. Minimally invasive surgery usually requires a light source, a camera and other surgical instruments outside a hole at simultaneously. Challenges from the crowded surgical environment could be changed by developing a new type of smart surgical devices [81]. Self-folding tools driven by chemical or heat can save more space, which make it a possible.

The shapes of self-folding tool model-based by biological appendages are always called microgrippers. To open the microgrippers always need the trigger from thermal stimulus or chemical stimulus. All of the driven mechanisms are releasing the stored stress by changing mechanical parameters of polymeric. In addition, method of magnetic guidance can be used to drive the deployment of microgrippers by embedding ferromagnetic layers on the surface.

To evaluate the function of the self-folding microgrippers as a surgical tool, biopsy of vitro trials were conducted for further exploration. Biopsy experiment in vitro was conducted by removing part of the cells from bovine bladder tissue sample by microgrippers. The claws cut tissue cells and then removed it from the body by rotating the gripper triggered by magnet. Fig. 22 showed the tissue successfully removed [81].

4.7. Device for cardiac valve repair of SMP

The mitral valve does not close completely will lead to reverse flow. The preferred therapeutic method is valve repair comparing with replacement it. The contact between the valve leaflets will improve by implanting a prosthetic ring to reduce the orifice diameter. However, inserting a device will bring postoperative problems for heart. Lantada et al. reported a ring based on SMP for valve repair which can control the reduction of post-operative diameter remotely (Fig. 23) [82]. The method enables the heart stay in balanced situation during the operation and without excessively overload. The SMP ring was implanted to patient's body in a temporary state which reduced the impact of surgery on heart. Stimulating the embedded resistive elements in SMP ring, its diameter will reduce. Inductive heating also can be used for contraction of SMP ring by embedding magnetic particles into it [65].

The function of the prosthetic ring was evaluated by experiment in vitro with two pig hearts [82]. The recovery process of the ring was presented in Fig. 24.

4.8. Applications in repair of bone tissue

The tissue-engineered bone is one of the significant therapeutic tools for craniomaxillofacial (CMF) bone defects. It need biologic or bone transplantation as functional support to induce the bone tissue's growth. Generally, it is obtained from skull or mandible of the patient. However, autografts also have some limitations including the high incidence of complex grafting processes. Additionally, shaping and fixing the autografts and adapting to defect borders completely will be very difficult. Thus tissue engineering might be a potential alternative method for the treatment of bone defects. For critical-sized craniomaxillofacial bone defects, the superiority of tissue engineering is obvious, but scaffold design still needs to be improved. To match bone defects with irregular borders accurately will promote regeneration of bone tissue. Scaffold of SMP porous structure can adapt to a variety of irregular defects due to its own deform ability. Melissa A. Grunlan et al. have fabricated a SMP scaffold using photo-crosslinking of polycaprolactone. In this research, when the PCL was heated to the glass transition temperature or higher, the cylindrical scaffold turned soft and can mechanically fitted into any irregular shape. Lower the temperature, the shape was retained. The self-fitting behavior of it was shown in Fig. 25 [83].

Additionally, Zhou et al. also presented a smart porous nanocomposite scaffold which can release growth factors simultaneously. It could be compressed into small volume and returned its original shape triggered by body temperature. This highly interconnected scaffold was composed by poly (ε-caprolactone), which was fabricated through sugar leaching. The porous scaffold exhibited excellent shape recovery properties. By experiment in vivo, the micro-CT and histomorphometric results revealed that the SMP scaffold can promote new bone generation. Fig. 26 was the process of shape recovery of nanocomposite scaffold in vivo [84].

4.9. Applications in tissue engineering

Currently, the repair method for peripheral nerve injury is nerve autograft or artificial nerve elongation. Such methods require homology of nerves transplanted and control the length of repair artificially. However, it always accompany with secondary damage for the injured nerve tissue. Hu et al. implanted Schwann cells on surface of

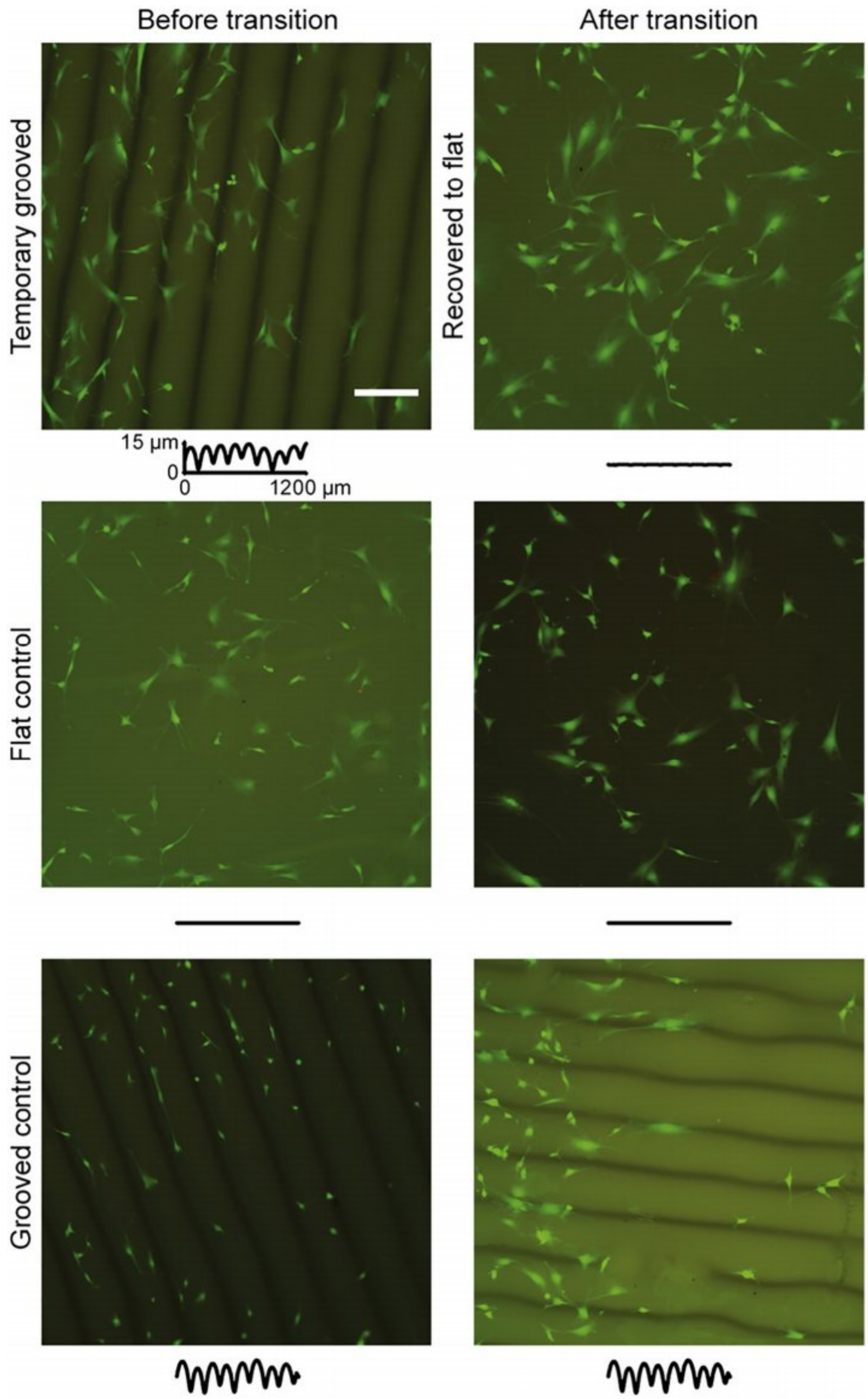


Fig. 29. State of cell viability is high [85].

poly sebacic acid esters of glycerol and carried out close observation for its growth, reproduction and apoptosis. Research indicated that this material can be used for nerve scaffolds. The recovery speed of SMP nerve conduits was controlled and safer and more efficient. It exhibited self-healing behavior for injured nerve in bodily fluids when sutured SMP nerve conduits and tension-free end, which can induced the orientated growth of tissue and cell and got the whole homologous nerve. The prototype of smart nerve conduit is designed, manufactured and characterized (Fig. 27) to verify the SMP system's feasibility [85].

Except for peripheral nerve injury, it is of great significance for enhancing implant cell adhesion and tissue ingrowth and other design of biomedical device. Cells can be used to study the mechanical properties of its surroundings, which are crucial for embryogenesis, postnatal tissue development and maintenance. During cell culture, topography or elastic modulus of substrates play a great role in study of underlying cellular mechanisms [86].

Cell culture substrates with defined topography is the major research approaches about cell echanobiology. However, present technologies only can passive control properties of substrate. Kevin A et al. have reported that SMP was used for cell culture systems which can

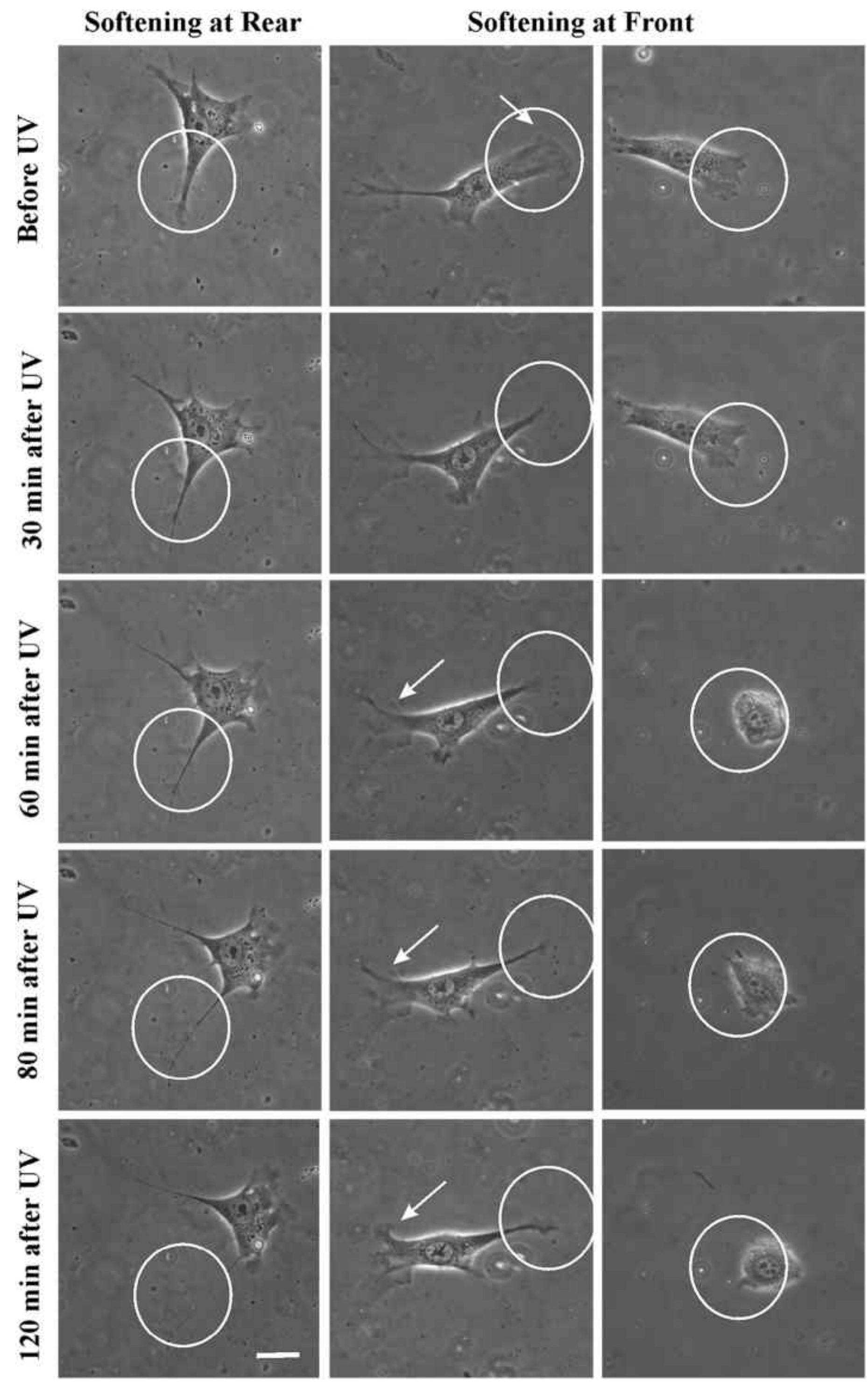


Fig. 30. Variation of cell with the rigidity change of substrates under the simulation of UV [86].

changed its surface morphology during culturing and remolded the cytoskeletal (Fig. 28). Cell viability was still higher than 95% after changing topography and elevating temperature, which meant that cell behaviors could be controlled by SMP fundus. As shown in Fig. 29, the cells were seeded in equilibrated grooved samples, adhered and spread for 9.5 h in 30 °C. The topographic changes were activated under the stimulus and recovered its original shape in the second 9.5 h. Finally, cell morphology grew stably in the last 9.5 h [86].

Furthermore, extracellular mechanical properties of substrate including rigidity have a great impact on morphology, growth, migration, and differentiation of cells. Many researchers have investigated the impact of separate substrata with fixed stiffness on cellular growth. To meet the requirement of cellular growth for spatial and temporal manipulation of mechanical properties, Margo T. Frey et al. have developed modulatable hydrogel which can change its rigidity driven by UV in acceptable range.

Fig. 30 illustrated the SMP as substrate to probe the effects of extracellular mechanical properties on adherent cells. It is expected to get more widely used in tissue engineering and regenerative medicine [87].

Fig. 31. Fig. 31 Variety of closure devices available in congenital heart disease [87–91].

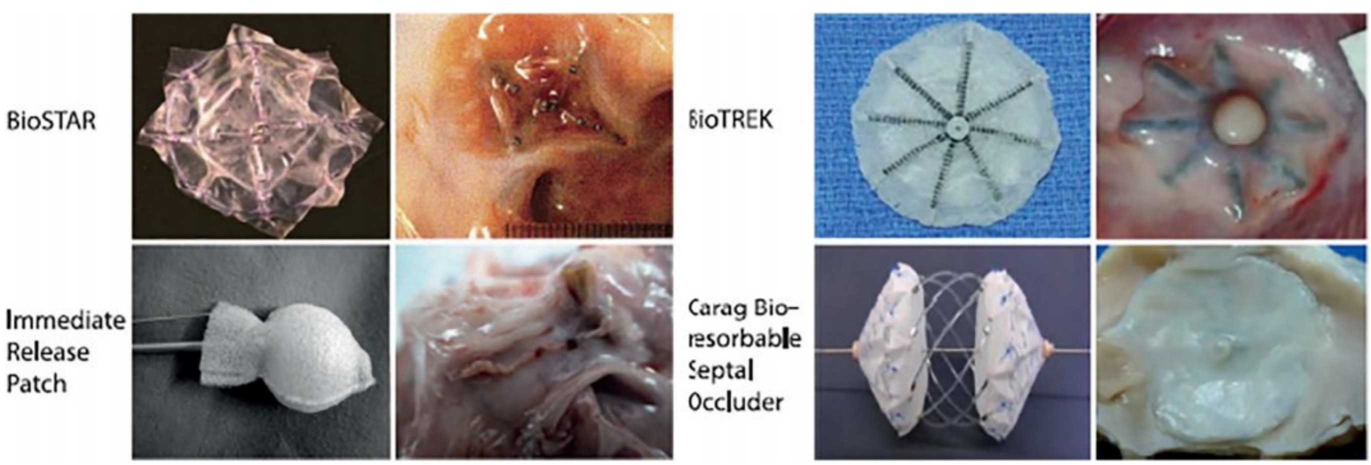


Fig. 32. Some of the bio-resorbable closure devices (left panel) and their images after implanted for 1–3 months (right panel) [87].

4.10. Occluders for congenital heart disease

Congenital heart disease is also known as abnormal anatomy caused by dysplasia and other reasons, which is the most common category of congenital malformations accounting for about 28% of the congenital malformations. It has been widely used in interventional treatment for congenital heart disease since the closure devices were developed. The present closure devices for congenital heart disease are made primarily of NiTi alloy fiber, which delivered by a delivery system in a compressed state and recovered its original shape on target location. After six months, tissues around defect covered the whole area. Listed in Fig. 31 are a variety of closure devices available in congenital heart disease.

However, none of the device is prefect, and every device has its own weaknesses and strengths. The atrial septal defect closure devices based on shape memory Ni—Ti alloy have some problems without exception. It is easy to cause thrombus and hemolysis due to its stronger rigidity, non-biodegradable. Thus several bioresorbable septal occlude devices such as BioSTAR have been developed substituting the conventional polyester fabric, in which 90% of the structure was replaced by bioengineered collagen [92,93]. Its bioresorbing started 30 days later and replaced by host tissue totally in two years [93]. Finally, as shown in Fig. 32, only the cobalt-based alloy framework was left. But it is still exist with some remaining issues, such as potential risks of vascular injury, longer procedural time. Later, the BioTREK was developed which was completely bioresorb without little metal framework. Besides, the engineering company developed the Carag Bioresorbable Septal Occluder, which was a self-centering double disk. The device was fabricated by polylacticcoglycolic acid and started to degrade in the seventh month and completely resorbed about 20 months later. However, it only had three sizes for defect [88].

There are several issues for bioabsorbable devices to be solved, such as potential high-residual, device malposition in process of reabsorbed. However, it will be a great development of closure devices if it is successful [93,94].

The SMP-based cardiac occlude device is expected to solve the non-degradable problem of existing closure devices for congenital heart disease. Based on the characteristics of designable molecular structure, biocompatibility and biodegradability and combined with the 3D printing technology, it is expected to solve the problem of complicated technology of closure devices caused by the complicated structure. It is possible to redesign the structure of closure devices and fabricated by 3D printing technology. By this method, the obtained structure is integrated which reduces the possibility of thrombus happened on surface of the instrument. Besides, because of the integrated structure of support part and choke film, the possibility of falling off of choke film is avoided. In addition, the simple and effective way to stimulate the deployment of the occluder is expected to be successful and gain application.

5. Summary and perspective

With the unique property of shape memory effect including shape deployment, shape recovery and shape self-adaptation, SMP plays a significant role in biomedical field to meet the requirement of new surgical and medical devices for special features of materials. Because of having high design variety, different biomedical shape memory materials can be developed by modifying their chemical and physical structure to meet the requirements for various applications. Furthermore, direct or indirect driven by temperature, SMP can also be actuated by pH, solution, light and even multi-physics fields. SMP with two-way SME and multi-way SME have potential development in biomedical science. Combining with its good biocompatibility, biodegradability, simple and effective stimulation mode and multi-SME, SMP is expected to a broaden application in biomedical fields.

Acknowledgement

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